Diagnosing Schizophrenia from Activity Records using Hidden Markov Model Parameters

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***Abstract*—The diagnosis of Schizophrenia is mainly based on qualitative characteristics. With the usage of portable devices which measure activity of humans, the diagnosis of Schizophrenia can be enriched through quantitative features. The goal of this work is to classify between schizophrenic and non-schizophrenic subjects based on their measured activity over a certain amount of time. To do so, the periods in which a subject was resting or active were identified by the application of a Hidden Markov model (HMM). The trained model parameters of the HMM, such as the mean or variance of activity during the state of rest or activity, are used as classification features for a logistic regression model. Our results indicate that the features from the HMM are significant in classifying between schizophrenic and non-schizophrenic subjects. Moreover, the features outperform the features derived through other methods in literature in terms of goodness-of-fit and classification performance.**

***Index Terms*—Hidden Markov models, actigraphy, logistic regression, lasso regression, time series analysis**

I. Introduction

Schizophrenia is a severe mental disorder, negatively affecting the sick subject's quality of life. Globally, schizophrenia is one of the top 10 main triggers for disability [1]. The diagnostic practice of schizophrenia largely depends on subjective tools, like self-reports, clinical assessments and observations [2]. However, sensor data collected from motor activity recordings could be an objective and reliable method with a huge potential to either relieve or support existing subjectively diagnostic methods [3]. Motor activity commonly records with wrist-worn piezoelectric accelerometers, measuring movements in the three-dimensional space. Previous studies have successfully been able to discriminate between depressed patients and controls when applying various machine learning techniques in such data [4]. Studies comparing the motor activity of schizophrenic patients to mood disorder patients and healthy controls utilizing nonlinear mathematical models have identified schizophrenia as a distinctive subtype in motor activity. Characterized by complexity and irregularity in activity patterns [5], [6], as well as having a distinct profile regarding the distribution of active and inactive periods [7]. In addition, a recent systematic review found schizophrenic patients to be associated with reduced mean motor activity, irregular activity patterns and reduced quality of sleep [8].

Sleep disturbance is a common symptom of several psychiatric disorders, and relates to disturbed circadian rhythmicity [9], [10]. The circadian rhythm is an biological pulse driven by a internal clock located in the brain. The clock synchronizes humans to the diurnal cycle of day and night, and cues a complex system of recurring interlocked biological rhythms, like the sleep-wake cycle, shorter rest-activity patterns, regulation of hormone levels, as well as numerous other internal processes [11]. Although the brain clock mainly controls this internal system, external factors like social life patterns, stressful life events and exposure to artificial light both impact and have a potential to disturbs this intricate dynamic system [12]. In schizophrenia, sleep disturbance is a common symptom of a disturbed and unsynchronized circadian system [13]. In motor activity, both diurnal fluctuations of the circadian system and patterns of social rhythms are recognized.

The goal of this paper is to explore the potential of using activity records to diagnose subjects with schizophrenia. Therefore, a dataset with activity records of subjects with schizophrenia and a control group is used to train a machine learning procedure to classify if a subject has schizophrenia or not. The machine learning procedure consists of a *two steps*.

In the first step, the circadian rhythm is modelled by two different states, the resting state and the active state. The state of a subject's activity is not observed, and thus Hidden Markov models (HMMs) are applied as an unsupervised learning method. The HMMs are chosen as it has already been successfully applied to model states of activity on motor activity time series, acceleration data or physiological data [14]–[18]. Different HMMs will be explored in this paper.

In the second step, the trained parameters from the HMMs are used as features in machine learning models to classify between schizophrenic and non-schizophrenic subjects. Thus it is assumed that the difference between schizophrenic and non-schizophrenic subjects is comprised within the model parameters of the HMMs.

The main contribution of this work is the introduction of quantitative features derived from the parameters of HMMs. The HMM parameters were found to be significant in explaining the difference between schizophrenic and non-schizophrenic subject based on their measured activity, namely the variance of the active state and the transition probability of switching between the resting to the active state. The model with the features developed in this paper achieves a comparable performance to the model which includes the features from the literature. Taking into account the diversity of patients within the application area HMM features have the advantage to be able to model processes which consist of different stages that occur in orders (both definite or typical).

II. Related Work

In the following, we will discuss related work from the field of psychology and automatic analysis.

A. Schizophrenia

Schizophrenia is a chronic psychiatric disorder characterized by symptoms like hallucinations, delusions, disorganized speech and behavior, diminished motivation and faded self-expression. Globally the disorder affects approximately one percent of the population, and the personal burden of disease is high for affected individuals. Humans diagnosed with schizophrenia typically experience reduced social function, a disappearing capability of self-care, and reduced ability to educational and occupational function [1]. The diagnostic criteria for schizophrenia are that symptoms are persistent over time, and that either hallucinations, delusions or disorganized speech are present, together with at least one additional symptom, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [2].

B. Automatic Analysis

The analysis of sleep/wake patterns and the quantification of the circadian rhythm has been based on actigraphy. Studies have shown that actigraphy is useful in detecting sleep patterns, sleep disorders or even neurobehavioral disorders [19], [20]. However, the relationship between sleep/wake patterns and mental disorders, especially severe mental disorders such as schizophrenia, based on actigraphy has not been sufficiently studied [10], [21].

A great part of research focused on a combined quantitative and qualitative analysis of the sleep/wake pattern. Due to the additional qualitative analysis, mostly basic quantitative methods are applied. Commonly the total activity, the mean activity or the standard deviation of the daily and nightly activity are measured [22]–[28].

Besides mean and standard deviation, more elaborate methods for quantitative analysis have been used in the literature. In [27], the author fits a cosine function to the activity time series and extracts the parameters. Characteristics of wake/sleep patterns like the intra-day variance (IV) and the inter-day stability (IS), which are introduced by [29] are applied by [30] to differentiate between schizophrenic and non-schizophrenic participants of a study. Witting et al. [29] also introduced the measure of the most active 10 hours (M10) and the least active 5 hours (L5). These measures are applied in [31] analyzing sleep/wake patterns of schizophrenic patients. Sano et al. [32] evaluated the cumulative distribution of the wake and rest periods, which are defined by some threshold. In [5], Hauge et al. applied Fourier analysis to analyze the variance between schizophrenic and non-schizophrenic subjects in low and high-frequency ranges.

HMMs as an unsupervised learning algorithm have already been used in the literature to model the sleep/wake pattern based on activity time series [33], [34]. Albert et al. [35] applied an HMM for toddler activity classification, and besides sleep/wake patterns, they distinguished different movement patterns like crawling, walking, being carried, etc. based on the toddlers' recorded activity. Liu et al. [36] applied a HMM on activity time series in combination with the heart rate measured by commercial devices.

Huang et al. [18] introduced a HMM to improve the classification between wake and sleep by incorporating the cosine structure of the circadian rhythm. They identified three states of activity, resting, active, and highly active, to study the effect of multi-drug chemotherapy on patients at home. Carr et al. [14] based their analysis on the same ground as [18], and used the classification of the wake/sleep pattern to predict the depression score of patients with bipolar disorder.

Both Huang et al. and Carr et al. use the Hidden Markov to decode at what time a subject is in a certain state. Based on the decoded signal, Huang et al. and Carr et al. extract classification features. In the presented approach, the classification features are directly derived from the model parameters of the HMM.

III. Data Description

The data set is publicly available and contains actigraphy data collected from 54 persons, 22 diagnosed with schizophrenia and 32 in a control group [37]. The activity is measured by an actigraphy device called Actiwatch model AW4 provided by Cambridge Neurotechnology Ltd, England. The device records the intensity of its acceleration along the x, y and z axes. The activity was recorded at a frequency of 32 Hz. A total activity count is derived for one minute intervals [37]. The recording duration varied from subject to subject and ranged from 9 to 20 days. In addition to the sensor data, demographic data and medical assessments during the observation period are available.

IV. Explorative Data Analysis

The time series shown in Figure 1, reveal the circadian rhythm of a subject. The periods in which a subject is active appears in blocks. The periods between the blocks are seen as resting periods. As expected, the resting periods have a lower mean and lower variance and is shorter in time than the active periods. These observations match with known human behavior since resting periods are in general shorter than active ones.

It is known that a subject's rest and active pattern is affected by the day and night rhythm. This is related to social norms and the daylight patterns [38]. Thus, the time series observed are likely to follow some sort of 24h seasonality. This observation underlines the assumption that periods of resting are generated by another distribution than periods of being active.

The difference between resting and active states is further analyzed by studying the mean and standard deviation of the daily and nightly activity. The activity measured during 9 am and 9 pm is considered as daily activity, whereas the activity

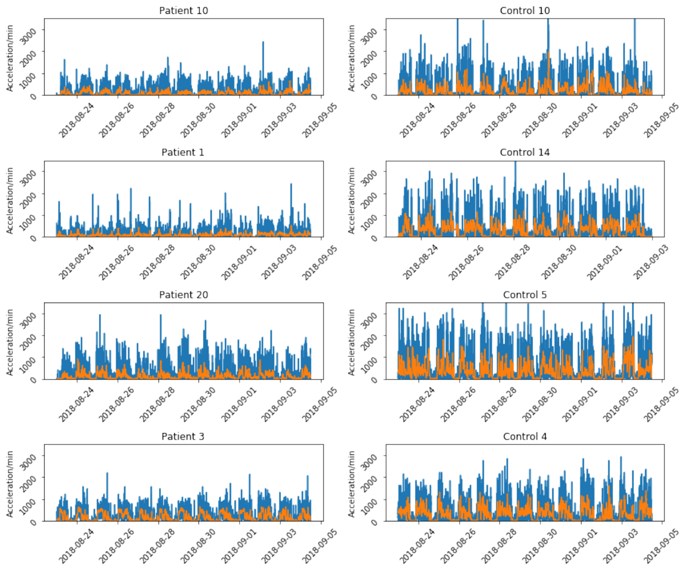

Fig. 1. Sample time series where the left and right column shows patients and control, respectively. The blue and orange curves shows the original times series and 30 seconds moving average, respectively.

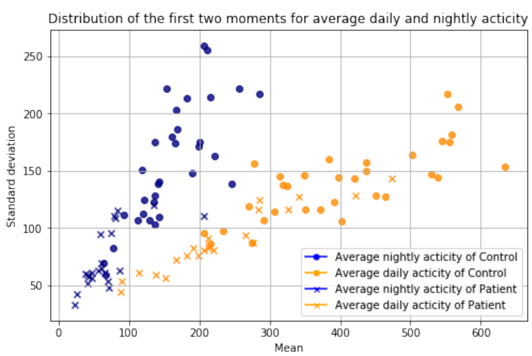

Fig. 2. Comparing day and night activity distributions of example individuals from the control and patient group.

measured between 9 pm and 9 am is considered as nightly activity.

Figure 2 shows two dimensional plots of mean values and and standard deviations. We observe that daily and nightly activity is linearly separable. Furthermore, the figure shows that the mean and standard deviation of activity for schizophrenic patients during night and day tends to be lower than for the control group. Therefore, we will model the nightly and daily activity of schizophrenic and control subjects with different statistical distributions.

V. Methodology

The overall objective of the developed methodology is to use the activity measurements to classify if a subject is schizophrenic or non-schizophrenic. First, HMMs are used to model activity patterns of schizophrenic patients and control using HMMs, and is described in Sections V-A and V-B. Secondly, the model parameters of the HMMs are used as features in logistic regression classification methods, and is described in Section V-C. The introduced features are evaluated by comparing with features from the literature in therms of classification performance. Hidden Markov models can model hidden variables of an observed time series. In this work, the observed time series is the recorded activity and the hidden variables are a subjects state of being active or resting. To model the hidden variables, various model parameters are estimated, which will be used as features for classification. Section V-A reviews on the idea and theory behind Hidden Markov models and section V-B presents how their application is used in this work. Logistic regression is considered as a method, which provides interpretability. Moreover, $l1$ regularization can be applied to select features. Hence, section V-C introduces the logistic regression with least absolute shrinkage and selection operator (LASSO) for feature selection [39].

A. Hidden Markov Models

A HMM is an extension of the Markov Chain which describes a random process which fulfills the Markov property. The Markov property states that the future is independent of the past, given the present [40]. Let $\{X\}_n$ be a time-discrete stochastic process of random numbers taking values of a finite set S.

The set of time steps is denoted with $t \in T$. The finite set S will be referred to as the state space and the elements in S are referred to as states i, j, [41]. If the process is in state i at time t, it is noted as $X_t = i$. The conditional probability of being in state j at time $n+1$, given the information on all previous states, is equal to the conditional probability of being in state j at time $n+1$, X_{n+1} given only the previous state $X_n = i$. The probabilistic dependence on the past states is only connected to the future through the present state, [41]. The Markov property is satisfied if for all indices in T and all states of $i, i_{n-1}, ..., i_0, j, j_{n-1}, ..., j_0$ in S the equation (1) counts.

$$\begin{aligned} &P(X_{n+1} = j | X_n = i) = \\ &P(X_{n+1} = j | X_n = i, X_{n-1} = i_{n-1}, ..., X_0 = i_0) \end{aligned} \tag{1}$$

The HMM extends the Markov process by differentiating between the observed stochastic process and a latent stochastic process. The latent or hidden stochastic process fulfills the Markov property [40] and can only be deduced from the observable process. For each observable random variable Z_n a latent variable X_n is introduced. From the joint probability the elements of an HMM can be derived.

$$\begin{aligned} &P(X_1, ..., X_n, Z_1, ..., Z_N) = \\ &P(Z_1) \prod_{n=2}^{N} P(Z_n | z_{n-1}) \prod_{n=1}^{N} P(X_n | Z_n) \end{aligned} \tag{2}$$

The initial state has a special status, since it does not have a previous state. The initial state probability is given by $\pi = \{\pi_i\}$ The conditional probability $P(\mathbf{X}|\mathbf{Z})$ is called emission probability. The emission probability is a probability distribution for each time step on X given the state Z, $b_i(n) =$

$P(\mathbf{X}|Z_n = i)$ where the emission probabilities represent the probability that the observation at time t was generated by state i. In the case of a Gaussian HMM, the emission probability are Gaussian distributed. Therefore, the emission probability can be described by the first two moments of the Gaussian distribution, mean and variance. These two parameters are used as classification features and interpreted as the mean and variance activity during a certain activity state, active or resting. The factors $P(Z_n|Z_{n-1})$ represent a Markov chain and are the probabilities to transmit from one state into another in consecutive time steps. The transmission probabilities can be expressed in a matrix $A = \{a_{ij}\}$. Depending on the number of states k, the transition matrix becomes the size $A \in \mathcal{R}^{k\times k}$. The equation is given by,

$$a_{ij} = P(Z_n = i|Z_{n-1} = j) \tag{3}$$

The transition probabilities express the likelihood of switching from state j to state i, for a next time step. The transition probabilities are considered as the other model parameter which is used as classification feature.

B. Identifying active and rest periods

The classification of schizophrenic and non-schizophrenic subjects is assumed to be improved by using the parameters of an appropriate model. In this work, the idea is derived that the circadian rhythm can be described by two states - the rest and the active state. The number of hidden states is already determined by the assumptions of only two states of activity. The observed activity data is a continuous-time series where each observation is the average of 32 samples, and therefore, due to the central limit theorem, are fairly normally distributed for rest and active states. Therefore, a Gaussian Mixture Hidden Markov is applied.

C. Classification

The classification of schizophrenic and non-schizophrenic subjects is based on extracted features of their activity time series. The model parameters of the HMM are used as classification features. To evaluate the proposed features, the features are assessed based on their classification performance compared to a baseline classification. The classification is performed by logistic regression with least absolute shrinkage and selection operator (LASSO) for feature selection [39].

1) Baseline Classification: The most commonly used features for the classification of schizophrenia based on activity time series are reviewed and used as baseline classification. The baseline classification is performed by logistic regression which only considers the classification features from the literature [10], [42], [43]. The features derived from the literature are summarised in Table I. The inter-daily stability (IS) and the intra-day variability are introduced by [29]. The IS gives an insight into the day-to-day variation, and IV captures circadian disturbances and a potential split-up of the circadian rhythm. The root mean square successive difference statistic is introduced by [44] and calculated as the standard deviation of the differentiated time series.

Features for Baseline Classification	Literature Source
Mean activity & Standard Deviation	[4], [14], [18], [29], [30], [32], [37], [45]–[47]
Inter-daily Stability (IS) & Intra-daily Variability (IV)	[18], [29], [48], [49]
Root mean square successive differences (RMSSD)	[5], [46]
Autocorrelation coefficient	[46]

TABLE I
OVERVIEW OF QUANTITATIVE FEATURES OF ACTIGRAPHY TIME SERIES IN DERIVED FROM THE LITERATURE.

2) Classification Procedure: To classify between schizophrenia and control, we use the trained parameters from the HMM as features in a logistic regression model.

Before the logistic regression model is applied, the correlation matrix of the used features is analyzed. To avoid multicollinearity and allow a feasible parameter estimation the transition probabilities of staying in a state, active or resting, are removed. High correlation between the transition probabilities occur due to the normalization of the rows of the transition probability matrix. The probability to stay in the resting state and the probability of transit from the resting state to the active state sum up to one. Besides of that, LASSO copes with correlated feature sets by penalizing its coefficients.

First, the LASSO logistic regression model is conducted to perform feature selection. The regularisation parameter C characterizes the sparsity of the model, and is estimated by finding the best performing model according to the area under the receiver operating characteristic (AUC) and average precision.

For the final comparison of the different regression model the Matthew correlation coefficient (MCC) is applied. The MCC is a reliable performance measure as it takes all the four cases from the confusion matrix into consideration.

Figure 3 presents the course of the AUC and average precision for different values of C. The performance of the regression model including the HMM parameters is presented.

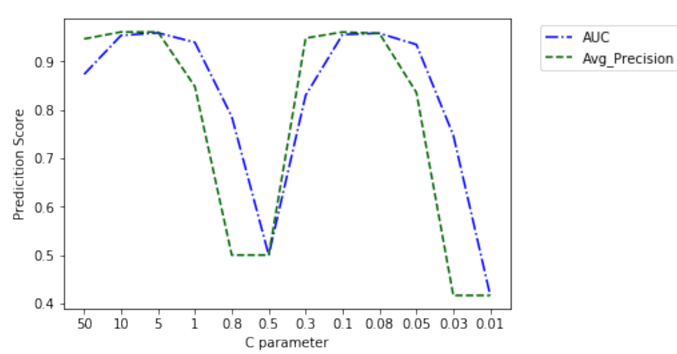

Fig. 3. The AUC and the average precision obtained by the lasso regression for different penalty parameters C.

Classification performance is evaluated based on leave-one-participant-out cross-validation. The average precision of the leave-one-participant-out cross-validation, AUC is used as performance metrics. The significance of the single coefficients is evaluated through their t-test p-values. The model fit is evaluated through the pseudo R^2 [50]. The pseudo R^2 is the quotient of the maximum likelihood estimator and the LL-Null model.

VI. Experimental Results

The classification results of the baseline classifier and the classification model containing the introduced model parameters as classification features are compared. The goal is to evaluate the model parameters from the HMM as classification features compared to already established features from the literature. Thus, the classification procedure is performed for the baseline classifier and the derived parameters from the HMM, which are listed below.

- The mean value of the two states
- The variance of the two states
- The transition probabilities

Features	MCC	Average Precision	AUC
Literature Features			
Mean IS IV	0.82	0.95	0.93
Mean IS RMSSD	0.78	0.93	0.93
RMSSD IS IV	0.74	0.94	0.93
HMM parameters			
Variance active Trans01 Trans10	0.82	0.93	0.95
Mean resting Variance active Trans10	0.78	0.94	0.94
Mean resting Variance active Trans01	0.78	0.95	0.96

TABLE II
CLASSIFICATION PERFORMANCE FOR DIFFERENT SETS OF HMM MODEL PARAMETER FEATURE.

Table II summarises the best performing sets of features. For each final model three feature parameters are selected. The feature selection procedure includes the overall mean, the root mean square successive differences and the intra-day variability as well as the inter-daily stability as literature features. Regarding the Hidden Markov model parameters, the mean activity for the resting and active state, the variance of the active state and the transition probabilities to switch between the resting and active state are selected. The transition probabilities are noted as $Trans01$ and $Trans10$. The best model for both feature sets, HMM model parameters and literature feature, scores a MCC of 0.82. The model including the HMM parameters achieves a better AUC, whereas the model with the literature features achieves a better average precision. The performance of the features sets is comparable and underlines the value of the new introduced features based on the HMM model parameters.

VII. Conclusion

In this work, new features for the classification of schizophrenia were introduced and evaluated. The model parameters of a fitted HMM were assumed to provide valuable information for the classification. The presented model was able to find a fairly accurate classification between schizophrenic patients and the control group.

The potential of the newly introduced features has only been analyzed by one classification method, namely LASSO logistic regression. LASSO regression is known for that correlated variables are mutually exclusive by regulation. Some included variables are correlated with each other. The presented approach allowed the regularization of potentially excluded valuable feature variables, before evaluating them.

Thus, for an overall conclusion on the significance and the predictive value of the HMM parameters, each variable has to be analyzed independently. Moreover, more than only one classification method should be applied. Both mentioned improvements, independent variable analysis and testing different classification methods, are interesting directions to explore for future work.

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