Analysis of actigraph parameters for relapse prediction in bipolar disorder: a feasibility study

D. Novák, F. Albert, F. Španiel

Abstract— **The paper presents a framework for early identification of prodromal syndromes od mania or depression in bipolar disorder. The framework may mitigate relapses and improve patient functioning. The methodology consists of long-term actigraphy monitoring and simplified self-assessment tool to determine manic or depression events. Eight patients were involved in the feasibility study, spanning period of 150 months, resulting in 17 relapses and 3 hospitalizations in total. We concluded that the most promising parameter extracted from actigraphy recording is a circadian rhythm's interdaily stability. Using developed trend analysis applied on interdaily stability parameter, we achieved sensitivity and specificity about 65, resp. 68. We hypothesized that this performance is both mainly due to missing values in data and due to small amount of relapses.**

I. INTRODUCTION

Bipolar disorder is an episodic and recurrent condition that is frequently disabling daily life. Bipolar Disorder is associated with an increased suicide risk [1]. Annual insurance payments were greater for medical services for persons with bipolar disorder than for patients with other behavioral healthcare diagnoses. Primary goals of the treatment of bipolar disorder are to stabilize the patient and prevent the recurrence of episodes [2]. The early identification of prodromal symptoms of mania or depression may allow rapid interventions that mitigate relapses and improve life quality of patient. Dysregulation of the sleep wake cycle and other circadian rhythms may underlie the pathophysiology of bipolar disorder [3]. One possible way how to quantify circadian rhythms and sleep patterns is use of actigraph technology. The advantage of actigraphy over traditional polysomnography is that actigraphy can conveniently record continuously for 24-hours a day for days, weeks or even longer. This paper is focused on feasibility study of analysing relapse events (bipolar, mania) using long-term actigraphy monitoring and a self-assessment of patient's mood.

II. METHODOLOGY

A. Experimental Set-up

Two types of data were monitored: objective data represented by movement activity recordings by use of actigraphy and subjective data acquired by questionnaire. Movement activity was recorded using Actiwatch device (Camntech, Cambridge, UK). Actiwatches were configured to record movements in 2-minute epochs. Patients worn the device on the non-dominant wrist, the most common site for activity-based measurement. Actiwatch data were downloaded quartly using the ActiReader. Regular self-assessment of patient's mood was performed by a questionnaire. Questions are depicted in Table I. The values of each answer varied between 0 to 9. A score of 0 represents very faint feeling to the concrete question. A score of 9 represents very strong feeling to the concrete question. Technically, the questionnaire was sent by SMS message once a week. Additionally, during quarterly ambulatory visit, patient was asked to fill Young Mania Rating Scale (YMRS) and Hamilton Rating Scale for Depression (HRSD) [2] to clinically determine a possible relapse. Missing data exclusion criteria were based on Someren [4] who recommended that periods over 60 minutes without movement, even during sleep, are extremely unlikely to occur naturally.

TABLE I
SELF-ASSESMENT QUESTIONNAIRE

ID	Question
1	I feel like I am able to do anything
2	I really feel well inside
3	It seems to me that I will not succeed at anything
4	I am depressed
5	I feel full of energy
6	I feel speed up
7	I have racing thoughts
8	I am overly active
9	I am restless
10	I am impulsive
11	My moods change a lot
12	I feel like people are out to get me
13	I feel like the world is against me
14	I feel iritated
15	I feel argumentative
16	I get distracted easily
17	I cannot concentrate well
18	I sleep well

B. Data Set-up

Inclusion criteria for the study were a primary diagnosis of BD-I with no significant comorbidity, not working shiftwork, absence of a physical disability that may interfere with recording of ambulatory wrist movement, and a currently stable clinical state. In total, eight patients were monitored within 2006-2013 period. Two patients (n.2 and n.3) were withdrawn from the study due to systematic no-cooperation. All patients except of patient n.2 were medicated (alternatives of lithium). The basic characteristics are summarized in Table II. Data from questionnaire for patient n.7 and 8 were not available (NA). The legend is the following: Dur-

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involvement of a patient in the study in months, #SMS-number of questionnaires filled (sent by SMS), number of events (mania or/and depression), #Vis-number of ambulatory visits, #Hos-number of hospitalizations, Mis-percentage of missing actigraphy data.

TABLE II
BASIC STUDY STATISTICS

ID	Sex	Age	Dur	#SMS	#Event	#Vis	#Hos	Mis
1	F	41	80	340	14	19	2	26
4	M	34	6	16	0	7	0	10
5	M	42	5	12	0	5	0	0
6	F	37	14	23	3	6	1	4
7	F	31	7	4	NA	NA	NA	53
8	F	27	37	NA	NA	NA	NA	14

C. Sleep period detection

Sleep disturbance is recognized as an essential aspect of affective illness. Therefore, it is important to detect sleeps' periods and to extract parameters from the sleep period in actigraph recording. First, the actigraph signal was smoothed by median filter $N = 20$. Secondly, three windows of different length were defined ($l_1 = 10, l_2 = 120, l_3 = 30$ samples). In the next step, an algorithm was searching $l_1 - 1$ non-zero samples from the left of ith-sample and l_1 zero samples to the right. All such as samples were stored into array P. Consequently, in the array P the algorithm was detecting such as index where l_2 samples (to the right) contain 75% zero values. This sample determines the beginning of the sleep. The detection of the end of sleep is similar. The end of sleep is determined by the first value between sleep-beginning tags, where l_3 samples are non zero.

D. Feature calculation

Standard parameters based on published algorithms for measures on actigraphy data were calculated. The extracted parameters can be divided into three parts: Night-Sleep analysis and Day-Awake analysis [5] and Circadian Rhythm Analysis [4]. Regarding Sleep analysis, the following parameters were extracted:

Assumed Sleep T_S,

$$T_S = t_{s1} - t_{s2} \tag{1}$$

where t_{s1} is wake time and t_{s2} time of fall asleep.

Actual awake time T_A,

$$f\left(x\right)\begin{cases}0: & \sum_{y-t_{s1}}^{t_{s2}} a(x+y)\cdot w_A y \leq w_A \\ 1: & \sum_{y-t_{s1}}^{t_{s2}} a(x+y)\cdot w_A y > w_A\end{cases} \tag{2}$$

$$T_A = \sum_{t=t_{S1}}^{t_{S2}} f_A(a(t)), p_A = \frac{T_A}{T_S}\cdot 100 \tag{3}$$

where a represents actigraphy data, T_A is number of samples that represent physical activity, p_A is share of activity time in percentage, w_A is awake distribution.

Actual sleep time T_{AS}:

$$T_{AS} = T_S - T_A, p_{AS} = \frac{T_{AS}}{T_S}\cdot 100 \tag{4}$$

where T_{AS} is time of sleep without physical activity, p_{AS} is percentage share

Number of sleep bouts n_S:

$$f_{nS}\left(x\right)\begin{cases}0: & w_S(a(x-1)) = 0 \vee w_S(a(x)) = 1 \\ 1: & w_S(a(x-1)) = 1 \wedge w_S(a(x)) = 0\end{cases} \tag{5}$$

$$n_S = \sum_{t=t_{S1}}^{t_{S2}} f_{nS}(data(t)) \tag{6}$$

where n_s is number of segments with activity lower than a threshold and w_s is sleep distribution, Definition of number of wake bouts n_A is similar.

Sleep efficiency p_{ef}:

$$p_{ef} = \frac{T_S - T_A}{T_S} \tag{7}$$

Additionally the rest of sleep parameters were similarly calculated accordingly to (1) - (5), namely: Number of minutes immobile T_I, number of segments without activity n_I, number of segments that last one minute or less n_{I1}, fragmentation index I_f, total activity score S_A and minutes marked as active T_M.

Considering Day-Awake analysis, we detected periods of day-inactivity $NAPs$ bounded by two constants: $NAP_{min} = 10min$ and $NAP_{max} = 90min$. Furthermore, number of NAP per each day $NAP_{eachday}$ and total length of NAPs NAP_{total} were extracted. Next, total daytime activity was operationalised using the M10 variable which is defined in the next paragraph.

Another group of parameters is derived from Circadian Rhythm Analysis established by Someren [4]: IS (Interdaily Stability), IV (Intra-Daily Variability), L5 (provides the average activity level for the sequence of the least five active hours) and M10 (indication of the phase of the most ten active hours).

E. Trend analysis

We suggest to find specific trends in extracted features before an event of depression or mania. Our idea is similar to shapelets which were defined by Keogh [6]. Informally, shapelets are time series subsequences which are in some sense maximally representative of a class. From point of temporal data mining, the class is here represented by depression or mania. However, due to low data resolution when each day is represented by one value of a feature, shapelets could not be applied. Therefore, an alternative concept based on extensive search approach and using simpler shapes is proposed. We call the basic shapes primitives. We assume that mania or depression event is marked by a presence of a primitive some time before the event.

The explanation of the alternative concept to Keogh optimization is straightforward. Firstly, the data sets must fulfill the following criteria: An event (mania od depression) gray

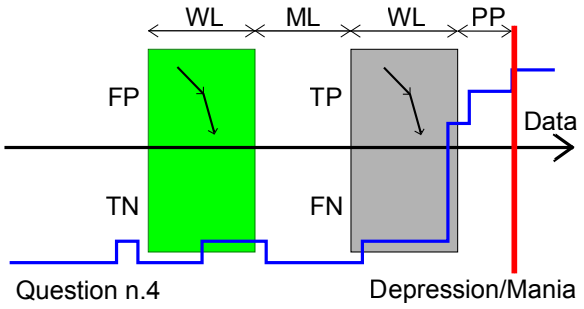

Fig. 1. Example of primitive [-1,-1] detected in data before event of a relapse (mania or depression). Legend: WL:window length, ML:minimum length, PP:prediction window, FP:false positive, FN:false negative, TP:true positive, TN:true negative

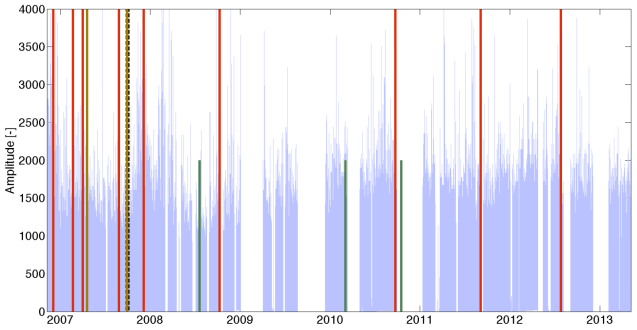

Fig. 2. Example of actigraphy data of patient n.1. Red line marks depression events, green line detects subjective depression events, orange markers indicate two hospitalizations and dashed black line visualizes start of the lithium treatment.

box in Fig. 1 has length of WL days, must precede the event by PP days and must be separated by ML days from a normal green box. The normal green box in Fig. 1 is of WL day long, is separated from the event green box by ML days and responses to question no.4 "I am depressed" must be below threshold 2. Parameter PP determines the minimum length in days before occurring relapse. To summarize, the green box determines periods when mood is stabilized while the gray box marks off depressive or mania events. Secondly, several basic primitives consisting of combination three $[p_1, p_2, p_3]$ or two $[p_1, p_2]$ samples (days) were established. For example, primitive [-1,1,0] represent decrease, increase and change of trend in a respective parameter. Finally, using extensive-search, the algorithm is searching such a primitive among set of $P = \{[p_1, p_2, p_3], [p_1, p_2]\}$ assuring that a corresponding ROC curve has the largest area under this curve. The ROC curve is defined by trade-off between sensitivity (Se) and specificity (Sp) values parametrized by WL value. To calculate Se and Sp, we defined false positive as appearance of a primitive (or primitives) in the whole Normal window, true negative as no-show of the primitive. Similarly, true positive is indicated by the primitive presence in the Event window, false negative as primitive missing in the Event window - see example in Fig. 5, where several primitives of [-1,-1] in the IS time series were detected.

III. Results and Discussion

Complete actigraphy record of patient n.1 over span of 6 years is depicted in Fig. 2. Events of depressions are visualized by vertical red lines, hospitalization are determined by orange lines. There are many missing values in the record, some of them are of considerable length. For example, note major drop-outs of more than 2 months between 2009-2011 period. Additionally, the patient was allowed not to wear the actigraph during vacations explaining regular drop-outs during summer periods.

The sleep detection algorithm detects precisely beginning and end of sleep periods as is shown in Fig. 3. Apparently, the user forgot to take an actigraph device after evening hygiene, no activity was detected from the night 28th till the morning 29th when the user started wearing the actigraph again.

The next phase was focused on data processing from sms questionnaire. The question 1 and 4 from Table I are shown along with depression (clinically confirmed during ambulatory visits and subjectively defined as events marked by question n.4 ¿5) and hospitalization events for patient n.1 in Fig. 4. It is important to determine the minimum number of questions which may reflect relapse onset. Therefore, we performed correlation analysis using gathered questionnaires across all patients with the aim of determining minimum set of independent questions.The following set of questions $Q = \{4, 6, 7, 8, 15\}$ was determined on 0.05 significance level. Several depression events visually correlate with value of question n.4 as can be seen in Fig. 4. Question n.1 is antagonistic to question n.4 confirming the consistency of responses in case of patient n.1. Similarly, correlation analysis was performed on a set of actigraphy parameters resulting in the following set of features $F = \{n_i, T_{AS}, T_M, IV, IS, M10, L5, NAP\}$.

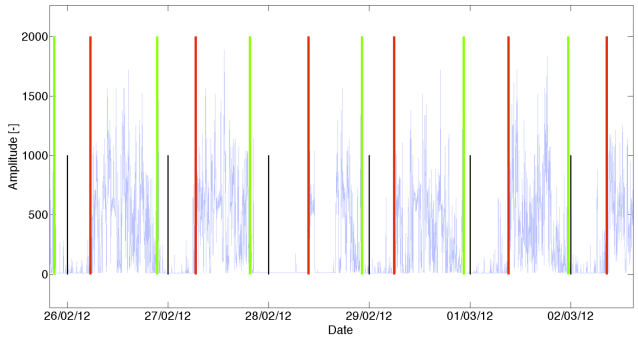

Fig. 3. Example of sleep detection in case of patient n.1. Red line marks start of sleep, green line detects send of sleep ,black marker indicates midnight.

Having independent features, we performed trend analysis using three and two points based primitives. Extensive search resulted in finding primitive [-1,-1] - see Fig. 5. This primitive applied on IS signal delivered the best performance in terms of maximization area under ROC. IS-Interdaily Stability quantifies the degree of regularity in the activity-rest pattern with a range of 0 to 1 where a value of 0 indicates a total lack of rhythm and a value of 1 indicates

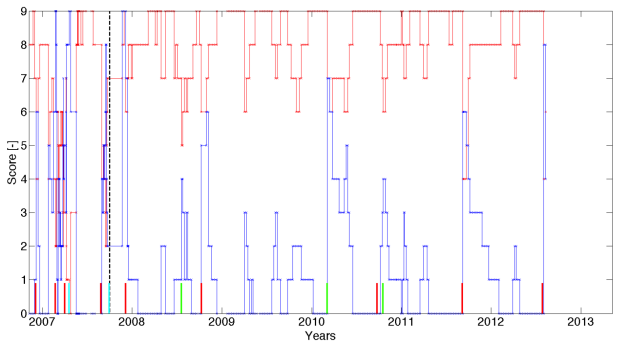

Fig. 4. Visualization of two antagonistic questions 1 (red) and 4 (blue) for patient n.1. Red line marks depression events, green line detects subjective depression events, orange markers indicate two hospitalizations and dashed black line visualizes start of the lithium treatment.

a perfectly stable rhythm. As can be observed, patient no.1 alternates along 0.5 value. An example of primitive detection is depicted in Fig. 5. Note the presence of two FP detection in green windows marked by asterisk and one FN detection marked by cross symbol.

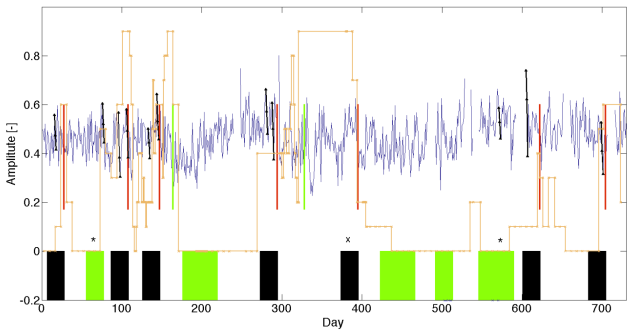

Fig. 5. Example of primitive detection [-1,-1] for patient no.1. Trend analysis parameters were set up to WL=22 and PP=0. Blue line is IS time series. Red line marks depression events, green line represent subjective depression events, black line with arrows visualize primitive [-1,-1]. Orange line is equal to question n.4 "I feel depressive".

Finally, comparison of two primitives [-1,-1] and [-1,0,1] applied on the IS parameter is depicted in Fig.6. The best trade off between Se and Sp values is about $Se = 65\%$, $Sp = 68\%$. The framework presented here determined the methodology for a bigger clinical trial. During this feasibility study we had to cope with low cooperability of patients resulting in total loss of 30% actigraphy data - see Table II. Furthermore, some patients did not send regularly subjective questions. Only three patients persisted in the study for a period longer than 12 months. Additionally, 17 depressions events were diagnosed while no mania event was presented in our data set. We postulate that online approach for actigraphy monitoring and implementation of alert system in case of missing data (actigraph records or questionnaire) is absolutely necessary for succesfull completion of long-term monitoring in such as ambitious project focusing on patients suffering from severe psychiatric disorder.

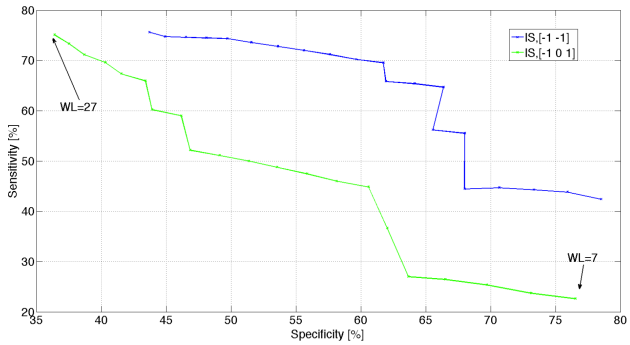

Fig. 6. ROC curve for all patient. ROC is paramatrized by WL parameter, $WL = 7, \ldots, 27$. Two primitives are depicted: [-1,-1]:blue line and [-1.0,1]:green line.

IV. CONCLUSIONS AND FUTURE WORKS

We presented the basic framework for early identification of syndromes of mania or depression. The framework may mitigate relapses and improve patient quality of life. The methodology consisted of long-term actigraphy monitoring and simplified self-assessment tool to determine manic or depression symptoms. We concluded that the most promising parameter exctracted from actigraph data is Interdaily Stability. Using proposed trend analysis and the IS parameter, we achieved sensitivity and specificity about 65%, resp. 68%. To increase performance, online monitoring of movement activity is essential. However, current actigraphic technology does not permit real-time monitoring of activity. This significantly limits its use for this purpose. Therefore, we designed own system which enables to monitor actigraphy in real time without recharging the battery for a period of one year (not covered in this paper) with similar technical parameters to existing offline commercial systems. We plan to use this solution in an ambitious clinical study involving more than 70 patients monitored for 12 months.

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REFERENCES

[1] R. J. Baldessarini, M. Pompili, and L. Tondo, "Suicide in bipolar disorder: Risks and management," *CNS Spectr*, vol. 11, no. 6, pp. 465–471, Jun 2006.

[2] A. P. Association, "Practice guideline for the treatment of patients with bipolar disorder (revision)," *Am J Psychiatry*, vol. 159, no. 4 Suppl, pp. 1–50, Apr 2002.

[3] M. Bauer, P. Grof, N. Rasgon, T. Bschor, T. Glenn, and P. C. Whybrow, "Temporal relation between sleep and mood in patients with bipolar disorder," *Bipolar Disord*, vol. 8, no. 2, pp. 160–167, Apr 2006.

[4] E. J. Van Someren, D. F. Swaab, C. C. Colenda, W. Cohen, W. V. McCall, and P. B. Rosenquist, "Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods," *Chronobiol. Int.*, vol. 16, no. 4, pp. 505–518, Jul 1999.

[5] S. Ancoli-Israel, R. Cole, C. Alessi, M. Chambers, W. Moorcroft, and C. P. Pollak, "The role of actigraphy in the study of sleep and circadian rhythms," *Sleep*, vol. 26, no. 3, pp. 342–392, May 2003.

[6] L. Ye and E. Keogh, "Time series shapelets: A new primitive for data mining," in *Proceedings of the 15th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, ser. KDD '09, 2009, pp. 947–956.