Analyzing a psychiatric domain using a new knowledge discovery methodology

Jorge Rodas[1], Karina Gibert[2], J. Emilio Rojo[3], and Ulises Cortés[1]

[1] Software Department, Technical University of Catalonia, Barcelona, Spain
{jr,ia}@lsi.upc.es
[2] Department of Statistics and Operational Research, Barcelona, Spain
karina@eio.upc.es
[3] Hospital of Bellvitge, Barcelona, Spain
jrojo@csub.scs.es

Abstract. A new methodology for analyzing repeated very short-serial measurement on time in a medical ill-structured domain is introduced. This methodology is based on a combination of *clustering based on rules* with some Inductive Learning (AI) and clustering (Statistics) techniques. This proposal focuses on results obtained on a real application of this kind of data, where common statistical analysis (time series analysis, multivariate...) and artificial intelligence techniques (knowledge based methods, inductive learning) of such data are often inadequate because of the intrinsic characteristics of those domains.
Keywords: Knowledge Discovery, Serial Measurement on time, ill-structured domains.

1 Introduction

A great quantity of medical information is obtained from domains without structure and when it would be necessary to make a decision about what is good knowledge and what is not is a very difficult problem. These kind of domains are included in what is named by [3] as *ill-structured domains*(ISD). Some of their features are: *heterogeneous data*, *additional knowledge of the domain*, and *partial and non-homogeneous knowledge*.

The application presented here fits on the definition of an ISD. Moreover, it presents some additional particularities such as some serial measurement over time. Therefore, finding a consistent methodology to handle them, extracting useful information from them, and being able to find profiles in this kind of data is the goal of this work.

The structure of the paper is as follows: Firstly, an explanation of the case of study it can be found in section §2. Section §3, introduces the problem and goals. In section §4 the methodology to solve the problem is introduced. In section §5 the methodology application to real case is explained, and §6 give important results. Finally, section §7 draws some important conclusions about this work and point to various directions for future work.

2 Case study

2.1 Application Domain

An interesting psychiatric field of study corresponds to therapies for depression disorders or schizophrenia. The *Electro-Convulsive Therapy* (ECT) is a safe, effective, and widely used treatment for serious depression illnesses and other psychiatric disorders[1]. The ECT is based on electroshocks. An electroshock is an electrical current through the brain in order to induce seizures (convulsions) and to improve the psychiatric condition. ECT is a moderately complex procedure where an adequate seizure is necessary for therapeutical response; however, the brain biological events related to its efficacy are still unknown.

The neuropsychological effects of ECT are cognitive changes involving orientation, attention and calculation capability, memory loss, and recall (more details in [1]).

Many works studied the physiological response of ECT through heart rate, blood pressure, ..., and have been important for the understanding of main effects of ECT. However, at the moment, a formal technique for analyzing neuropsychological effects of ECT does not exist and there are only a few works about the effects of ECT on psychophysiological parameters such as *reaction times* (RT), directly related with memory loss. That is why this study is relevant. For the first time, the effects of ECT on both visual and audible reaction times are studied. In this work, the existence of a formal profile of reaction times and the identification of the attributes which have a direct influence on them (and, in consequence, on the cognitive state of the patient) is focused, as well as the establishment of a methodology for these kinds of domain.

2.2 Data Description

In this study, 13 patients with major depression disorders or schizophrenia and under ECT treatment are monitorized. The therapies are designed in such a way that the therapeutic ratio is optimized by selecting electrical stimulus parameters such as energy level, stimulus duration, pulse frequency, according to present standard practice. In addition, multiple responses from patients are monitorized by ElectroEncephaloGram (EEG), ElectroCardioGram (ECG), and ElectroMioGram (EMG); and a rigorous evaluation of patients' neuropsychological effects was done.

The Vienna Reaction Unit is a standard protocol for measuring reaction times, among others, based on visual and audible stimuli. Four tests were carried out: Simple Visual (S5), Simple Audible (S6), Complex Visual (S7), and Complex Visual-Audible (S8)at 2, 4, 6, 12, and 24 hours after every ES application.

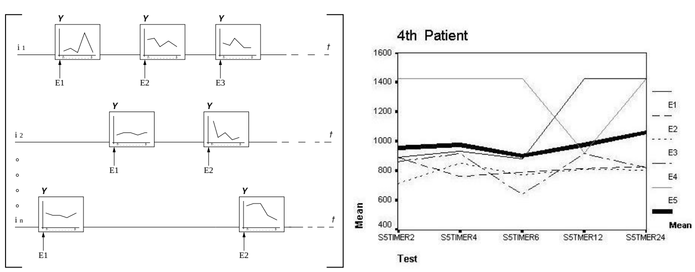
The following parameters, were registered for each test (for more details about variables see [6]): *Reaction times*, *number of wrong decisions*, *number of wrong reactions*, *number of no reactions*, *number of incorrect reactions*, *number of right reactions*. In fact, there is a lot of information recorded for each electroshock such as: *applied energy*, *impedance*, *frequency*, *arterial pressure*, *medical* *complications*, *VIENNA protocol baseline results*, *VIENNA protocol results after ES application for all tests S5-S8*, among others.

Besides that, there is additional information about each patient such as: age, weight, education level, blood and urine analysis, previous electroencephalograms, electrocardiograms, and electromiograms. For more details about vienna unit and its protocol, measures, attributes in datasets and others see [6, 7].

3 Problem formulation and Goals

3.1 Problem formulation

The representation of a series of *individuals* $(i_1..i_n)$ in which n_i occurrences of a given *event* E take place at different time points $(E_1 \ldots E_n)$ is shown in figure 1(a). Connected to each event occurrence, there exists an attribute of interest Y which affects the behaviour of the individual. Therefore, the study of the evolution of Y on individual i during a given very short time period $[t_1, t_r]$ which immediately follows to every occurrence of E is the objective desired.



(a) (b)

Fig. 1. (a) Individuals; (b) curves of Test S5 from 4^{th} patient.

Hence, a certain small number of measurements of Y is taken for each individual and for each occurrence of E. In this particular case, such a number is fixed (r) for all the occurrences of E and the time points where Y will be measured are also fixed.

For example, regarding to the real application which is supporting this research,

$I = \{i_1, .., i_n\}$ is a set of patients, E is the application of an *electroshock* to a given patient at a given time point $E_1 \ldots E_n$.
Y is the attribute of interest corresponding, for instance, to the patient's reaction time to a given *luminous stimulus*. The measurement of this attribute is performed during the first 24 hours after the application of each ES, in particular after 2h, 4h, 6h, 8h, 12h, and 24h $([t_1, t_r])$. Measuring this attribute is of special interest for the study of the side effects resulting from a therapy based on electroshock.

Such a scenario generates information structured as follows:

1. For each i a set of quantitative or qualitative characteristics $X_1, .., X_K$ are available. This can be represented on a matrix, named X, where x_{ik} $i = \{1, .., n\}$, $k = \{1, .., K\}$ is the value taken by X_K for an individual i.
2. For each occurrence of E, a sequence of measurements of Y in all the fixed time points is obtained. Let E_{ij} $i = \{1..n\}$, $j = \{1..n_i\}$, be the j-th occurrence of the event E on the individual i. Hence, for a given individual i there exists a number n_i of occurrences of E. If time counting starts from 0 at each occurrence of E, it is possible to set $t_1..t_r$ as the time points where Y is going to be measured after the occurrence of E_{ij}. The measurements of Y generate a second data matrix named Y.

The attributes of interest are given by Y_r^{ij}, where $i = \{1..n\}$ is the individual, $j = \{1..n_i\}$ indicates the j-th occurrence of E to the individual i and $r = \{1..R\}$ indexes the instant, since the occurrence of E_{ij}, when Y was measured. It must be specified that *the measurement times points are the same* with respect to the occurrence time of all the events for all the individuals.

Once an i, j has been determined, the measurements of Y in the time period of $t_1..t_r$ (the rows of matrix Y) may be graphically represented by *very short curves (r is usually small)* apparently independent among them.

In fact, each individual is independent of the others. As a consequence, *the amount of events and the instant* at which they occur may differ from individual to individual with no other underlying pattern.

Nonetheless, all the events occurred on the same individual are affected by his/her characteristics, which causes all the series relative to a particular individual $\{Y_1^{ij}, .., Y_r^{ij}\}$, $j = \{1..n_i\}$ to receive this common influence from the individual.

Therefore, in the matrix Y, the individual i may be regarded as a *blocking factor*, defining packets of curves which are not independent among them at all. A block is, thus, constituted by all the series $\{Y_1^{ij}, .., Y_r^{ij}\}$, $j = \{1..n_i\}$ which follow any occurrence of E on the same individual. Those series are composed of a small set of measurements of a specific time period. However, the number of measurements is the same after each event and those measurements are equally distributed along time, considering the event occurrence as the starting time point. In particular, a set of *very short serial measures on time with a blocking factor* is going to be analyzed.

The purpose of this work is to find the characteristics of the individuals, among $X_1, .., X_K$ which are related to the temporal evolution of the attributes of interest Y. This is not a trivial situation, as it will be seen next.

For those features relative to the individual (represented by a single row of the matrix X), there exist several sequences of measurements of Y placed at random in the time line (represented in n_i rows of the matrix Y). So, first of all it is necessary to look for a way of manipulating the X and Y matrices together.

If there were a common pattern for occurrences of E in all the individuals, a single serie per each individual could be considered and it could be analyzed by means of the *intervention policy* from statistical time series field. This kind of situation would imply a too rigid hypothesis for a number of real situations that are trying to cover. For example, the electroshock therapy applied to a patient consists of a *variable* number of sessions that depend on each patient, and their distribution in time is decided according to medical criteria for each particular case (some patients receive one per month, others one per week. . .). The cadence of ES may not be constant throughout the treatment (it is common to increase the time between sessions as the patient gets better). For this reason, to face the problem assuming this hypothesis is not wished, and consequently resort to a classical temporal analysis it cannot be possible.

Indeed, such situations are not exceptional in the medical field, and they have been a subject of formal study in other fields. In the context of temporal series, a method commonly used in such cases is either the reduction of each block of series to a single series which summarize the whole set, either using the *mean* at every time point (*thick line*, see figure 1(b)), or the reduction of every series to small set of independent indicators such a *mean area* or a *mean tendency* per series [4]. This would allow the measurements of Y to be reduced to a single row for each individual, and the matrices X and Y would become compatible and would enable a classical analysis.

However, in a number of cases if the average series for each individual is built, *too much* relevant information will often be lose since variability depends both on each event and individual effect. Using such a transformation the conclusions get on the study may be very far from reality.

Regarding the real application which is working, a pertinent instance of the above comments is represented by figure 1(b).

> This figure shows lines joining the reaction times on a *simple visual test* (S5) measured at 2, 4, 6, 12 and 24 hours after every ES applied to the 4^{th} patient. This patient receives an ECT of 5 electroshocks and each curve represents his/her reaction-time evolution.
>
> As it could be seen in figure 1(b), building a unique prototype curve from mean reaction times (thick line) as a representation of the patient's evolution is not very correct, since variability due to ES is too high and too much relevant information will be lost. Also, differences in the patient's reaction of different ES would be lost if only a prototype line is considered for each patient. Nevertheless, this mean can give an idea of a patient's general evolution trend, which will be useful afterwords.
>
> In fact, there is a significant change from patient to patient curves, and from test to test. So, it is difficult to find a general pattern from specific patient curves.
>
> Furthermore, there is no standard quantity of ES to be applied to a patient. So, reducing patient's information to only one record in the database is not the proper way to proceed. Therefore there is an interest in maintaining all the curves of all the patients in the same database, but taking into account this *patient effect* for the analysis.

3.2 Goals

This work involves several goals at different levels:

1. Concerning the particular domain where this type of serial measurements is given: *Facilitate the study of this type of domains*, *determine a set of steps to be followed for analyzing domains with this type of structure*, and *obtain significant and easy-to-interpret results.*
2. Concerning methodology: *Establish a new methodology, which combines AI and statistics tools to solve the problem presented in §3.1*, and *obtain an explicit knowledge model as a formal description of the structure of the target domain.*

4 Methodology

Next, a first approach of the methodology is presented and it will be described, in section §5, on the basis of a certain experience with a concrete real application.

1. *Extraction of a baseline matrix from the serial measurements database.*
2. *Hierarchical clustering of the individuals using* Y_0*.*
3. *Use of attributes of individual features to interpret the classes obtained.*
4. *Rules induction from comparison between classes and individual features attributes.*
5. *Construction of a matrix of differences for measuring the effect of a given event occurrence.*
6. *Clustering Based on Rules of matrix D with knowledge base KB.*
7. *Interpretation of resulting classes.*

5 Analysis

According to the considerations exposed in §3.1, determining if there are different patterns on reaction time curves and its relationship with the characteristics of patients has great interest.

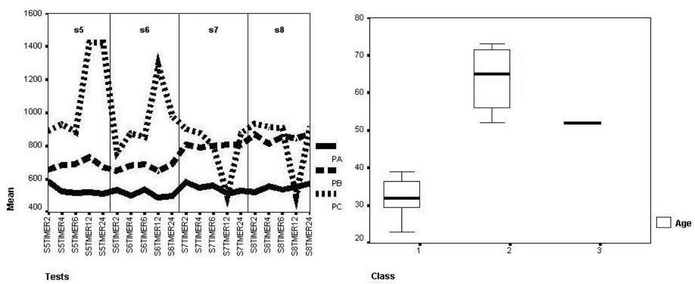
It has already been justified that matrices X and Y are not directly mergeable. So, the analysis will be done by the steps presented in §4.

5.1 Extraction of Y_0 from matrix Y

The first step consists on doing the extraction of the baseline reaction times matrix Y_0 from matrix Y. This new matrix Y_0 will contain the data which determine initial conditions of patients before ECT begins (a priori patterns for each patient). These data, corresponding to reaction times taken before for each psychophysiological tests (S5-S8) and each patient.

5.2 Hierarchical clustering of patients using Y_0

A *hierarchical method* (see [6]), was used to carry out the clustering of matrix Y_0. The results are 3 classes: *Class A (c5)*={patients: 1,3,6,7 and 13}, *Class B (c8)*={patients: 2,5,8,10,11 and 12}, and *Class C (P04)*={4^{th} patient} (more details in [5]. In figure 2(a), a representation—using mean curves—of the general evolution of baseline reaction times for every test (S5-S8) in each class throughout a 24-hour period previous ECT can be found. Each curve in the figure is composed by the mean values calculated from all the patients in the same class and test.



(a) (b)

Fig. 2. (a) Three classes curves for tests S5 to S8; (b) multiple Box-plot of Age.

A particular curve (class C) which contains a single patient it can be seen in figure 2(a). It was verified that the 4^{th} patient reacted in a particular way due to a drug provided to him/her just before initiating the baseline tests. On the other hand, as a general trend, a regular response in class A can be seen and the reaction times have (in general) the same level for all the tests. The reaction times of class B show a small increment with respect of those in class A for test S5 and S6 (the simple ones), but an important increment of time is shown in complex tests S7 and S8.

5.3 Use of matrix X to interpret the classes obtained before

Some attributes of matrix X are analyzed looking for those that discriminate the classes. They are used to illustrate the interpretation of classes and to obtain particular features from them. The *multiple boxplots* [8] for each *illustrative* attribute *versus* the 3 classes were carried out.

Studying these attributes, it is remarkable the behaviour of one of them the *age*, which is shown in figure 2(b). In agreement with both advice of the expert and this figure, it was concluded that the attribute *age* has an important influence in the baseline curves behaviour. As it can be seen, class A has *all* the baselines of young patients (down to 40 years old), class B has the baselines of patients over 50 years old. Class C has only the baselines of 4^{th} patient. The expert decided to omit Class C after confirming his/her singular behaviour. Therefore, taking this into consideration, there are 2 groups of patients described by: (1) *young patients with lower and more regular baselines reaction times for all the tests (S5-S8)*, and (2) *mature patients with higher baselines reaction times, in particular, with very greater times in complex tests (S7 and S8)than in single ones (S5 and S6).*

5.4 Rules induction

Two simple logical rules that make a clear description of groups A and B mentioned in the last step were obtained:

$$KB = \begin{cases} \text{If AGE} \leq 40 \rightarrow \text{class A (Baselines of young patients)} \\ \text{If AGE} > 50 \rightarrow \text{class B (Baselines of mature patients)} \end{cases}$$

From this result, it was decided to include this information for posterior analysis, performing separate processes for young and mature patients.

5.5 Construction of a differences matrix *D*

The serial measurements over time are repeated for each patient after every ES and no independence among them can be supposed, since there are groups of series belonging to the same patient. Therefore, the study of the ECT effects should be analyzed through the comparison on the reaction times of each patient *before* and *after* a given ECT. To do this, a new database was built containing the differences between the *before* and *after* reaction times of a given electroshock hour to hour. This new database matrix D was used because its data measures the *effect* of every electroshock by itself independently of the characteristics of the patient (this is one of the ways commented in §3.1 for dealing with a blocking factor).

5.6 Clustering Based on Rules of matrix *D*

ClBR is a methodology particularly useful for *ill-structured domains*. The main advantage of this methodology is the possibility of management of an incomplete knowledge base and a clustering method to work together. Like most *KDD* processes, it combines prior knowledge from the expert with an automatic clustering method. It is an iterative and interactive process, structured in two major phases which finally organize the single set of objects into a set of classes that are presumed to be interpretable (more details and advantages in [3]).

KLASS+. It is an autonomous clustering tool oriented to ill-structured domains, that implements *clustering based on rules* method for finding the structure of a dataset (more details about KLASS+ in [3]).

Application of clustering based on rules to Matrix D. Basically, two local clustering processes were performed: one for young patients' ECT, and the other for mature patients' ECT. Both hierarchies were afterwords integrated together and a single partition of the ES can be found. The analysis gives 4 classes (figure 3): two (cy50 and cy48) for the group of young people and two (cm33 and cm31) for the mature one.

5.7 Interpretation of resulting classes

Figure 3 represents the general trend of any class about the electroshock effect on reaction times for the tests S5-S8. Each curve represents a class and it is obtained building the average of all the curves that are in that class. It can be seen that in classes cy48 and cm33, the effect of every electroshock is increasing the reaction times; in general terms it can be set, that, the ES—in these classes—produce a deterioration on the patients (decreasing their reaction capability). On the other hand, in classes cy50 and cm31, the reaction times decrease and differences between after and before are negative; thus the ES in these classes produce a positive evolution on the patients.

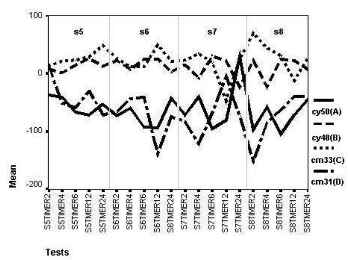


Fig. 3. Four class curves for tests S5 to S8.

6 Results

To do this work, two databases were used. The first one relative to patients' data and the last one relative to reaction times after an ES application (matrix Y).

An analysis in two steps was made: (1) *Baseline reaction times classification.* The baseline reaction times were analyzed because these times represent the patients' initial conditions. Two rules were derived from this analysis and the groups of young and mature patients were delimited by them. (2) *Clustering Based on Rules of reaction times differences.* This method—using Klass+—was applied, using as a Knowledge-Base the results of the previous analysis. The differences between reaction time were used because they measure the *effect* of the electroshock by itself, independently of the characteristics of the patient. This study showed us the patients' evolution after each ES throughout a therapy period. For the present application it can be seen that this methodology can improve the quality of the results, even when a small set of very simple rules is used. In this case, interpretability of classes improved on combining the knowledge base with the clustering process. On the other hand, any single cluster technique could never incorporate age as a clustering criterion in reaction time analysis. For more information about the results mentioned before see [6, 5].

7 Conclusion and Future Work

Based on the real life application mentioned before, the KDSM methodology was designed. It allows to discover new knowledge using series of periodically repeated measurements on a set of individuals (patients).

Application of KDSM to the measurements on ECT provided very satisfactory results, from a *psychiatric* point of view. It has been seen that the curves of RT on each patient, are not inherent to the patient, neither to the global observation of all the therapy. On the contrary, every patient may react in a different way in each ES session. In view of these results, experts think that this is due to some causes either external or internal to the patient but which can be or not present in each ES session. For the moment, these causes are not well identified, though there already are some hypotheses with which the psychiatrists are starting to work with. This is clearly new knowledge in the area of psychiatry that has modified the way how research is carried out in this field. This works are in progress at present.

With the obtained results it is admitted to say that it is possible to efficiently handle this kind of information by our KDSM methodology—presented in §4—which combines several AI and Statistics tools which has allowed the identification of knowledge which is novel, useful and relevant in the area of the application, according to the classic requirements of KDD [2].

As a future work, it is interesting to see the kind of relation between others patients' variables and the last classification. The next step will be the establishment of a definitive methodology for solving the problem formulated in §3.1.

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