

# Predicting Mood Changes in Bipolar Disorder through Heartbeat Nonlinear Dynamics: a Preliminary Study

Gaetano Valenza<sup>1</sup>, Mimma Nardelli<sup>1</sup>, Antonio Lanata<sup>1</sup>, Claudio Gentili<sup>2</sup>, Gilles Bertschy<sup>3</sup>, Enzo Pasquale Scilingo<sup>1</sup>

<sup>1</sup>Department of Information Engineering and with the Research Centre "E. Piaggio", School of Engineering, University of Pisa, Pisa, Italy; <sup>2</sup> Department of surgical, medical, molecular, and critical area pathology, section of psychology, University of Pisa, Pisa, Italy;

<sup>3</sup> Department of Psychiatry and Mental Health, Strasbourg University Hospital, INSERM U1114, University of Strasbourg, Strasbourg, France

## Abstract

*Bipolar disorder is characterized by mood swings alternating from depression to (hypo-)manic, including mixed states. Currently, patient mood is typically assessed by clinician-administered rating scales and subjective evaluations exclusively. To overcome this limitation, here we propose a methodology predicting mood changes using heartbeat nonlinear dynamics. Such changes are intended as transitioning between euthymic state (EUT), i.e., the good affective balance, and non-euthymic state. We analyzed Heart Rate Variability (HRV) series gathered from four bipolar patients involved in the European project PSYCHE, undergoing 24h ECG monitoring through textile-based wearable systems. Each patient was monitored twice a week, for 14 weeks, being able to perform normal (unstructured) activities. From each acquisition, the longest artifact-free segment of heartbeat dynamics was selected for further analyses. Sub-segments of 5 minutes of this segment were used to estimate trends of HRV linear and nonlinear dynamics. Considering data from a current observation at day  $t_0$ , and past observations at days  $(t_{-1}, t_{-2}, \dots)$ , personalized prediction accuracies in forecasting a mood state (EUT/non-EUT) at day  $t_{+1}$  were 74.18% on average. This approach is intended as a proof of concept of the possibility of predicting mood states in bipolar patients through heartbeat nonlinear dynamics exclusively.*

## 1. Introduction

Bipolar Disorder (BD) is a mental illness characterized by alternating phases of depression (negative pole), with symptoms similar to unipolar depression, phases so-called manic or hypomanic (positive pole), with symptoms related to pathological hyperactivity, and mixed states between negative and positive poles [1]. In the intervals be-

tween these episodes, patients typically experience periods of relatively good affective balance, which are called euthymia (EUT). The duration of each phase and the interval between the one and the other are extremely variable from subject to subject, and can occur in different moments in the life of a single patient. BD is a leading cause of premature mortality due to suicide and associated medical conditions, such as diabetes mellitus and cardiovascular disease [2]. Despite the fact that the recurrent nature of manic and depressive episodes often leads to high direct and indirect health care costs, the clinical assessment and management of this condition is still ill-defined. Currently, the patient mood is typically assessed by clinician-administered rating scales and subjective evaluations exclusively [3].

To this extent, previous studies pointed out possible biomarkers to be taken into account to objectify the diagnosis of BD [4–7]. Specifically, features of hormonal, immunologic, and Autonomic Nervous System (ANS) dysregulation [4, 5] were significantly associated to BD, also estimated by analyzing Heart Rate Variability (HRV) series [6, 7]. As a counter-proof, vagus nerve stimulation appears to be a promising intervention for the treatment of BP [8]. However, none of these studies have reached an acceptable level of accuracy for clinical use in order to forecast the clinical course in single patients.

A very important form of BD prevention against potential self-destructive acts or excessive aggression towards others could be related to the use of ANS signs to actually predict the moment in which the subject is going to move from the euthymic state to a pathologic one among those mentioned above. To this extent, in this study, we propose a methodology predicting mood changes using heartbeat linear and nonlinear dynamics. Such changes are intended as transitioning between euthymic state (EUT), i.e., the good affective balance, and non-euthymic state.

Data used in this study were gathered in the framework of the European project PSYCHE (Personalised monitor-

ing SYstems for Care in mental HEalth), which aimed to longitudinally study BD patients through comfortable wearable systems [9–15]. We recently demonstrated that this system is able to obtain an automatic classification of mood states in BD patients using a multivariate HRV feature analysis [9–14]. In addition, we provided evidences that linear and nonlinear cardiovascular dynamics is affected by mood swings occurring during the current and past clinical course [10, 11]. In other words, in BD, the "current" mood state can be dependent on the previous mood state, and therefore contains information related to the subsequent state as well. To this extent, we here describe first preliminary results using a novel methodology able to predict mood changes using HRV data exclusively.

## 2. Materials and Methods

We analyzed HRV series gathered from four bipolar patients (2 females, age:  $27.5 \pm 5.8$ , range: 23–36) undergoing 24h ECG monitoring through textile-based wearable system. Patients were recruited in the clinical center of University of Strasbourg, France. Each patient was monitored twice a week, for 14 weeks, being able to perform normal (unstructured) activities. Accordingly, each patient is represented by a series of consecutive mood states. Inclusion/exclusion criteria adopted for patients recruitment can be found in [9, 10].

A general block scheme of the signal processing chain for mood prediction is shown in Figure 1. From each acquisition the longest artifact-free segment of signal was selected through a previously developed methodology for artifact detection and removal [9], and visual inspection. Sub-segments of 5 minutes of this segment were used to calculate significant features, which were defined in the time and frequency domains, as well as from nonlinear analysis (see [16] for calculation details and related literature review). A detailed list of these parameters is reported in Table 1.

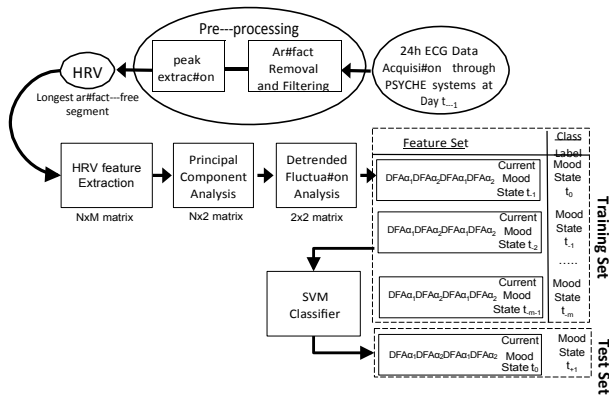


Figure 1. Block scheme of the proposed signal processing chain for mood prediction between EUT/non-EUT class.

Table 1. List of HRV features used to estimate linear and nonlinear ANS dynamics in patients BD, within a long-term acquisition.

Time domain	Frequency domain	Nonlinear Analysis
Mean RR	VLF peak	Poincaré SD1
Std RR	LF peak	Poincaré SD2
RMSSD	HF peak	Approximate Entropy (ApEn)
pNN50	VLF power	Sample Entropy (SampEn)
RR triangular index	VLF power %	DFA $\alpha_1$
TINN	LF power	DFA $\alpha_2$
	LF power %	RPA Shannon Entropy
	LF power n.u.	RPA Lmin
	HF power	RPA Lmax
	HF power %	RPA Lmean
	HF power n.u.	RPA DIV
	LF/HF power	RPA REC
		RPA DET

In this way, for each acquisition of each patient, we obtained a representative  $N \times M$  matrix ( $N$ : number of windows  $\times$   $M$ : number of features), describing the evolution over time of the feature space. Principal component analysis was then applied on this matrix, and the first two dimensions were retained for further analyses. This choice was justified by the fact that, in most cases, such first two dimensions explained more than 90% of data variance. The time evolution of each these dimensions was synthesized through Detrended Fluctuation Analysis (DFA), taking the  $\alpha_1$  and  $\alpha_2$  parameters as estimates for the short- and long-term correlation, respectively. Along with the features coming from DFA analysis, current mood state was also included as an input feature. This choice is motivated by the fact that, in a previous study [10], we demonstrated that mood changes in bipolar patients can be represented as a stochastic process with Markovian properties. In other words, considering data from a current observation at day  $t_0$ , and past observations at days  $(t_{-1}, t_{-2}, \dots)$ , we aim to perform a personalized prediction of a mood state between EUT/non-EUT at day  $t_{+1}$ . A graphical representation of this concept is shown in Figure 2.

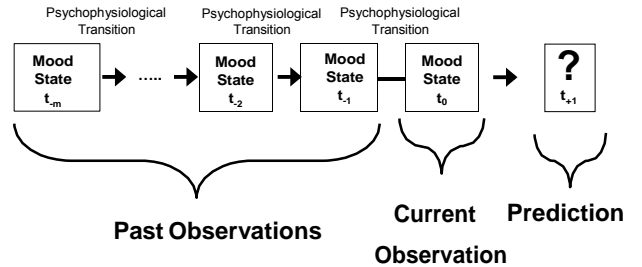


Figure 2. Graphical representation of mood state temporal dynamics of a given patient with BD.

Finally, the actual prediction of the future mood state relied on Support Vector Machine (SVM) algorithms. Specifically, we adopted common nu-SVM ( $\nu = 0.5$ ) having a radial basis kernel function with  $\gamma = \nu^{-1}$ , with

$n=5$  equal to the diminution of the feature space.

A sufficient number of initial acquisitions was used as training set. Specifically, this set included at least one example of EUT, and non-EUT state. All of the algorithms were implemented by using *Matlab*® v7.3 endowed with an additional toolbox for pattern recognition, i.e., LIB-SVM [17].

### 3. Results

In this preliminary study, results were achieved considering data gathered from 4 patients with BD:  $P_1$ ,  $P_2$ ,  $P_3$ , and  $P_4$ . As mentioned in the previous section, from each acquisition of each patient, the longest artifact-free segment of signal was selected. Minimum length of such a segment was 5.21 hours, gathered from an acquisition of  $P_2$ . Personalized prediction accuracies in forecasting the mood state (EUT/non-EUT) at time  $t_{+1}$  are shown in Table 2. In this table, the second column reports the total number of acquisitions used for the accuracy estimation, whereas the third column reports the number of acquisitions used for the initial training set ( $x : y$  means that the initial training set was considered from acquisition  $x$  to acquisition  $y$ ).

Table 2. Experimental Results expressed as prediction accuracy for each patient. The total number of available acquisitions ('N. Acq.', second column), and the number of acquisitions taken as initial training set ('Training Acq.', third column) are also reported.

Patient ID	N. Acq.	Training Acq.	Prediction Acc.
$P_1$	22	1:5	70.6%
$P_2$	18	1:3	75%
$P_3$	19	1:5	73.33%
$P_4$	22	1:5	77.78%

Considering group-wise results, the average accuracy of prediction was 74.18%, with average sensitivity of 60.3%, and average specificity of 81.1%.

### 4. Discussion and Conclusion

We reported promising results suggesting that it is possible to forecast mood states in BD using heartbeat dynamics exclusively, gathered from ECG. Here, we reduced the problem to predict two possible states: euthymic state, i.e., the good affective balance, and non-euthymic state, i.e. every mood state of BD among depression, hypomania, and mixed state.

This novel approach should be intended to be a 'proof of concept' of the possibility to predict mood states, and early detect mood switching in BD. From a clinical point of view, outcomes of this work are very relevant. Knowing in advance whether the patient is getting better or not

could effectively help clinicians to optimize the therapy and make changes in time, if necessary. On the other hand, understanding if the patient is going to have a relapse is very important and informative to perform a more accurate clinical monitoring, and plan a treatment at very early stage.

Data of long-term cardiovascular dynamics used in this study were gathered through the PSYCHE platform, developed in the framework of the European project PSYCHE [9–14]. Briefly, the PSYCHE platform consists of a wearable sensorized t-shirt, embedded with fabric-based electrodes, which acquires ECG, respiration signals, and body activity, and a smartphone, which collects data from the wearable system via Bluetooth technology. The platform can also be used to record voice parameters and subjective data (e.g., mood agenda, sleep agenda) as well.

In agreement with the aims of the PSYCHE project, the proposed forecasting methodology is fully personalized, and is based on long monitoring acquisitions regardless of specific activity performed by patients. Each patient observation, in fact, was represented by time-varying HRV linear and nonlinear estimates. Then, further multivariate signal processing synthesized the patient mood state in a 5-dimension feature space. Of note, this approach relies on our previous study [10], which demonstrated that mood changes in bipolar patients can be represented as a stochastic process with Markovian properties, i.e., current mood state depends on the previous one. This is in line also with clinical observations: for instance, a cycle in which mania follows depression and precedes euthymia is associated with a longer depressive status and a lesser intense response to mood stabilizers as compared to a cycle in which depression follows mania and precedes euthymia [18].

Results of this preliminary study are very encouraging and promising. At a group-wise level, sensitivity (the probability that the output of the classifier is euthymia when the next mood state of the patient will be euthymic) was 60.3%. It is not so high but, as a preliminary achievement, we consider it as satisfactory and promising. We also consider this result partially due to the fact that the class non-EUT actually includes three mood states, making therefore the EUT class likely to be underrepresented. Specificity, instead, was as high as 81.1%.

Although previous studies suggested possible biomarkers to support the diagnosis of BD [4–7], none of these studies have shown predictive capability of such biomarkers, while reaching an acceptable level of accuracy for clinical use. A possible explanation for these negative results can be that mood disorders are more heterogeneous, in terms of psychophysiological, neuroendocrine and neurobiological correlates, than relatively simple clinical phenotypes usually adopted for clinical and also for research purposes. This might result in gathering subjects in groups that, although homogeneous in a clinical descriptive point of view, are extremely dishomogeneous in terms of en-

dophenotypes.

In conclusion, considering the results of accuracy, sensitivity and specificity, we can state that the proposed methodology is able to predict the next mood state with acceptable reliability. However, we are aware that more acquisitions, possibly with more frequent transitions, can remarkably improve prediction performances. An ideal mood switch predictor, in fact, would require all possible transitions among mood states, i.e. 16 classes given by depression to euthymia, depression to depression, depression to mania, depression to mixed state, euthymia to depression, euthymia to euthymia, euthymia to mania, etc. Machine learning systems able to discriminate a so high number of classes are very challenging and require a very huge amount of data.

Future work will focus on the investigation of which feature would provide major information in forecasting the next mood state.

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Address for correspondence:

Name: Gaetano Valenza

Full postal address: Largo Lucio Lazzarino, 1, 56122, Pisa (Italy)

E-mail address: g.valenza@iee.org