HHS Public Access

Author manuscript

IEEE Trans Biomed Eng. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

IEEE Trans Biomed Eng. 2018 December ; 65(12): 2684–2691. doi:10.1109/TBME.2018.2813265.

Electroencephalogram based Detection of Deep Sedation in ICU Patients Using Atomic Decomposition

Sunil Belur Nagaraj,
Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.

Lauren M McClain,
Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.

Emily J Boyle,
Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.

David W Zhou,
Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.

Sowmya M Ramaswamy,
Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.

Siddharth Biswal,
Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.

Oluwaseun Akeju,
Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.

Patrick L Purdon, and
Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.

M Brandon Westover
Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.

Abstract

Objective: This study was performed to evaluate how well states of deep sedation in ICU patients can be detected from the frontal electroencephalogram (EEG) using features based on the method of atomic decomposition (AD).

Correspondence to: Sunil Belur Nagaraj.

Methods: We analyzed a clinical dataset of 20 minutes of EEG recordings per patient from 44 mechanically ventilated adult patients receiving sedatives in an intensive care unit (ICU) setting. Several features derived from AD of the EEG signal were used to discriminate between awake and sedated states. We trained support vector machine (SVM) classifiers using AD features and compared the classification performance with SVM classifiers trained using standard spectral and entropy features using leave-one-subject-out validation. The potential of each feature to discriminate between awake and sedated states was quantified using area under the receiver operating characteristic curve (AUC).

Results: The sedation level classification system using AD was able to reliably discriminate between sedated and awake states achieving an average AUC of 0.90, which was significantly better ($p < 0.05$) than performance achieved using spectral (AUC = 0.86) and entropy (AUC = 0.81) domain features. A combined feature set consisting of AD, entropy and spectral features provided better discrimination (AUC = 0.91, $p < 0.05$) than any individual feature set.

Conclusions.—Features derived from the atomic decomposition of EEG signals provide useful discriminative information about the depth of sedation in ICU patients.

Significance.—With further refinement and external validation, the proposed system may be able to assist clinical staff with continuous surveillance of sedation levels in mechanically ventilated critically ill ICU patients.

Keywords

Sedation level monitoring; Atomic decomposition; Support vector machine; Critical care; Intensive care unit

I. Introduction

Sedatives are often given to intensive care unit (ICU) patients to reduce agitation, help patients tolerate medical procedures, facilitate mechanical ventilation and reduce pain to ensure patient comfort and safety [1], [2]. However, it is important to maintain appropriate sedation levels as both over- and under sedation can result in adverse outcomes such as delirium, extended ICU stay and mechanical ventilation with increased risk of hospital-acquired infections [3], [4]. Current state-of-the-art methods use subjective or numerical scoring methods to assess the level of sedation in ICUs such as the COMFORT scale, the Ramsay scale, and Richmond Agitation-Sedation Scale (RASS). These methods are based on descriptive behavioral assessments of patients' responses to external stimuli and sometimes difficult to assess during deep sedation states [5].

Numerous EEG-based monitors have been developed to monitor patients' level of consciousness under anesthesia using spectral and entropy features [6], [7], [8], [9], [10]. However, such methods have shown to be problematic in the operating room environment, and are largely untested in the ICU environment [11], [12], [13], [14]. Feature engineering for classification problems can be broadly divided into hypothesis driven, data driven and empirical (trial and error) approaches. Compelling scientific justification can be given for the first two approaches; the trial and error approach is less principled. In hypothesis driven approach, one selects one or a small number of hand-crafted features to use for EEG signal

analysis, based on a mechanistic, neurophysiological and/or statistical grounds, or by generalizing from prior observations. Examples include entropy- and complexity-based measures and bispectral analysis. A weakness of this approach is that it is often overly simplistic when applied to heterogenous populations, e.g. patients with varied medical conditions, as in the present study. While this variability can in principle be overcome by developing more complex statistical models and features, this approach is often slow and prone to human error. On the contrary, the data driven approach combines five ingredients: 1) systematic automated processes for selecting features and tuning model parameters, 2) flexible models (i.e. numerous candidate features from which to select and/or flexible statistical models), 3) large data sets to provide sufficient power and variability to efficiently select features and tune model parameters, 4) methods to avoid overfitting, and 5) rigorous model validation procedures to provide unbiased estimates of performance. The data driven approach has the advantage of placing less emphasis on human judgement in tuning model parameters and selecting features. A potential danger of this approach is model overfitting, i.e. creating feature sets or models that perform well in training but do not generalize to new instances, hence the need for (4) [15]. The data driven approach is central to the field of machine learning. Examples of poorly-executed studies in which investigators neglect one or more of steps 1-5 are plentiful. Nevertheless, rigorous application of all five elements of the data-driven approach has allowed machine learning approaches to successfully address numerous real-world applications. We follow the data driven approach in this work.

In recent years, sparse representation methods have shown promise in EEG signal classification tasks. In these methods, the EEG signal is sparsely represented through linear combinations of basis functions (‘atoms’) from either a model-based or data-derived dictionary and classified based on several criteria. The objective of this paper is to investigate whether AD features are useful for classifying sedation levels in ICU patients. AD is a popular non-stationary signal analysis technique which is well suited for background EEG analysis [16], [17]. This method decomposes a given signal into a series of elemental signal templates or atoms. The atoms selected during the decomposition provide meaningful information about the underlying signal. The main advantage of using AD is that an application-specific dictionary can be easily designed. AD selects atoms from the dictionary that are highly correlated with the EEG signal under analysis. Features derived from these selected atoms during decomposition of EEG signals can be used to discriminate between sedated and non-sedated EEG classes. This data-driven approach using AD can be considered an “adaptive method” since AD can adapt itself to the data by selecting atoms from the dictionary coherent with the signal under analysis. This takes some burden/ opportunity for error away from the designer.

Further support for AD comes from contrasting it with alternative data-driven unsupervised feature learning methods. Unlike other popular unsupervised feature learning techniques such as principal component analysis, Wavelet decomposition, or independent component analysis, which produce compact representations of reduced dimensionality, AD learns a representation that is sparse and overcomplete: the dimension of the feature vector is larger than the input, but only a small number of components are non-zero for any given input [18], [19]. Sparse-overcomplete representations have been found to have several advantages in many different real-world problems. High-dimensional representations increase the

likelihood that signal categories will be easily separable, and sparsity often encourages features that admit an interpretation of the input data in terms of a small number of meaningful parts by extracting the structure hidden in the data. Finally, spare-overcomplete representations are motivated by substantial evidence that biological vision uses such representations in early visual areas [20], [21].

In this work, the potential of AD using Gabor representation of the signal (Gabor dictionary) [22] to provide useful information for automatic classification of sedation levels is examined. First, optimal sparsifying bases from the dictionary of Gabor atoms are identified. After obtaining suitable dictionary atoms, several features are derived from the AD of the EEG signal. We use these features to train a binary classifier (SVM) to discriminate between two states : “awake” versus “sedated”. In addition, the performance of SVM classifier trained on several features commonly used in sedation level prediction system is compared with the SVM classifier trained using AD features.

II. Dataset

Medical grade Sedline brain function monitors (Masimo Corporation, Irvine, CA) were used to acquire electroencephalogram (EEG) signals from 200 ICU patients admitted at Massachusetts General Hospital (MGH), Boston, USA undergoing mechanical ventilation. Patients received several sedative and analgesic drugs simultaneously managed according to usual care in three different medical and surgical ICUs. Signals were recorded with a preamplifier bandwidth of 0.5 to 92 Hz, sampling rate 250 Hz, and 16-bit, 29 nV resolution. Recording electrodes were placed on the forehead approximately at positions Fp1, Fp2, F7, and F8, with reference 1 cm above Fpz and ground at Fpz. Electrodes were periodically monitored and adjusted or reapplied as needed to ensure impedances < 5 $k\Omega$ in each channel. The recordings were performed under an IRB approved protocol. Frontal EEG channels arranged in bipolar montage FP1–F7 (left hemisphere) and FP2–F8 (right hemisphere) were used in this study.

The Richmond agitation-sedation scale (RASS) was used to access the sedation levels of patients in this study. The RASS scale is presently among the best available tools for measuring sedation level in ICU patients, has been validated and shows good inter-rater reliability [23]. The scale ranges from −5 to +4 based on the patients’ level of consciousness: +1 to +4 = increasing level of agitation with +4 referring to combative state, 0 = calm and alert, and −1 to −5 = increasing level of sedation with −5 referring to unarousable state. RASS scores were assigned at approximately 2-hour intervals by trained ICU nurses and clinical research staff who received intensive, standardized training on performing RASS assessments, reducing between-rater variability. The ability of the proposed system was tested to discriminate between two RASS groups that are clearly distinguishable from a clinical viewpoint: awake [0,–1] versus sedated [–4, –5]. This grouping was done to determine if a combination of features obtained from the AD of the EEG signal contains useful information for determining a patients’ level of sedation.

In this study, since the primary intention was to develop a patient-independent binary classification system we only included patients who had both awake (0/−1) and sedated

(−4/−5) RASS assessments and the remaining patients were excluded. In addition, we excluded patients with brain injuries present on ICU admission, because these patients often have pathological EEG features that are only indirectly related to level of consciousness, thus including them would substantially complicate the analysis. This resulted in a total of 44 patients (32 males, 12 females). Twenty minutes of EEG data preceding the time of RASS assessment from each patient (10 minutes awake and 10 minutes in the sedated state) were extracted for the analysis. In total, the dataset included a total of 880 minutes (44 patients * 10 minutes awake + 44 patients * 10 minutes sedated = 880 minutes) of two channel EEG. Table I summarizes demographic and clinical characteristics of 44 patients used in this study.

III. Automatic Sedation Level Classification system Using Atomic Decomposition

The outline of the AD based sedation level classification system using support vector machine (SVM) is shown in figure 1. The initial step involves preprocessing signals and segmenting them into short duration epochs. Each EEG epoch is then decomposed using AD and several features are extracted from the parameters of atoms used during decomposition. The feature vectors are then fed to the classifier and the probability of each sedation level is obtained for each EEG epoch. The highest probability state is selected as the state estimate.

A. Preprocessing and epoch selection

The EEG signal is filtered using a bandpass filter set at 0.5-32 Hz since there is minimal neural activity in the EEG above 20 Hz or so that is directly relevant to sedation monitoring [24]. Using a 5 second moving window, we used the following criterions (satisfying at least one of them) to remove artifacts in the EEG signal: (1) abnormally high signal amplitude (> 500 μV)–representing movement artifacts ; (2) average amplitude of signals across channels < 0.5* average amplitude of the first channel–representing loose electrode artifacts. In this study, the frequency range for analysis is restricted to 32 Hz to reduce the influence of muscle artifacts though there is minimal useful information in the EEG above the 20 Hz or so for the purpose of sedation monitoring [24], and there may be substantial noise or contribution from artifactual sources at higher frequencies (≥ 25 Hz) particularly in ICU EEG signals. Nevertheless, we elected to include information up to 32Hz. Including this higher frequency information might help for two reasons: First, some drugs which affect level of sedation induce high frequency effects (for example ketamine). Second, artifacts themselves, related to high frequency muscle artifact arising from facial tension or movements, may indicate the patient is awake. In addition, while we remove high amplitude segments (> 500 μV) and our bandpass filter has a low-frequency cutoff of 0.5Hz to remove baseline drift, neither of these choices completely remove low-frequency eye blink artifacts. This again is not necessarily a disadvantage, because eye blink artifact may provide useful information regarding level of consciousness (may provide evidence the patient is awake). We note that eye blinks are visible in the EEG but are not cortical in origin. For our purposes (inferring level of consciousness), this is not a problem: we aim to allow our algorithm to take advantage of any discriminative information that is present in the EEG signal. For these

reasons, we chose to include the full beta range up to 32 Hz, and to leave retain segments with amplitude > 500 μV.

The EEG signal is then divided into δ s short duration epochs with 50% overlap between epochs. This was performed to identify optimal EEG epoch duration that could best distinguish between awake and sedated states instead of fixed duration. The optimal value of δ will be obtained during cross validation of the proposed system and is reported in the results section.

B. Feature extraction using AD

AD technique uses a redundant time-frequency dictionary to sparsely represent a given signal. Let $\mathbf{D} \in \mathbb{R}^{N \times M}$ ($M \geq N$) be an overcomplete dictionary of M atoms, where each atom is of length N. Using the linear combination of atoms from the dictionary, any given EEG signal $\mathbf{X} \in \mathbb{R}^{N \times 1}$ can be represented (or approximated) as

$$\mathbf{X} = \mathbf{D}_{\gamma}, \quad (1)$$

where $\gamma \in \mathbb{R}^{M \times 1}$ is the weighted set of sparse coefficients associated with dictionary atoms [25]. This technique is used to find a suitable signal approximation within a given dictionary that concentrates the original signal energy in as few non-zero coefficients as possible. This means that the initial few atoms selected by the AD algorithm will contain the most salient information. Several AD methods are available to solve (1) which includes: Matching pursuit (MP) [26]. Orthogonal matching pursuit (OMP) [27] and Basis pursuit (BP) [28]. In this study, OMP is used to decompose EEG epochs [27]. It is a variation of the MP algorithm proposed by Mallat and Zhang [26] that uses a least-squares, rather than the inner product, to minimize the error in the signal approximation. An advantage of OMP is that the residual is always orthogonal to previously selected atoms. This means that the same atom can never be selected twice and therefore, requires fewer iterations to converge compared to MP [25], [27].

C. Dictionary for AD

Selection of a suitable decomposition dictionary influences the performance of the AD algorithm. Traditionally, dictionaries consisting of orthogonal bases such as Fourier and orthogonal wavelet bases have a minimum number of atoms to span the Hilbert space due to limitations in time (Fourier) and frequency (wavelet) localization [28]. However, sparse descriptive representations can be obtained using a time-frequency (TF) dictionary consisting of atoms completely spanning the time-frequency plane [29]. In this work, we use Gabor dictionary consisting of Gaussian functions that are scaled, translated and sine-modulated [29] for decomposition given by,

$$\phi(t;\xi) = \frac{1}{\sqrt{m}} g\left(\frac{t-\alpha}{m}\right) e^{j\beta t}, \quad (2)$$

where $\xi = [\alpha, m, \beta]^{\tau}$ are the parameters of the Gabor atom and $g(t) = e^{-\pi t^2}$ is the Gaussian window function. The factor $1 / \sqrt{m}$ normalizes the function $g(t)$. Here $m > 0$ is the scale of the function, α is the translation in time, and β is the frequency modulation. The dictionary is then defined as

$$\mathbf{D} = \phi(n; \xi_i) \mid_{t \to nT_s}, 0 \leq t < \delta, \xi_i = [\alpha_i, m_i, \beta_i]^T, \in \mathbb{R}^{NXM}. \quad (3)$$

Here T_s is the sampling time, $n = 1, 2, \ldots, N-1$ and δ is the duration of EEG epoch. Atoms are normalized to have unit energy. We use an overcomplete Gabor dictionary **D** with the following atom parameters: scale m which controls the time-width of the Gabor atom φ is obtained using a dyadic sequence $m = 2^q$, where $0 \leq q \leq L$, N is the length of the atom given by $N = 2^L$, and we chose the values of α and β in the range $\alpha \in \{2^1, 2^2, \ldots, 2^{10}\}$ and $\beta \in \{2^{10}, 2^9, \ldots, 2^1\}$. We restricted the values of α and β in this range to reduce computational complexity.

D. AD Feature extraction

Let K be the number of atoms selected during AD of the EEG epoch. The following 6 features are derived from AD of the EEG epoch described below:

1) Signal-to-error (SER) ratio: Let x be the short duration EEG epoch and $\hat{x}$ be the reconstructed EEG epoch using K number of atoms using AD. The signal-to-error ratio can be obtained as

$$F1 = 20 \log_{10} \left(\frac{\|x\|_2}{\|x - \hat{x}\|_2} \right), \mathrm{dB} \quad (4)$$

2) Area under the inner product: This feature is defined as the area under the absolute value of the inner product between the atoms selected during AD and the signal given by

$$F2 = \left(\sum_{k=1}^{K} | \langle \phi_k, x \rangle | \right)^2 \quad (5)$$

3) Atom parameters: The mean and standard deviation of the scale (m) parameters ($F3$, $F4$) and frequency (β) parameters($F5$, $F6$) corresponding to K selected atoms during AD were obtained which resulted in four features. These features have been previously used for classifying different patterns in environmental sounds [30].

In total, six features are extracted from the AD of each δ sec EEG epoch for each channel. The median across channels is then obtained.

IV. Classification and performance assessment

We used leave-one-subject-out cross-validation (LOSOCV) to train and validate the performance of the proposed sedation level classification system instead of *k*-fold cross-validation for the following reasons: (i) Reducing the number of training samples (using *k*-fold) reduces the amount of training data, increasing the likelihood of overfitting to the training sample. This reflects the well known bias-variance tradeoff (large training set, small testing set → reduced chance of overfitting, higher variance in estimates of average test performance; smaller training set, larger testing set → increased chance of overfitting, reduced variance in estimates of average test performance), (ii) The EEG can vary markedly between individuals in the same sedation level. Pooling the testing set for validation (using 5 or 10-fold) would make it difficult to evaluate how well the model works in individual patients. Because it is important to us to know how well the method works in individuals, LOSOCV is the more appropriate approach for our study, and (iii) When compared to *k*-fold, LOSOCV method provides a better estimates of the true generalization error [31]. This means that the classification system will provide similar or near-similar performance when tested on the unseen long recording testing data which is the case in the neuro iCUs where a patient can have EEG recording up to 3 days. In each iteration of LOSOCV, we used data from 43 patients as training and the one remaining patient's data for testing. This process is repeated until the recording from each patient has been used once for testing (44 iterations in total).

The area under the receiver operator characteristic (AUC) was used as a performance metric in this study. Initially, the training set was formed using data from all patients except from the testing patient which divided overall data in the ratio 43:1 between training and testing sets. In each iteration, features in the training set were normalized using the box-cox transformation [32], which estimates a parameter λ. This value of λ, estimated from the training data, is used to normalize the testing data. During the procedure for optimizing SVM model and parameter tuning, we strictly did not include any data from the testing patient. The classification system requires selection of several parameters before testing on the testing set. During the training step, awake and sedated EEG epochs are labelled as 0 and 1 respectively. For parameter optimization and model selection we employed a LOSOCV procedure, embedded within each iteration of the overall LOSOCV training procedure. That is, for each set of 43 patients in the LOSOCV training iteration, we identified the values of parameters [δ, σ, K, and C] that yielded the highest mean AUC on the LOSOCV. This procedure acted only on the 43 patients training data. In each iteration, the training set consisted of 86 samples from 43 patients (43 segments of 10 minutes each (1 segment per patient) during the awake state, and 43 segments of 10 minutes each (1 segment per patient) during the sedated state, resulting in 860 minutes of EEG epochs in total); it did not include the left-out test patient in any given round of LOSOCV. After obtaining optimized values for [δ, σ, K, and C], we used them to train the final SVM model and validate the trained classifier on the left-out patient. This resulted in a total of 43 LOSOCV iterations and for every iteration, the SVM model parameters for Gaussian kernel function: σ (kernel width) and C (regularization constant) were varied in the range [2^{-4}, 2^{-3}, …, 2^{12}] and [2^{-5}, 2^{-4}, …, 2^{8}] respectively. In every training iteration, δ and K are varied in the range [1-20] s and

[2-100] atoms, respectively and the optimal parameters that maximized the AUC are obtained. It should be noted that at every LOSOCV iteration, different SVM model and parameters are obtained.

In the testing step, the trained binary classifier model using optimal parameters (δ, K, σ and C that maximize the mean AUC) is tested on the remaining (left out) patient to generate an automated annotation of sedation level. Using Platt scaling [33], the binary output of the SVM classifier is converted into a continuous probability scores through a sigmoid function to provide a probability of a patient being in a sedated state. Figure 2 illustrates the cross-validation procedure used in this study.

V. Results

Results are reported as mean (IQR) unless otherwise stated.

The sensitivity, specificity and AUC of the proposed classification system using AD method are 81.33 (68.7 - 98.4)%, 81.06 (69.7 - 98.6)% and 0.9 (0.80 - 0.99) respectively. Different values of δ and K were selected in each iteration of LOSOCV. The maximum likelihood estimate of the hyperparameter values identified across the training iterations were an epoch duration of $\delta = 8$ sec and a decomposition level of $K = 10$ atoms. Figure 3 demonstrates this process of decomposition using a sample EEG epoch.

For comparison, we also test the performance of the proposed system using features developed for measuring sedation levels which can be grouped into two categories:

1) Spectral (10 features): Power in sub-band: $F7$ = delta (0.5-4 Hz), $F8$ = theta (4-8 Hz), $F9$ = alpha (8-12 Hz), $F10$ = spindle (12-16 Hz), $F11$ = beta (16-32 Hz) and $F12$ - $F16$ - their corresponding normalized power (normalized with total spectral power) [24], [34], [35]. These drug-specific spectral features showed significant correlation with level of consciousness in healthy volunteers during general anesthesia and sedation [24], [36].

2) Entropy (9 features): $F17$ = Lempel-ziv complexity [37], $F18$ = spectral entropy, $F19$ = state entropy [38], $F20$ = response entropy [38], $F21$ = Renyi entropy [39], $F22$ = Shannon entropy [40], $F23$ = sample entropy [41], $F24$ = approximate entropy [42], and $F25$ = permutation entropy [43].

The spectral features were estimated from the power spectral density (PSD) of the EEG epoch using Fast Fourier Transform (FFT). These additional features were also normalized using similar normalization scheme described in section IV. Table II compares the performance of the sedation level classification system using AD, spectral and entropy features. Figure 4 shows the distribution of individual features across all patients in classifying awake versus sedated EEG epochs. The performance of the system using AD features outperforms the system trained using either spectral or entropy features. The performance of the system using AD features is significantly better ($p < 0.05$ using Wilcoxon rank sum test) than the performance using spectral and entropy features. Figure 5 shows the ROC curve for different feature sets using the SVM classifier model. It is clear from table II and figures 4, 5 that the combined feature set provides better discrimination

than any individual feature set. In the ICU, multiple drugs are given to the patient as a part of routine care and different sedative drugs have different effects (for example: dexmedetomidine operates differently than propofol [24] or benzodiazepines) on EEG independent of changes in sedation state. Moreover, the association between deeper levels of sedation and increasing levels of organ failure can significantly impact the EEG. As a result, there is a large heterogeneity in the dataset making it difficult to classify between sedated states (see figure 6) resulting in large variance in the performance of the classifier. In addition, this variability is a result of our use of evaluating the method on individual patients rather than on pooled data, coupled with the large between-patient variability in EEG signals. This highlights the challenge of creating reliable physiologically-based sedation monitoring in the ICU population. Additionally, we also performed 10-fold cross validation to assess the performance of the proposed system on an epoch-by-epoch basis. The results are summarized in the appendix table A1.

Since the proposed binary classification system provides a continuous probability score after post-processing the SVM output, it was observed that the probability score was higher during awake state and lower during sedated state. To test if the proposed method can be used to provide a meaningful continuous levels of sedation, we test the output of the binary SVM classifier (trained only on awake and sedated epochs) to assign a probability score to EEG epochs from the testing patient in all RASS states (+4 to −5). We then obtained the Spearmans rank correlation (ρ) between the probability score output from the binary SVM model and the continuous RASS scores which resulted in a mean $\rho = 0.47(0.34 – 0.63)$, better than a chance-level mean correlation of $\rho = 0.1(0.02 – 0.17)$ suggesting that the system can provide substantial, albeit imperfect, information about levels of sedation and with further development, the overall performance could be improved. An example illustrating this is shown in figure 7.

From the sample 8 s EEG epoch shown in figure 3, we would expect large EEG amplitudes with greater envelop variations in the awake state compared to the deep sedation where EEG may be greatly suppressed. This raises an important question: can we distinguish between awake and deep sedation states just by looking at the variations in the EEG envelope?. The background EEG signal is nonstationary with time varying amplitude and frequency characteristics which can be considered as a colored random noise with modulation in amplitude or amplitude modulation (AM). Therefore, features derived from AD (in this case F1 and F2) were more discriminative compared to other features (see figure 4). However, when only F1 and F2 features were used for classification, a mean AUC of 0.87 was obtained but when all the AD features were used (F1-F6) the system provided a mean AUC of 0.90. This suggests that the classification is not just based on EEG envelope variations at different sedation levels but also depends on the variations in the frequency. To demonstrate this, we used the Hilbert transform to obtain the EEG envelope (AM) of the bandpass filtered EEG epoch and used the mean AM as a feature to test the performance of the classification system. The classification system resulted an AUC = 0.76 (0.63 - 0.81) suggesting that variations in EEG envelop or signal amplitude differences in awake and deep sedation alone may not be sufficient to discriminate between two states.

VI. Discussion

In this paper, we presented an AD-based approach to predict levels of sedation in mechanically ventilated ICU patients from the frontal EEG using features derived from atoms in the Gabor dictionary. The proposed method is patient-independent, i.e, the SVM model trained is independent of data from testing patients. In addition, the method predicts sedation levels on a continuous scale (probability estimates) which can be beneficial in continuous sedation level monitoring. Although several methods exist to estimate sedation levels, the potential of AD for this purpose has not been previously explored. We found that the highest classification performance is obtained by using a short duration 8 second EEG epoch. Clinically, this short duration segment analysis can be useful in reducing the "time-delay problem" in implementations of realtime sedation level monitoring in the ICU [45]. In addition, we did not alter the EEG dataset to remove eye blinks and eye-movements artifacts. On the contrary, presence of eye-blinks adds additional information about the patients level of sedation: e.g. eye blinks may indicate the patient is awake. Therefore by using the dataset with artifacts encountered during real-time ICU EEG recordings, we obtained a robust assessment of our classification system.

AD methods provide sparse representation of the EEG signal. The primary intention of using AD in this study was to extract several discriminatory information for sedation level classification without any intention to recover or sparse representation of the actual EEG signal. We observed that the performance of the sedation level prediction system depends mainly on the number of decomposition atoms and the duration of the EEG epoch. The main assumption using AD for feature extraction is that the dominant characteristics of the EEG signal can be obtained by initial few atoms. By extracting several features from the AD representation of the EEG, it was possible to improve the performance of the proposed system when compared to other commonly used features.

To the best of our knowledge, this is the first attempt to study the potential of AD based features to assess sedation levels in ICU patients using EEG and is novel for this application (in ICU patients). We used following keywords in Pubmed and Google Scholar to search for literature using AD to assess the depth of anesthesia: *Depth of Anesthesia*+ *Matching Pursuit, Depth of Anesthesia*+ *Atomic Decomposition, Sedation Level*+ *Atomic Decomposition, Sedation Level*+ *Matching Pursuit, Depth of Anesthesia* + *Gabor Dictionary*. However, we did not find any existing literature using MP/AD for sedation level/ depth of anesthesia assessment. The closest work we found was the application of MP algorithm for spectral analysis of spindle activity during dexmedatomidine infusion in comparison with sleep spindles but not to assess sedation levels or depth of anesthesia [46].

The commercial BIS index is proprietary, and thus running it on our data to compare results was not possible. BIS is known to be based on features estimated from the power spectrum, burst suppression ratio, and the bispectrum of the EEG signal. This index was developed on adult patients under propofol general anesthesia in the surgical setting and has been shown to perform less well for other drugs and in ICU settings [11], [13]. Our proposed system is (i) based on a large set of quantitative EEG features different from those known to be included in BIS, and (ii) is tailored to assess depth of sedation for ICU patients.

Though features obtained using AD show promise, the performance of the proposed system trained using other more conventional types of dictionaries, including Fourier, wavelet, the discrete cosine transform etc can improve the performance (in addition to gabor dictionary). Further, differences between datasets can have a high impact on the performance of the proposed system which makes it difficult to compare the results with other state-of-the-art methods.

Future work will address several limitations of this study. First, we did not provide any information about the sedative dosage and type of sedatives to the classifier. This is important as different sedatives produce different EEG signatures [24]. Second, we did not include a measure of severity of disease that affects the EEG morphology [47]. Several studies have demonstrated changes in EEG patterns in patients with conditions such as sepsis [48], encephalopathy [49], seizures [47] etc. This suggests that by adjusting for a measure of severity of illness (for example APACHE II), we might improve the performance of the proposed system. Third, we performed two-class classification in this study. As the goal of this paper was to explore the potential of AD method to distinguish between sedation states, we did not focus on multiclass RASS classification. The major reason for this approach was that we did not have enough dataset to support a 10-class RASS classification. In addition, intermediate RASS assessments are subject to inter-rater variability - for example, it is easy to distinguish between RASS= 0 and −5 but difficult to distinguish between RASS = −2 and −3, RASS =−3 and −4 and so on which can result in sedation level annotation noise. Due to this we evaluated the potential of AD features that can best discriminate between two extreme levels of sedation and later extend it to generate continuous levels of sedation (see figure 7). This technique of training the classifier on binary scores and testing it on continuous scores using probability output as a surrogate measure to predict sedation level is novel for this application (monitoring sedation levels in the ICU). We also hypothesize that including drug information to further specialize / tune the model might improve performance, at least in principle. In addition, future work on sedation monitoring may benefit from exploring ways to take into account EEG effects that are drug-specific [24], [36].

The proposed EEG-based patient independent automated system has advantages over conventional purely behavioral assessment-based methods for assessing depth of sedation in the ICU. First, EEG-based sedation level monitoring is objective, free from human inter-observer variability. Second, it can be performed on a continuous basis. Third, interpreting the output of the classification system in a probabilistic way makes it flexible and suitable for following EEG trends at different sedation levels. Fourth, the AD method can be considered as an “adaptive” method in which the dictionary atoms can be designed and selected depending on the anesthetic or sedative used in the ICU. Finally, the results obtained in this study provide progress towards application of non-stationary signal analysis [50] and dictionary learning [51] methods for designing continuous sedation level prediction system.

VII. Conclusion

The performance of several features for detecting sedation levels in ICu patients is presented. The classification system shows promising results using AD to differentiate between awake and sedated states when compared to spectral and entropy features. Combining all features together slightly improves system performance. The results obtained in this study represent progress towards developing a real-time automated sedation level monitoring system in ICU patients. In future work we will improve the performance of the proposed system by addressing several limitations outlined in this study.

Acknowledgments

This material is based upon works supported by NIH-NINDS 1K23NS090900-01 (MBW, SBN), Andrew David Heitman Foundation (MBW), Rappaport Foundation (MBW).

Appendix

TABLE A1

10-fold cross validation to compare the performance of the sedation level classification system on an epoch-by-epoch basis. The combined feature set (AD+Spectral+Entropy) outperformed individual feature set.

Feature set (No. of features)	Mean AUC (IQR)
AD (6)	0.88 (0.86–0.89)
Spectral (10)	0.87 (0.86–0.88)
Entropy (9)	0.83 (0.82–0.84)
AD+Spectral (16)	0.90 (0.88–0.92)
AD+Entropy (15)	0.86 (0.84–0.88)
AD+Spectral+Entropy (25)	0.92 (0.89–0.93)

References

[1]. Devlin JW, “The pharmacology of oversedation in mechanically ventilated adults,” Current opinion in critical care, vol. 14, no. 4, pp. 403–407, 2008. [PubMed: 18614903]

[2]. Mascia MF, Koch M, and Medicis JJ, “Pharmacoeconomic impact of rational use guidelines on the provision of analgesia, sedation, and neuromuscular blockade in critical care.” Critical care medicine, vol. 28, no. 7, pp. 2300–2306, 2000. [PubMed: 10921556]

[3]. Gehlbach BK and Kress JP, “Sedation in the intensive care unit,” Current opinion in critical care, vol. 8, no. 4, pp. 290–298, 2002. [PubMed: 12386488]

[4]. Ouimet S, Kavanagh BP, Gottfried SB, and Skrobik Y, “Incidence, risk factors and consequences of ICU delirium,” Intensive care medicine, vol. 33, no. 1, pp. 66–73, 2007. [PubMed: 17102966]

[5]. De Jonghe B, Cook D, Appere-De-Vecchi C, Guyatt G, Meade M, and Outin H, “Using and understanding sedation scoring systems: a systematic review,” Intensive care medicine, vol. 26, no. 3, pp. 275–285, 2000. [PubMed: 10823383]

[6]. Jospin M, Caminal P, Jensen EW, Litvan H, Vallverdú M, Struys MM, Vereecke HE, and Kaplan DT, “Detrended fluctuation analysis of EEG as a measure of depth of anesthesia,” Biomedical Engineering, IEEE Transactions on, vol. 54, no. 5, pp. 840–846, 2007.

[7]. Li X, Li D, Liang Z, Voss LJ, and Sleigh JW, “Analysis of depth of anesthesia with Hilbert-Huang spectral entropy,” Clinical Neurophysiology, vol. 119, no. 11, pp. 2465–2475, 2008. [PubMed: 18812265]

[8]. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, and Shafer SL, "Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy," The Journal of the American Society of Anesthesiologists, vol. 100, no. 6, pp. 1353–1372, 2004.

[9]. Kreuer S, Biedler A, Larsen R, Schoth S, Altmann S, and Wilhelm W, "The narcotrend–a new EEG monitor designed to measure the depth of anaesthesia a comparison with bispectral index monitoring during propofol-remifentanil-anaesthesia," Der Anaesthesist, vol. 50, no. 12, pp. 921–925, 2001. [PubMed: 11824075]

[10]. Sigl JC and Chamoun NG, "An introduction to bispectral analysis for the electroencephalogram," Journal of clinical monitoring, vol. 10, no. 6, pp. 392–404, 1994. [PubMed: 7836975]

[11]. Tonner PH, Wei C, Bein B, Weiler N, Paris A, and Scholz J, "Comparison of two bispectral index algorithms in monitoring sedation in postoperative intensive care patients," Critical care medicine, vol. 33, no. 3, pp. 580–584, 2005. [PubMed: 15753750]

[12]. Nasraway SA, Jr, "The bispectral index: Expanded performance for everyday use in the intensive care unit?*," Critical care medicine, vol. 33, no. 3, pp. 685–687, 2005. [PubMed: 15753773]

[13]. Arbour R, "Impact of bispectral index monitoring on sedation and outcomes in critically ill adults: A case series," Critical care nursing clinics of North America, vol. 18, no. 2, pp. 227–241, 2006. [PubMed: 16728309]

[14]. Walsh TS, Ramsay P, Lapinlampi TP, Särkelä MO, Viertiö-Oja HE, and Meriläinen PT, "An assessment of the validity of spectral entropy as a measure of sedation statein mechanically ventilated critically ill patients," Intensive care medicine, vol. 34, no. 2, pp. 308–315, 2008. [PubMed: 17898996]

[15]. Cawley GC and Talbot NL, "On over-fitting in model selection and subsequent selection bias in performance evaluation," Journal of Machine Learning Research, vol. 11, no. 7, pp. 2079–2107, 2010.

[16]. Durka PJ, Matysiak A, Montes EM, Sosa PV, and Blinowska KJ, "Multichannel matching pursuit and EEG inverse solutions," Journal of Neuroscience Methods, vol. 148, no. 1, pp. 49–59, 2005. [PubMed: 15908012]

[17]. Jouny CC, Franaszczuk PJ, and Bergey GK, "Characterization of epileptic seizure dynamics using Gabor atom density," Clinical Neurophysiology, vol. 114, no. 3, pp. 426–437, 2003. [PubMed: 12705423]

[18]. Olshausen BA, "13 sparse codes and spikes," Probabilistic Models of the Brain, p. 257, 2002.

[19]. Teh YW, Welling M, Osindero S, and Hinton GE, "Energy-based models for sparse overcomplete representations," Journal of Machine Learning Research, vol. 4, no. 12, pp. 1235–1260, 2003.

[20]. Lennie P, "The cost of cortical computation," Current biology, vol. 13, no. 6, pp. 493–497, 2003. [PubMed: 12646132]

[21]. Simoncelli EP, "Statistical modeling of photographic images," in Handbook of image and video processing. Elsevier Inc, 2005.

[22]. Gabor D, "Theory of communication," Electrical Engineers - Part I: General, Journal of the Institution of, vol. 94, no. 73, pp. 58, 1 1947.

[23]. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, and Elswick R, "The richmond agitation–sedation scale: validity and reliability in adult intensive care unit patients," American journal of respiratory and critical care medicine, vol. 166, no. 10, pp. 1338–1344, 2002. [PubMed: 12421743]

[24]. Purdon PL, Sampson A, Pavone KJ, and Brown EN, "Clinical electroencephalography for anesthesiologistspart i: Background and basic signatures," The Journal of the American Society of Anesthesiologists, vol. 123, no. 4, pp. 937–960, 2015.

[25]. Goodwin MM and Vetterli M, "Matching pursuit and atomic signal models based on recursive filter banks," Signal Processing, IEEE Transactions on, vol. 47, no. 7, pp. 1890–1902, 1999.

[26]. Mallat S, A Wavelet Tour of Signal Processing, Third Edition: The Sparse Way, 3rd ed. Academic Press, 2008.

[27]. Tropp J and Gilbert A, "Signal recovery from random measurements via orthogonal matching pursuit," Information Theory, IEEE Transactions on, vol. 53, no. 12, pp. 4655–4666, 12 2007.

[28]. Chen S, Donoho D, and Saunders M, “Atomic decomposition by basis pursuit,” Society for Industrial and Applied Mathematics: Review, vol. 43, no. 1, pp. 129–159, 2001.

[29]. Mallat SG and Zhang Z, “Matching pursuits with time-frequency dictionaries,” IEEE Trans. on Signal Proc, vol. 41, no. 12, pp. 3397–3415, 1993.

[30]. Chu S, Narayanan S, and Kuo C-C, “Environmental sound recognition with time–frequency audio features,” Audio, Speech, and Language Processing, IEEE Transactions on, vol. 17, no. 6, pp. 1142–1158, 2009.

[31]. Vapnik V, Estimation of Dependences Based on Empirical Data: Springer Series in Statistics (Springer Series in Statistics). Secaucus, NJ, USA: Springer-Verlag New York, Inc, 1982.

[32]. Box GE and Cox DR, “An analysis of transformations,” Journal of the Royal Statistical Society. Series B (Methodological), pp. 211–252, 1964.

[33]. Platt JC, “Probabilistic outputs for support vector machines and comparisons to regularized likelihood methods,” in Advances in large margin classifiers. Citeseer, 1999.

[34]. Akeju O, Pavone KJ, Westover MB, Vazquez R, Prerau MJ, Harrell PG, Hartnack KE, Rhee J, Sampson AL, Habeeb K et al., “A comparison of propofol-and dexmedetomidine-induced electroencephalogram dynamics using spectral and coherence analysis,” The Journal of the American Society of Anesthesiologists, vol. 121, no. 5, pp. 978–989, 2014.

[35]. Kortelainen J, Väyrynen E, and Seppänen T, “Depth of anesthesia during multidrug infusion: separating the effects of propofol and remifentanil using the spectral features of EEG,” IEEE Transactions on Biomedical Engineering, vol. 58, no. 5, pp. 1216–1223, 2011. [PubMed: 21216702]

[36]. Brown EN, Lydic R, and Schiff ND, “General anesthesia, sleep, and coma,” New England Journal of Medicine, vol. 363, no. 27, pp. 2638–2650, 2010. [PubMed: 21190458]

[37]. Schartner M, Seth A, Noirhomme Q, Boly M, Bruno M-A, Laureys S, and Barrett A, “Complexity of multi-dimensional spontaneous EEG decreases during propofol induced general anaesthesia,” PloS one, vol. 10, no. 8, p. e0133532, 2015. [PubMed: 26252378]

[38]. Haenggi M, Ypparila-Wolters H, Bieri C, Steiner C, Takala J, Korhonen I, and Jakob SM, “Entropy and bispectral index for assessment of sedation, analgesia and the effects of unpleasant stimuli in critically ill patients: an observational study,” Critical Care, vol. 12, no. 5, p. 1, 2008.

[39]. Liang Z, Wang Y, Sun X, Li D, Voss LJ, Sleigh JW, Hagihira S, and Li X, “EEG entropy measures in anesthesia,” Frontiers in computational neuroscience, vol. 9, p. 16, 2015. [PubMed: 25741277]

[40]. Bruhn J, Lehmann LE, Ropcke H, Bouillon TW, and Hoeft A, “Shannon entropy applied to the measurement of the electroencephalographic effects of desflurane,” The Journal of the American Society of Anesthesiologists, vol. 95, no. 1, pp. 30–35, 2001.

[41]. Shalbaf R, Behnam H, Sleigh J, and Voss L, “Measuring the effects of sevoflurane on electroencephalogram using sample entropy,” Acta Anaesthesiologica Scandinavica, vol. 56, no. 7, pp. 880–889, 2012. [PubMed: 22404496]

[42]. Bruhn J, Bouillon TW, Radulescu L, Hoeft A, Bertaccini E, and Shafer SL, “Correlation of approximate entropy, bispectral index, and spectral edge frequency 95 (SEF95) with clinical signs of anesthetic depth during coadministration of propofol and remifentanil,” The Journal of the American Society of Anesthesiologists, vol. 98, no. 3, pp. 621–627, 2003.

[43]. Olofsen E, Sleigh J, and Dahan A, “Permutation entropy of the electroencephalogram: a measure of anaesthetic drug effect,” British journal of anaesthesia, vol. 101, no. 6, pp. 810–821, 2008. [PubMed: 18852113]

[44]. van der Maaten L and Hinton G, “Visualizing data using t-SNE,” Journal of Machine Learning Research, vol. 9, pp. 2579–2605, 2008.

[45]. Pilge S, Zanner R, Schneider G, Blum J, Kreuzer M, and Kochs EF, “Time delay of index calculationanalysis of cerebral state, bispectral, and narcotrend indices,” The Journal of the American Society of Anesthesiologists, vol. 104, no. 3, pp. 488–494, 2006.

[46]. Huupponen E, Maksimow A, Lapinlampi P, Särkelä M, Saastamoinen A, Snapir A, Scheinin H, Scheinin M, Meriläinen P, HIMANEN S-L et al., “Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep,” Acta anaesthesiologica Scandinavica, vol. 52, no. 2, pp. 289–294, 2008. [PubMed: 18005372]

[47]. Smith S, “EEG in neurological conditions other than epilepsy: when does it help, what does it add?” Journal of Neurology, Neurosurgery & Psychiatry, vol. 76, no. suppl 2, pp. ii8–ii12, 2005.

[48]. Young G, Bolton C, Austin T, Archibald Y, Gonder J, and Wells G, “The encephalopathy associated with septic illness.” Clinical and investigative medicine. Medecine Clinique et Experimentale, vol. 13, no. 6, pp. 297–304, 1990. [PubMed: 2078909]

[49]. Kaplan PW, “The EEG in metabolic encephalopathy and coma,” Journal of clinical neurophysiology, vol. 21, no. 5, pp. 307–318, 2004. [PubMed: 15592005]

[50]. Boashash B, Time-frequency signal analysis and processing: a comprehensive reference. Academic Press, 2015.

[51]. Rubinstein R, Bruckstein AM, and Elad M, “Dictionaries for sparse representation modeling,” Proceedings of the IEEE, vol. 98, no. 6, pp. 1045–1057, 2010.

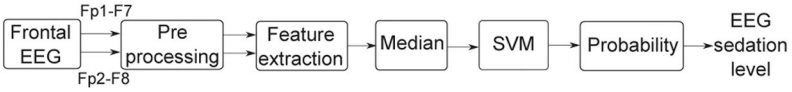

Fig. 1.
Architecture of the sedation level classification system used in this study.

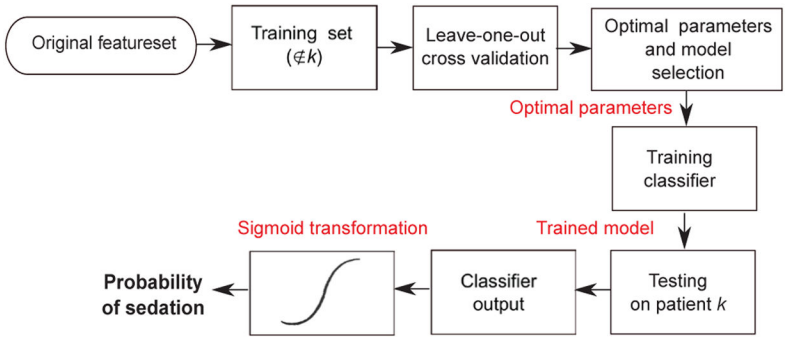

Fig. 2.

Illustration of the LOSOCV procedure for performance assessment of the classification system.

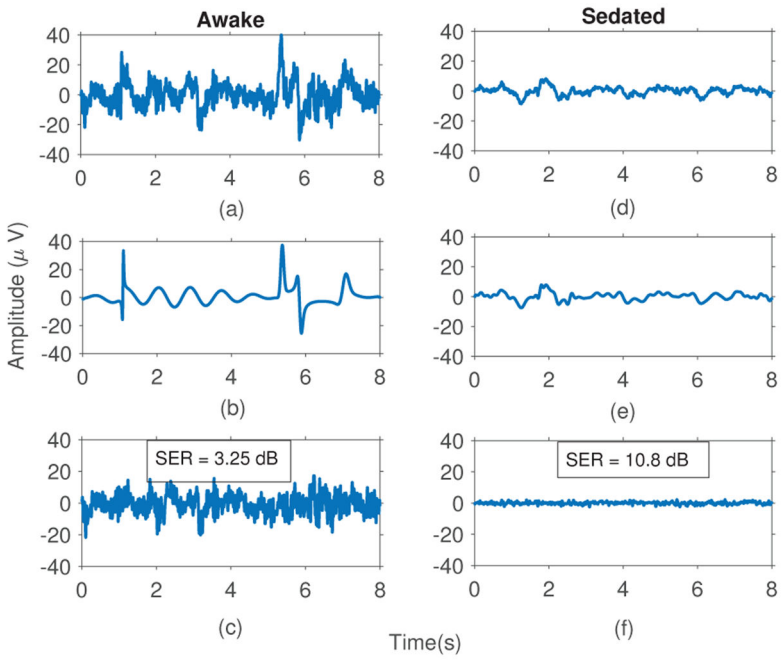

Fig. 3.

A sample example to illustrate atomic decomposition (using 10 atoms) of an 8 s awake and sedated EEG epoch using Gabor dictionary. a is the original, b is the reconstructed and c is the residual of the awake EEG epoch. Similarly, d,e,f corresponds to the actual, reconstructed and residual of the sedated EEG epoch. Note that *SER* for sedated EEG epoch is higher (~ 7.5 dB difference) when compared to awake EEG epoch. This suggests that atoms selected from Gabor dictionary during AD are coherent with sedated EEG epochs.

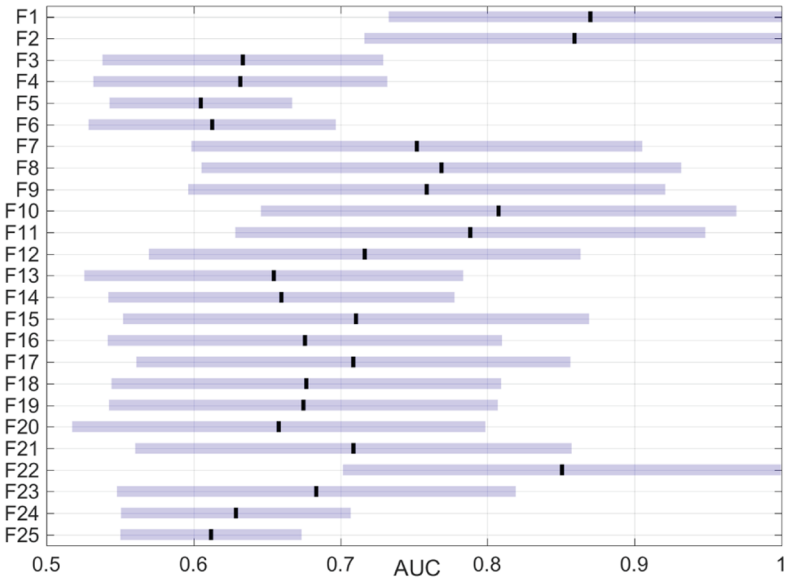

Fig. 4.

The distribution of AUC (mean ± SD) to discriminate between awake and sedated EEG epochs using individual EEG features from different feature groups (F1–F25). Here vertical black line represents the mean value and rectangular box shows the standard deviation.

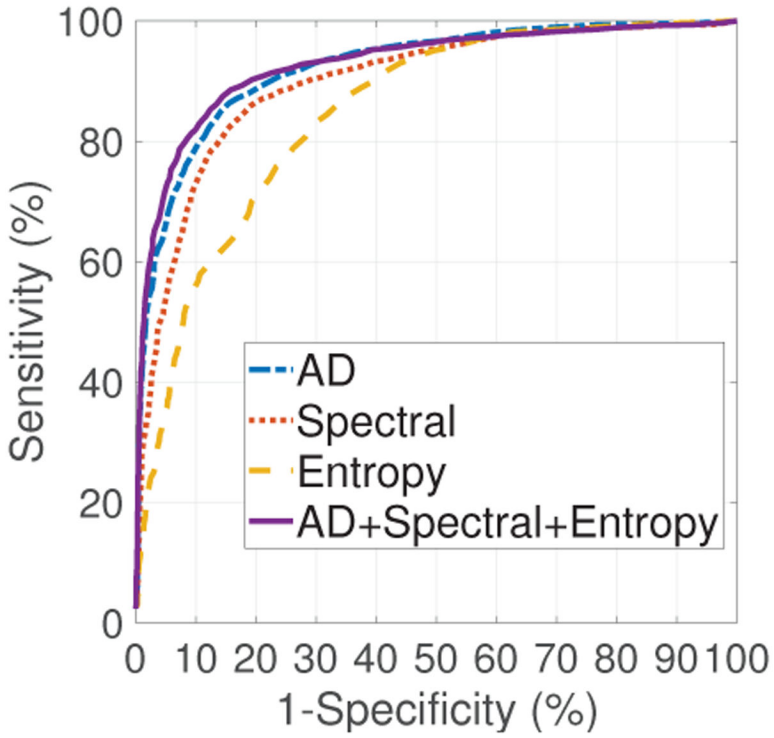

Fig. 5.
ROC curves for different feature set used in this study.

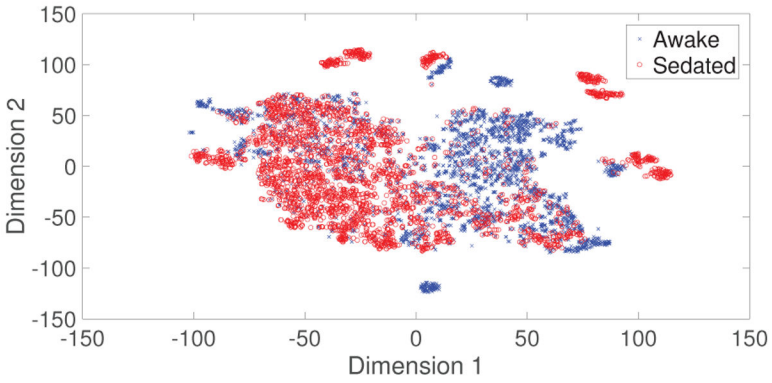

Fig. 6.

Two-dimensional visualization of the high-dimensional feature set (AD+Spectral+Entropy) using t-SNE algorithm [44] corresponding to all epochs from 44 patients. Due to the heterogeneous nature of patients, there are several overlapping clusters between awake and sedated states making it difficult to classify resulting in large variance of the classification performance. The t-SNE projection has 44× 150 = 6600 dots corresponding to all epochs from 44 patients (each patient has 150 dots: 75× 8 seconds epoch in awake state + 75 × 8 seconds epoch in sedated state).

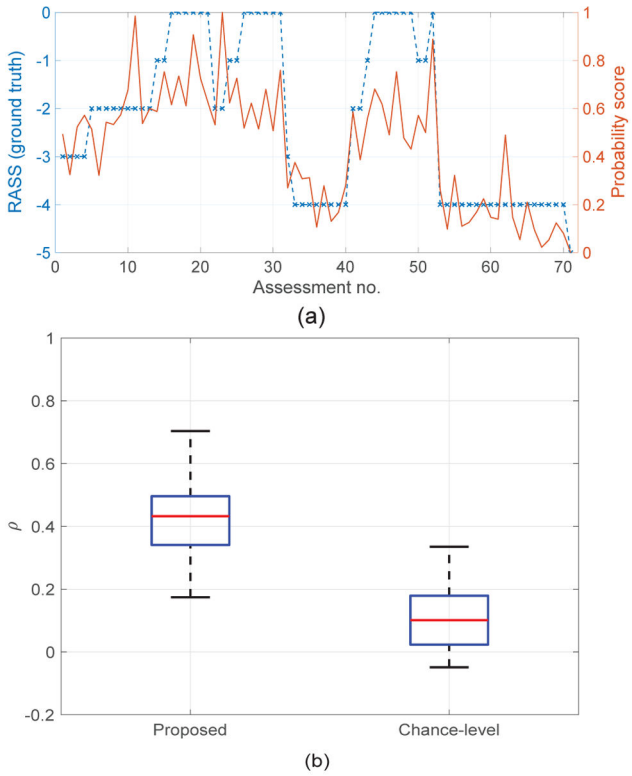

Fig. 7.

(a) Example of the correlation between the probability score of the SVM output with RASS assessments ($\rho = 0.72$ in this example). In this method, a trained binary SVM model (trained only on awake and sedated epochs) is used to obtain continuous probability score on the testing patient, (b) performance estimates of ρ using the actual predicted scores with actual RASS scores compared with chance level scores (by randomly shuffling the RASS scores on each bootstrap iteration)

TABLE I

Summary of patient demographic and clinical characteristics used in this study.

Characteristic	Value
Age (years), median (IQR)	61 (45-68)
Weight (kg), median (IQR)	91 (71-102)
Number of days in ICU, median (IQR)	15 (4-28)
Charlson comorbidity index, median (IQR)	4 (2-8)
APACHE II score at enrollment, median (IQR)	32 (14-38)
Infusion rate of sedative or analgesic agent in ICU - ($mg\ h^{-1}\ kg^{-1}$)	
Propofol	2.31 ± 0.76
Benzodiazepine	0.07±0.05
Dexmedetomidine	0.011± 0.005
Opiods	1.71± 1.03
Medical diagnosis during ICU admission - no.[++]	
Sepsis	11
Acute respiratory failure	29
Cardiogenic shock, myocardial ischemia, or arrhythmia	7
Neurologic disease or seizure	5
Obstructive sleep apnea	18
Other diagnosis	14

IQR = Interquartile range, SD = Standard deviation, APACHE = Acute Physiology and Chronic Health Evaluation II score.

[**] Drug infusion rate within 12-24 hour before the RASS assessments. Values are reported as mean ± SD.

[++] Number of patients with the given medical diagnosis used in this study. A patient can have multiple diagnosis during ICU admission.

TABLE II

COMPARISON OF THE PERFORMANCE OF DIFFERENT FEATURE GROUPS

Feature set (No. of features)	**Mean AUC (IQR)**
AD (6)	0.90 (0.79-0.97)
Spectral (10)	0.86 (0.71-0.91)
Entropy (9)	0.81 (0.69-0.95)
AD+Spectral (16)	0.88 (0.73-0.93)
AD+Entropy (15)	0.84 (0.72-0.94)
AD+Spectral+Entropy (25)	0.91 (0.81-0.98)