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A Multi-Relational Model for Depression Relapse in Patients with Bipolar Disorder

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Abstract

Bipolar Disorder (BD) is a chronic and disabling disease that usually appears around 20 to 30 years old. Patients who suffer with BD may struggle for years to achieve a correct diagnosis, and only 50% of them generally receive adequate treatment. In this work we apply a machine learning technique called Inductive Logic Programming (ILP) in order to model relapse and no-relapse patients in a first attempt in this area to improve diagnosis and optimize psychiatrists' time spent with patients. We use ILP because it is well suited for our multi-relational dataset and because a human can easily interpret the logical rules produced. Our classifiers can predict relapse cases with 92% Recall and no-relapse cases with 73% Recall. The rules and variable theories generated by ILP reproduce some findings from the scientific literature. The generated multi-relational models can be directly interpreted by clinicians and researchers, and also open space to research biological mechanisms and interventions.

Keywords:

Bipolar Disorder; Depression Relapse; Multi-relational Model; Inductive Logic Programming; Machine Learning.

Introduction

The Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association, organizes all psychiatric disorders and other problems into five different categories, or axes. Axis I disorders, the focus of this work, includes all psychological diagnostic categories such as depression, anxiety disorders, and bipolar disorder, among others, except mental retardation and personality disorders that fall into Axis II. A psychiatric disorder involving both manic and depressive episodes, Bipolar Disorder (BD), which falls into the Axis I category, is a chronic and disabling disease that usually appears around 20 to 30 years old. Patients who suffer with BD may endeavor for years to achieve a correct diagnosis, and only 50% of them generally receive adequate treatment. Commonly, the mood episodes lead to personal and professional problems, and due to the disease's progression character, the euthymic periods (without mood episodes) become gradually shorter [1]. A WHO study [2] evidenced the devastating impact of BD: all around the world, approximately 29.5 million people present BD, which occupies the 12th position relative to the major causes of moderate to severe incapacity. With 22.2 million people in such conditions, this study also reveals that 2.5% of the years of incapacity are related to BD episodes. Relapse prevention is the main target in BD treatment, since the relapse rate is around 50% at one year and 70% at four years treatment [1, 3, 4].

Due to this alarming picture, a number of researchers started to explore the aspects underlying the BD outcome, in particular, genetic, neurobiological, environmental and phenomenological factors, as well as the interactions between them. As BD presents multi-factorial and multidimensional characteristics, there appears to be an urgent necessity of new techniques to investigate patterns associated with the course of this disease, especially the computational and mathematical ones. Machine learning and data mining bring the possibility of new hypotheses discovery through the exploration of datasets (new or not), neuroimaging and biomarkers, thus opening space to the research of new biological mechanisms and interventions [5, 6].

In fact, machine learning have been already applied to the study of BD. Mourão-Miranda *et al*. [7] have applied Gaussian Process Classifiers (GPC), a machine learning approach that assigns a predictive probability of group membership to an individual person, to differentiate groups and to identify those at-risk adolescents most likely to develop future Axis I disorders. The work was done collecting information from functional magnetic resonance imaging after the teens performed two emotional face gender-labeling tasks (happy/neutral; fearful/neutral). Using GPC, neural activity to neutral faces presented during the happy/neutral experiment accurately and significantly differentiated groups, achieving 75% accuracy (sensitivity=75%, specificity=75%). More recently, Schnack *et al*. [8] used Support Vector Machines (SVM) to distinguish among three groups of patients. They scanned 66 schizophrenia patients, 66 patients with bipolar disorder and 66 healthy subjects on a 1.5 Tesla magnetic resonance imaging scanner. Three SVM were trained to separate patients with schizophrenia from healthy subjects, patients with schizophrenia from those with bipolar disorder, and patients with bipolar disorder from healthy subjects, respectively, based on their gray matter density images. The predictive power of the models was tested using cross-validation and in an independent validation set of 46 schizophrenia patients, 47 patients with bipolar disorder and 43 healthy subjects scanned on a 3 Tesla magnetic resonance imaging scanner. Schizophrenia patients could be separated from healthy subjects with an average accuracy of 90%. Additionally, schizophrenia patients and patients with bipolar disorder could be distinguished with an average accuracy of 88%. The model delineating bipolar patients from healthy subjects was less accurate, correctly classifying 67% of the healthy subjects and only 53% of the patients with bipolar disorder. In the latter group, lithium and antipsychotics use had no influence on the classification results. Application of the 1.5 Tesla models on the 3 Tesla validation set yielded average classification accuracies of 76% (healthy vs schizophrenia), 66% (bipolar vs schizophrenia) and 61% (healthy vs bipolar). Most of these works are based on image data. As far as we know, no work has been done on data col-

lected from clinical assessments such as demographic and bipolar disorder features collected from forms and from medical consultations.

In this work, besides working only with annotated clinical data, we also employ a non-propositional machine learning technique, Inductive Logic Programming (ILP), which combines inductive machine learning and logic programming [9]. Compared to other machine learning algorithms, an advantage of ILP is its use of relational logic as a representation language. Learning systems that use this kind of representative language are known as Relational Learning Systems (RLS). In this approach, objects are structurally described, i.e., according to their components and relationships between them. The employment of relational logic as a representative language allows the induction of predicates. As a consequence, the number of concepts that can be learned is expanded. RLS are highly expressive for representing concepts and are able to represent the domain knowledge in such a way that is directly intelligible for people – a fundamental characteristic whenever one aims to extract knowledge from a given domain [10].

In this study, we investigate the use of ILP to generate a multi-relational model for studies of depression relapse in patients with BD. Our study considers demographic and clinical features, organized in multiple tables, which makes the dataset suitable for relational learning [11]. We generate interpretable classifiers, based on first-order logic, that capture the correlation between features included in this study to find patterns of relapse and no-relapse in patients with BD.

Methods

We explored data from a cohort of 139 patients with BD, followed by periods of 6 months to 10 years, from the Bipolar Disorder Program from the Institute of Psychiatry of São Paulo State University outpatient clinic. These data are associated with 102 variables covering psychiatric and medical comorbidity and history of BD, and 109 variables collected during the patient follow-up including medication and symptoms of mood. All participants in the study signed a consent form approved by the Ethics Committee for Research Project Analysis at the Hospital das Clínicas, Faculty of Medicine, University of São Paulo for use of data collected during the follow-up in clinical research.

Initially we identified patients who had continuous periods of remission until depression relapse, or that remained in remission. For this study, we considered only the first depressive relapse of patients. A broader definition of a relapse included both syndromal episodes and subsyndromal clinical states, because reports in the prior literature indicate an association between subsyndromal clinical status of BD and worse clinical and functional outcomes [1, 12, 13]. After filtering, we had 108 patients, where 86 (79.6%) cases are of relapse and 22 (22.7%) are of not relapse, which is representative of the reality of BD patients' outcomes [1 ,3, 4], especially in a university outpatient clinic that treats patients with more severe disorders. All clinical data and follow-up data of the patients were used to generate the relational models. We consider cut-offs of 4 weeks for remission time and classification of mood states based on Hamilton Depression Rating Scale and Young Mania Rating Scale as defined by the International Society of Bipolar Disorder [14, 15, 16].

ILP allows the expert's knowledge to be encoded as background knowledge. We use this characteristic to create predicates that allow searching for relationships between visits of patients. Thus, the ILP system is capable of exploring rules seeking patterns between several visits of the same patient including baseline visit, previous visit to relapse and relapse visit.

Unlike most machine learning approaches, ILP treats its positive and negative training asymmetrically, focusing on inducing rules that match many positive examples and few (ideally zero) negative examples. In this study, we investigate the potential of ILP in two tasks: automatically finding rules that correlate features of (1) relapse and (2) no-relapse cases.

We used Aleph (A Learning Engine for Proposing Hypotheses) [17], an ILP system completely written in Prolog, that was developed at Oxford University. Aleph receives as input: the background knowledge (BK) specified as a logic program; the hypotheses specification (H); an optional set of restrictions (I) relative to acceptable hypotheses; and a finite set of examples $E = E^+ \cup E^-$, where E^+ consists of a "positive" set of examples and E^- a "negative" set of examples. Aleph searches for a hypothesis H, relative to the restrictions I, so that H implies all examples in E^+ and none in E^-. In other words, H is true for all examples in E^+, but it is false for every element of E^-. As a default mode, Aleph applies a covering procedure that constructs a hypothesis through the generation of rules, one by one, using the positive examples. The final outcome consists of a collection of rules (clauses) represented in First Order Logic, known as a theory.

Aleph has several parameters that can be set to guide the search for better rules. We changed the default values of four of these parameters:

clauselength: sets the upper bound on number of literals in an acceptable clause

minpos: sets the minimum number of positive examples that a rule is required to cover.

noise: sets the maximum number of negative examples that a rule is allowed to cover.

nodes: sets the upper bound on the nodes to be explored when searching for an acceptable clause.

We chose 10 for *clauselength* to get rules with the largest number of features and related visits of a patient. We chose 2 for *minpos* in order to produce rules that generalize beyond a single case in the training set at minimum. For *noise* we chose 0, disallowing any rules that misclassify even a single positive example in the training set. Due to the large number of variables, we set the maximum number of *nodes* as 2,000,000.

In our experiments, we use stratified 10-fold cross-validation for evaluating the results. We used the same folds in both experiments (relapse and no-relapse). Metrics presented are collected across all folds, and are related to the test sets. For each experiment, we report the contingency table (TP: True Positives, FN: False Negatives, FP: False Positives and TN: True Negatives), Accuracy (Acc), Recall (Rec), Precision (Prec) and Specificity (Spec). Recall gives the true positive rate, Precision gives the rate of correctly classified positives and Specificity gives the true negative rate.

A statistical analysis of the variables was performed. Sociodemographic and psychiatric characteristics at baseline were compared between relapse and no-relapse groups using the chi-square test for categorical variables (Fisher's exact test if cell counts expected <5), the Student's t-test for normally distributed continuous variables, and the Wilcoxon Mann-Whitney test for non-normally distributed continuous variables. Analyses were conducted using SPSS (V.15.0). All statistical analyses were conducted using a two-sided significance level of α=0.05.

Results

Socio-Demographic and Bipolar Disorder features

In the overall sample, mean age was 40.2 years old (sd. 11.5), ranging from 22 to 76; 72 (66.7%) were female, 84 (77.8%) were Caucasian, 47 (43.5%) were single and 41 (38.0%) married, 16 (14.8%) divorced and 4 (3.7%) widowed, the mean years of education was 11.78 (sd. 3.25) ranging from 3 to 18. The majority of patients, 99 (91.7%), was diagnosed with BD I. Of the 108 subjects evaluated, 86 (79.6%) had a depressive episode relapse. Table 1 shows socio-demographic and BD comparison between groups. No difference was observed regarding the medication in use at baseline: lithium - relapse group (RG) n=29, 33.7% vs. no-relapse group (NRG) n=9, 40.7%, (p=0.53); anticonvulsant - RG n=51, 59.3% vs. NRG n=12, 54.5%, (p=0.69); second generation antipsychotics - RG n=32, 37.2% vs. NRG n=7, 31.8%, (p=0.64); first generation antipsychotics - RG n=3, 4.7% vs. NRG n=0, 0.0%, (p=0.58); antidepressants - RG n=27, 25.0% vs. NRG n=2, 9.1%, (p=0.06).

Table 1– Socio-demographic and Bipolar Disorder characteristics in Relapse and No-Relapse Group

	Relapse	No-relapse	p
n (%)	86 (79.6%)	22 (20.4%)	
Female (n, %)	60 (69.8%)	12 (54.5%)	0.18
Age (mean, sd)	40.9 (12.0)	37.6 (8.9)	0.23
Years of education (mean, sd)	11.8 (3.3)	11.8 (3.0)	0.97
Caucasian (n, %)	69 (80.2%)	15 (68.2%)	0.19
Bipolar Disorder (n, %)	Type I 78 (90.7%) Type II 8 (9.3%)	Type I 21 (95.5%) Type II 1 (4.5%)	0.47
Presence of psychotic symptoms (n, %)	52 (60.5%)	12 (54.5%)	0.53
Age of BD onset (median, iqr)	18.5 (15.0-26.0)	27.0 (17.0-32.0)	0.03
Years with BD (median, iqr)	15.5 (10.0-23.8)	10.0 (6.0-16.0)	0.01
Rapid cycler (n,%)	8 (9.3%)	1 (4.5%)	0.49
Psychiatric comorbidity (n, %)	52 (60.5%)	13 (59.1%)	0.91
Suicide attempt	21 (24.4%)	5 (22.7%)	0.87

Multi-Relational Model

The theories obtained by Aleph were translated from first-order logic to English to make them easier to read. The theory derived for relapse (RG) was composed by four rules and the one derived for no-relapse (NRG) by two rules, which are described next.

Relapse (RG) theory

1. The patient did not have a binge eating disorder, did not have insomnia in the middle of the night in the visit before the relapse, did not have psychotic symptoms and has not been using hypnotic medication.
2. The patient presented loss of interest in activities (hobbies or work), indecision and vacillation in the relapse visit.
3. The patient was not a rapid cycler, was using two different medications, one of them was an anticonvulsant, and at the baseline visit he/she did not have insomnia in the middle of the night and suicidal thoughts.
4. The patient had the BD onset before 17 years old, and did not meet criteria for alcohol abuse lifetime, and at the relapse visit complained about subjective tension and irritability.

No-Relapse (NRG) theory

5. The patient did not present a depressed mood (sadness, hopeless, helpless, worthless) and somatic symptoms.
6. The patient had 13-17 years of education.

The quantitative results from 10-fold cross-validation for each experiment are presented in Table 2. Metrics presented are collected across all folds and are related to the test sets.

Table 2– Accuracy performance

	TP	FN	FP	TN	Acc	Rec	Prec	Spec
RG	79	7	9	13	0.85	0.92	0.90	0.59
NRG	16	6	4	82	0.91	0.73	0.80	0.95

Discussion

Aleph discovered several rules that confirm facts in the literature. Moreover, it discovered patterns that can predict in which conditions a new patient will have the next relapse occurrence, facilitating the immediate detection of the problem and suitable treatment.

As far as we know, this is the first study on the use of ILP to generate a multi-relational clinical model in BD. In addition, this is the first experiment in the major area of psychiatric disorders that explores machine learning classifiers to perform multi-correlation of patients' clinical features based on a longitudinal dataset. In a research area where the finding for interpretable and meaningful patterns is eagerly sought, ILP produced very good initial positive results. The generated rules selected clinical features associated with outcome in BD already described in the scientific literature. Moreover, the associations found by ILP are richer than the ones produced by the so-called black-box models. ILP also produces multivariate correlations as it can combine several variables in the same rule. As ILP is not based on numerical processing, we do not need to worry about missing values.

ILP Theories

BD patients have circadian rhythm genetic abnormalities making them especially sensitive to sleep changes [18]. Sleep disturbance in BD is associated with a more severe course of illness, presence of psychotic symptoms and use of anticonvulsants suicide attempts [19]. All these features were present in the relapse group rules. For example, Rule (1) and Rule (3) mention lack of insomnia, and Rule (3) correlates lack of insomnia and intake of anticonvulsants to a relapse. Anticonvulsants, especially valproic acid, valproate and divalproex are used as mood stabilizers in BD. Better rates of mood stabilization are observed when associated with lithium. When used in monotherapy, they are as effective as lithium [20]. Therefore it is expected that they have a strong role in relapse presence. Lamotrigine, another anticonvulsant with significant positive results in the treatment of BD [21] is included in this group. Anxiety and early age of BD onset are also associated with a poorer outcome [1, 22, 23], and included in Rule (4). BD is strongly associated with suicide. A review study about suicide and BD clinical samples described that between 14-59% of the patients have suicide ideation, 25-56% present at least one suicide attempt during their lifetime and 15-19% die from suicide [24]. Rule (3) is associated with rapid cycling, which was already observed in the literature. Moreover, the use of anticonvulsants in BD is also associated with impulsivity and irritability, both associated with suicide attempts.

Subsyndromal depressive symptoms are strongly associated with depressive relapse [13]. In all rules there is at least one depressive symptom. Interestingly, the rules also describe the absence of specific depressive symptoms as a predictor of depressive relapse. Rule (2) consists only of depressive symptoms. In the No-relapse theory, Rule (5) consists only of depressive symptoms, strengthening once more the power of subsyndromal role in depressive relapse. Rule (6) is associated with years of education. Education is associated with higher levels of resilience, the ability to cope with stress or adversity, which is positively associated with better outcomes [25].

A possible limitation concerning our sample is the difference of BD age onset and years with BD between groups. The early BD onset as a factor associated with relapse was observed in the statistical and ILP analyses. It is well known in the literature the negative impact of early age of onset in BD outcome [1]. Other limitations could be related to the follow-up and number of visits per subject, once they were naturalistically followed and the visits were scheduled according to mood changes. A structured follow-up program could reduce this bias in future machine learning studies.

ILP as a Classifier

Besides producing rules that can represent patient patterns and allowing for the representation of new background knowledge that can be incorporated in to the raw data, ILP rules can also work as classifiers that can predict relapse or no-relapse of future cases. Results in Table 2 show the expected performance of a classifier based on rules produced by Aleph on our dataset. As explained before, these results were generated using 10-fold cross-validation (which is a standard machine learning validation procedure) and results are reported for the test set.

The first row of Table 2 shows results for rules that can predict in which situation a patient will have a relapse. These rules are based on the four rules discussed in the Results section. This classifier has a very good accuracy of 85%, being able to correctly predict 92 out of the 108 patients. On the relapse class, it does quite well with a 92% Recall, meaning that it misclassifies only 7 patients that actually have a relapse. This has a very important clinical meaning, since psychiatrists can concentrate their attention on the most needed patients with a very regular follow-up, while scheduling other patients to a more spaced time interval. It is important to note that the current practice routine considers all patients as potential relapse cases.

The second row of Table 2 shows similar results, but from the point of view of the no-relapse patients. If we look at the error rate of this classifier, it can perform even better than the first classifier for relapse cases. In other words, if the classifier says that a case is no-relapse, only 4 actual relapse cases are misclassified, while most of the no-relapse cases (16 out of 22, 73%) are still correctly classified. This means that 73% of the actual no-relapse cases can have a different treatment and have less regular visits to the psychiatrist, again leaving more time for the psychiatrists to concentrate on the actual relapse cases.

These are very encouraging results which open a new path to novel discoveries in the area of mental disorders.

Conclusion

In this work, we use ILP to develop a multi-relational model that highlights patterns of relapse and non-relapse in patients with BD. The results confirm that ILP can generate accurate relational models. The models are easy to interpret, since they are based on a rule-based language helping the experts to better understand the found patterns. By using this language, the expert can also add new knowledge to the raw data. Rules pinpoint features that were already reported in the literature such as use of convulsants and cases of insomnia, among others, but more importantly, they correlate many variables, contrary to most studies in the literature that only find uni- or bivariate correlations.

We used 10-fold cross-validation on a set of 108 patients, 22 with no-relapse and 86 with relapse. Results show that we can achieve very good accuracy when predicting either class and very good Recall (up to 95% specificity on the no-relapse class), numbers that are better than the ones found in the literature so far.

Another advantage of ILP is that it can handle multiple tables, which is not so trivial with propositional methods that require that the data is represented in a flat table format. For example, in our experimental setting, each patient can have a variable number of visits per month (up to 45 non-consecutive visits in 125 months), and each visit is associated to several different characteristics (totaling 211 variables per patient). Generating a flat table for this kind of data keeping the absolute time of the visit would require a huge, sparse, and redundant table with 13,727 columns for each patient. In addition, models produced with the ILP learner would not be comparable with models produced with this flat table.

Some ILP limitations concern the rapid growth of the search space relative to database growth. Such situations may lead to a high computational cost for the rule construction, thus making it more difficult to find the best solution.

ILP and other approaches in machine learning could be especially useful in exploratory studies with a multifactorial approach, as translational research, and the possibility to find patterns with impressive precision. The mental disorder field could be explored as a tool to link neurobiology with clinical phenotype. More research in other areas of mental disorders must be done to fully uncover the ILP potential.

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