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# Computer-Assisted Method for Quantifying Sleep Eye Movements That Reflects Medication Effects

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*Abstract*— **A significant amount of data is not attended to clinically in routine sleep studies. Measures of sleep physiology not obvious to the human eye may provide important clues to disease states, and responses to therapy. For example, it has been noted that eye movements change significantly in patients exposed to antidepressant medications. This paper describes how eye movements were different in depressed patients who used antidepressant medications, compared to those who did not. Groups 1 and 2 included five patients each who used citalopram and venlafaxine respectively compared to five patients not taking any antidepressants. Autoregressive (AR) coefficients of eye movements recorded during sleep have been derived. These coefficients represent the shape of the sleep eye movements of all three groups and were classified using discriminant analysis. In this paper, an improved methodology has been used for this classification. This method includes eye movement detection with improved eye movement detection software and evaluation of AR coefficients with fixed segments. The AIC method has been used for determination of an appropriate model order of 27. AR coefficients are then derived on the basis of this optimized value and are then classified with a linear discriminant function. The overall average of the regular method accuracies were 76.4%, and 78.7% for groups 1 and 2 respectively. The overall average of the leave-one-out method accuracies were 75.5% and 77.5% for Groups 1 and 2. The results demonstrate that eye movements can be quantified and characterized with this approach. This methodology will allow the development of new metrics that may assist in disease classification, and response to treatment in a variety of neuropsychiatric conditions.**

## I. Introduction

HUMANS spend about one-third of their lives in a state of rest that includes a variety of unique physiological states. Each state has a unique physiological "signature" on the basis of electroencephalographic (EEG), electro-oculographic (EOG), and electromyographic (EMG) recordings that are captured in routine sleep studies. Although visual inspection of this information provides information that is important for clinical management of patients, there is a wealth of physiological information that is not apparent to the human eye.

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Patients are assessed in a sleep laboratory for a wide variety of clinical problems, and a great deal of data is collected. Assessment of patients for specific conditions such as sleep apnea is routine medical practice. However, patients rarely have one medical condition or one medication. The polysomnographic information that is collected could potentially be analyzed to find distinct patterns that may suggest other diagnoses, or subtypes of disorders. For example, depression is a syndrome, and is likely caused by more than one specific condition. Therefore, not every patient will respond to the same medication. Patterns that may be present in the unique physiology of each condition that may suggest specific medications may be more effective.

Sleep state changes have been noted in depression and after various medication exposures [1]. Some interesting slow eye movements are noted in stage N2 sleep after exposure to antidepressant medications such as fluoxetine [2], [3]. A way to quantify these changes may help detect patterns of physiology and track response to treatment that is not obvious to casual visual inspection of the sleep studies. We recently used a similar technique to demonstrate eye movements in patients exposed to the medication fluoxetine compared with controls [4].

The past researches in eye movement analysis has looked at electrocardiogram artifact elimination [5], [6], automatic sleep stage classification [7], [8], wavelet analysis of EOG changes [9], and EOG Segmentation using adaptive algorithms [10], [11]. The classification of sleep disorder subjects on the basis of medication exposure by analyzing EOG signals is a novel approach which is introduced in [4]. Our more developed method which is used in this paper has been applied to extract more physiological information about neuropsychiatric conditions.

In order to track the antidepressant medication effect on the shape of the signal an all-pole model has been used. Several reasons have brought all-pole models to the attention of engineers. First, all-pole (autoregressive) signals result of some physical process by which signals have been generated. However, even in those applications for which a zero-pole model is more suitable for the signal, one often finds an all-pole model being used. One reason is that all-pole models represent the signal in a sufficiently accurate manner for many different types of signals in many different types of applications. Another reason is the special structure that is found in the all pole equations leads to fast and efficient algorithms for finding the all-pole parameters [12].

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If white noise, $v(n)$, is filtered with a causal linear shift-invariant filter having a rational system function, the all-pole filter has the form,

$$H(z) = \frac{b(0)}{A_p(z)} = \frac{b(0)}{1+\sum_{k=1}^{p} a_p(k)z^{-k}} \quad (1)$$

which is known as an autoregressive process of order $p$ and will be referred to as an AR($p$) process. In other words, Equation 1 represents that AR($p$) is a wide-sense stationary process which may be generated by filtering unit variance white noise, $v(n)$, with an all-pole filter [12].

The Burg algorithm which has been used in this work to estimate AR coefficients is a popular method. Burg developed this method known as the maximum entropy method for spectral estimation. Unlike most other methods, it is guaranteed to produce a stable model [12]. An all-pole model for the data can be derived from AR coefficients. The algorithm recursively estimates the reflection coefficients of a lattice filter by minimizing the mean of the forward and backward least squares linear prediction errors [13].

The Akaike Information Criterion (AIC) [14] is a common method used for selecting an appropriate AR model order based on the input process. We assume that that the input process has Gaussian statistics: the AIC for an AR process is as follows:

$$AIC = ln(\varepsilon) + \frac{2p}{N} \quad (2)$$

where $\varepsilon$ is the modeling error, $p$ is the AR model order, and $N$ is the number of data samples. The second term in Equation (2) is the penalty for use of extra AR coefficients.

A linear combination of the components of $X$ known as a discriminant function can be written as

$$g(X) = W^t X + w_0 \quad (3)$$

$W$ is a *weight vector* and $w_0$ is the bias [15]. The following decision rule has been used for implementing a two category classifier: If $g(X) > 0$, decide $w_1$ and if $g(X) < 0$, $w_2$. Thus, if the inner product $W^t X$ exceeds the threshold -$w_0$, $X$ is assigned to $w_1$ and to $w_2$ otherwise [15]. $X$ can ordinarily be assigned to either class if $g(X) = 0$ [15].

The classification accuracy was estimated using the regular method and the leave-one-out method. In the leave-one-out method, one sample is excluded from the dataset and the classifier is trained with the remaining samples. Then the excluded signal is used as the test data and the classification accuracy is determined. This is repeated for all samples of the dataset. Since each signal is excluded from the training set in turn, the independence between the test and the training sets is maintained [16].

## II. Methodology

### A. Data Acquisition

We recorded eye movements as three EOG and two reference channels with the routine polysomnographic recording. The sampling rate was 128 samples per second. These AC channels are as follows [4]:

- **LOC**; a signal which is recorded by the electrode placed 1cm below and 1cm left of the left eye of the subject
- **ROC**; a signal which is recorded by the electrode placed 1cm above and 1cm to the right of the right eye of the subject
- **VOC**; a signal which is recorded by an electrode placed 1cm below the middle of the right eye of the subject
- **Mastoid Signals (A1, A2)**; signals recorded by an electrode placed on the over a bony surface and used as reference

To remove artifacts from EOG signals, processing and analysis are performed on signal differences between an EOG signal and references as follows: LOC-A2, ROC-A1, and VOC-A1, which we will refer to as EOG signals in this paper. Sleep staging was provided using routine scoring methods [17]. In this paper, three EOG channels were compared between 5 controls subjects and 5 depressed patients on citalopram as well as five subjects on venlafaxine. The subjects and controls were referred to the same sleep laboratory for routine clinical assessment of a variety of sleep problems. The groups in this study were chosen on the basis of their medication exposures only. Subjects provided written informed consent to analyze their signals under a protocol approved by the local research ethics board.

### B. Data Analysis

Figure 1 is a brief description of our data analysis. The EOG signals were applied to eye movement detection software. This software detects eye movements on basis of anti-phase detection on EOG channels and returns the indices of detected movements. The algorithm used for the detection has been discussed in [4]. The fixed segmentations of detected movements go to the next stage for evaluating AR coefficients. After the AR coefficients of these segments have been derived they are used as feature vectors to a classifier that detects which one belongs to the exposed (abnormal) group that used an antidepressant and which ones belong to the unexposed (normal) group.

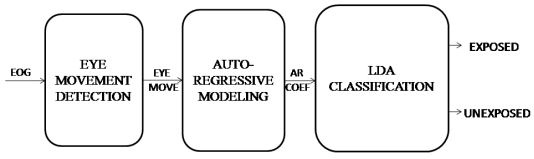


Fig.1. Block Diagram to Classify Patients Exposed and Unexposed to Medication

In order to derive the AR model of stationary signals, the EOGs which are non-stationary, must be segmented into stationary components. This segmentation can be done by using Kalman and Hysterisis filters, the fast RLS algorithm [10], [11] or fixed segmentation. In this paper, fixed segmentation has been used. Although this method is less precise than adaptive segmentation, it brings less complexity to the algorithm and it saves processing time. Usually the EOG signals are recorded for more than 6 or 7 hours. The

duration of eye movements are investigated in the range of 75 to 840 samples with the sampling rate of 128 samples per second. Fixed segmentation with durations of 300, 400, or 500 are preferable. Here, the EOG has been segmented to 300 samples, 150 samples before and 150 samples after detected eye movements. The segment including a marked rightward eye movement has been shown in Figure 2 for LOC and ROC in the Results section.

AR modeling of normalized detected eye movements has been derived by the AIC method. Figure 3 shows how the AIC values change versus the AR model order. The AIC plots have been derived for AR model order in the range of 0 to 100. The minimum AIC was derived for each case. The optimized AR model has the order of 27 which is in the range of minimum AIC values.

Thereafter, the Burg method has been applied to derive AR coefficients of each stationary segment. All AR coefficients of the 5 controls and 5 medication exposed subjects (for each medication) are grouped on the basis of sleep stages and type of movements: left and right. Vertical eye movements were not reliably detected and will require further assessment.

Finally, linear discriminant analysis has been applied to classify AR coefficients into normal and abnormal or in other words, unexposed to medication and exposed. This classification has been performed on two groups. **Group 1** includes five patients who used citalopram. **Group 2** includes five patients who used venlafaxine. The five subjects who are not exposed to antidepressant medications are the same for group 1 and group 2. This paper considers the result of all sleep stages for left and right movement classification. The accuracies of the regular method and the leave-one-out method are shown in the results Tables I-IV. SPSS software (version 16.0, Chicago, IL, USA) has been used to evaluate the "regular method" and "leave-one-out method" accuracies. The classification results consist of the number of correctly predicted unexposed (normal) and exposed (abnormal) states. The ratio of the number of correctly predicted states in each group to the total number of states in that group represents the classification accuracy of each case. The accuracy of these two cases is different and the two groups are identical in this statistical analysis. Since there is no priority of each case over the other, the mean of these two accuracies represents the accuracy of this classification. This accuracy is known as regular method accuracy. In the leave-one-out method, each case is classified using a discriminant function based on all cases except the given case [18]. In addition, classification tables in terms of true positive and false negatives have been considered in the paper [4].

## III. Results

Figure 2 shows 15.625 seconds (2000 samples) of LOC and ROC signal. The detection lines have marked a rightward movement. The difference between the x axis values of marked points determines the duration of this rightward eye movement which is in the range of 300 samples.

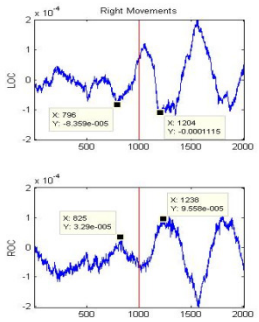


Fig.2. Segment Including an Eye Movement between the Two Marked Data points

Figure 3 represents the AIC values versus AR model order. This figure is the AIC plot which is derived from leftward movement/LOC channel/stage 1 and belongs to one of the group 1 patients. N is half of the segment duration. The AR model order where the AIC value is a minimum suggests an optimized model order. In this paper the model order of 27 has been chosen by comparison between different AIC plots.

The Figures 4, 5, 6, and 7 are the leave-one-out method accuracy results of Group 1 and 2 classifications. Figures 4 and 5 show the accuracy results of the classification which has been done on the AR coefficients of leftward and rightward eye movements for group 1. In these cases, the patients did not experience stage 4 sleep. The literature shows there are more fast movements in stage wake and REM which may be corrupted easier by artifacts.

Figures 6 and 7 show the leave-one-out accuracies for Group 2. The better results for stage 3 and stage 4 could be due to better detection of eye movements in this stage. The overall average of the regular method accuracies were in the range of 72% to 80%. The overall average of the leave-one-out accuracies were in the range of 71% to 80%.

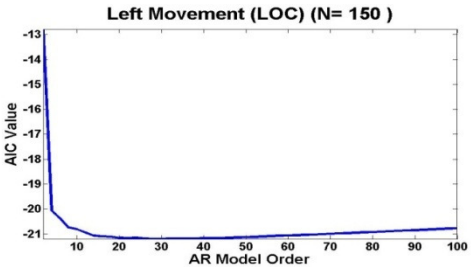


Fig.3. The AIC Value versus AR Model Order

## IV. Conclusion

The results demonstrate that eye movements can be quantified and characterized with this approach. This methodology will allow the development of new metrics that may assist in disease classification, and response to treatment in a variety of neuropsychiatric conditions.

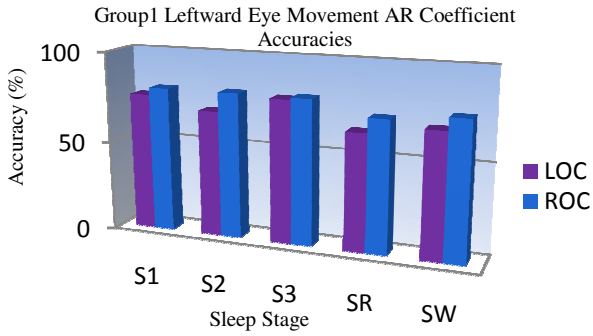


Fig.4. Group 1 Leftward Eye Movement AR Coefficient Accuracies

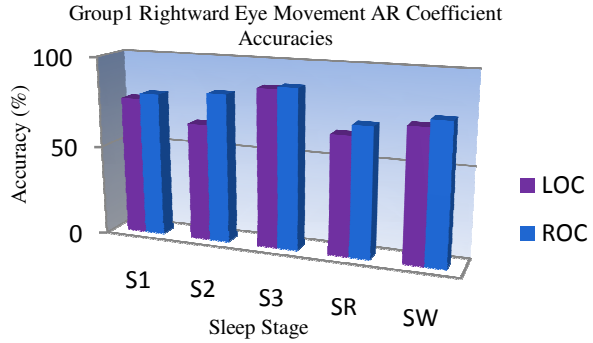


Fig.5.Group1 Rightward Eye Movement AR Coefficient Accuracies

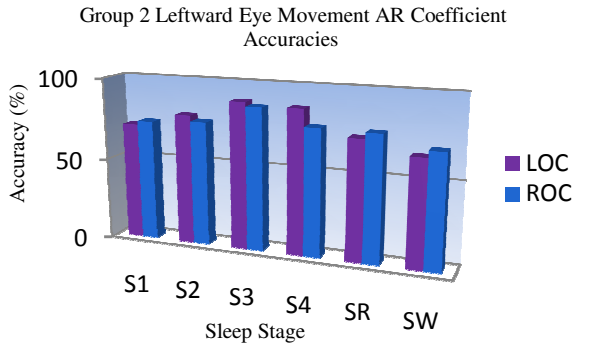


Fig.6. Group 2 Leftward Eye Movement AR Coefficient Accuracies

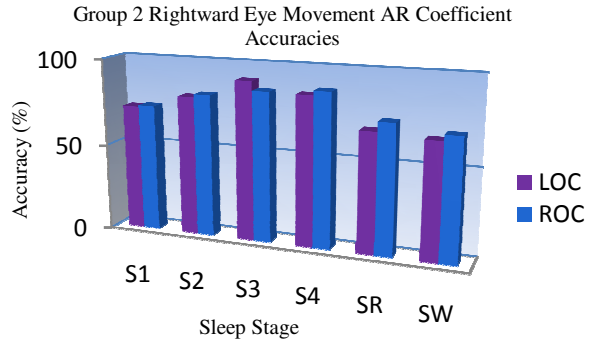


Fig.7. Group 2 Rightward Eye Movement AR Coefficient Accuracies


## ACKNOWLEDGMENT

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