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KNOWLEDGE EXTRACTION IN CLINICAL DATA

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Abstract

The introduction of electronic health records in clinical health care facilities lead to an exponential growth of clinical and medical data. Different projects are supporting the collection, management, integration, and analysis of clinical patients information.

In this work we focus on clinical data analysis with data mining disciplines, which are able to treat heterogeneous, noisy, and often incomplete data sets, as the ones in the clinical domain, using advanced computer science and statistics techniques. To extract valuable knowledge in order to get insights of various diseases is a major goal in clinical data analysis. Therefore, the focus of this work is on disease characteristic trials extraction with feature selection methods, and human understandable classification models extraction. An analysis workflow, composed of following steps is proposed: data collection and integration, preprocessing, outliers detection, missing values treatment, noise reduction, discretization, feature selection, model extraction, classification, and evaluation.

This workflow is applied on a real clinical data set from demented patients using different state of the art data mining systems, which are tested on trials extraction and samples classification. The particular type of ruled based classification is investigated as valid technique for aiding the clinical domain expert for formulating a diagnosis.

1. Introduction

Automatic knowledge extraction methods and tools are sound candidates to support medical doctors and scientist in the analysis of currently growing clinical patient data sets. The field of data mining, a discipline that comprises computer science, statistics, and artificial intelligence, is the right choice for dealing with this complex task. When analyzing clinical data sets, a supervised data mining methodology, i.e. classification, is suggested, as the considered patient samples are often previously assigned to a specific class or type by medical doctors [1], e.g. healthy and diseased. The focus in this work is therefore on supervised data mining (classification). Classification is the action of assigning an unknown object into a predefined class after examining its characteristics [2]. A great advantage is also to compute a clear human interpretable classification model which fits the data, e.g. "if-then rules" (for example *if HachinskiScore > 4 then the patient sample is healthy*). The classification model can be a valid aid for the medical doctors and investigators to extract the trials associated to a disease and to formulate a diagnosis for new patients. The field of clinical data mining spread in late nineties with the beginning of electronic patient health records collection [3]. The analysis of growing clinical patient data required efficient and effective methods. The authors in [1] provide a comprehensive review of clinical data mining by summarizing 84 papers in this domain. They highlight following main goals of this discipline:

- data understanding;
- healthcare professionals decision support, and
- definition of a methodology for medical data analysis.

In [4], an extended review of clinical data mining is provided, and supervised data mining (classification) is cited as the main technique for analyzing clinical patient sets. They describe a framework for constructing, assessing and exploiting data mining models in clinical medicine. The authors of [5] illustrate the high growth of clinical data and the major issues in clinical data sets: inaccuracy, complexity and frequent missing values. Other common problems in clinical data are:

- diverse trials (variables) names for same trials in different data sets;
- different adopted scales of the trials (also in the same data set);
- outliers coming from wrong measures;
- mixed (numeric - textual) variables types, e.g. some medical doctor rate the value of Blood Urea Nitrogen (BUN) with numbers and some others with words (low, normal, high); when integrating the trial, mixed type variables, like BUN = {12, 16, high, 9, 11, ...}, may be found.

In this work, methods to pre-process and classify clinical data are reported and a complete knowledge discovery process with different data mining algorithms on Italian demented clinical patients samples collected in diverse health care facilities is provided as an example to the reader. The paper is structured in the following way. The section *Methods* describes a complete automatic knowledge discovery process on clinical data, composed of following steps:

- data collection;
- data integration;
- data analysis.

The data analysis steps comprises preprocessing, missing values treatments, noise reduction, discretization, feature selection, classification, and model extraction. The section *Results and Discussion* provides to the reader a real world example of a knowledge discovery process

(data set collection, preprocessing, feature selection, classification and model extraction) applied to a clinical data set of demented patient collected in different Italian health care structures. The work ends with the *Conclusions*, where a reasoning towards a computer aided diagnosis with an intelligent decision support system for clinical data patient trials sample analysis is performed.

2. Methods

This section provides to the reader a clinical data analysis knowledge discovery process. The flow chart in figure 1 draws the clinical data mining process [30].
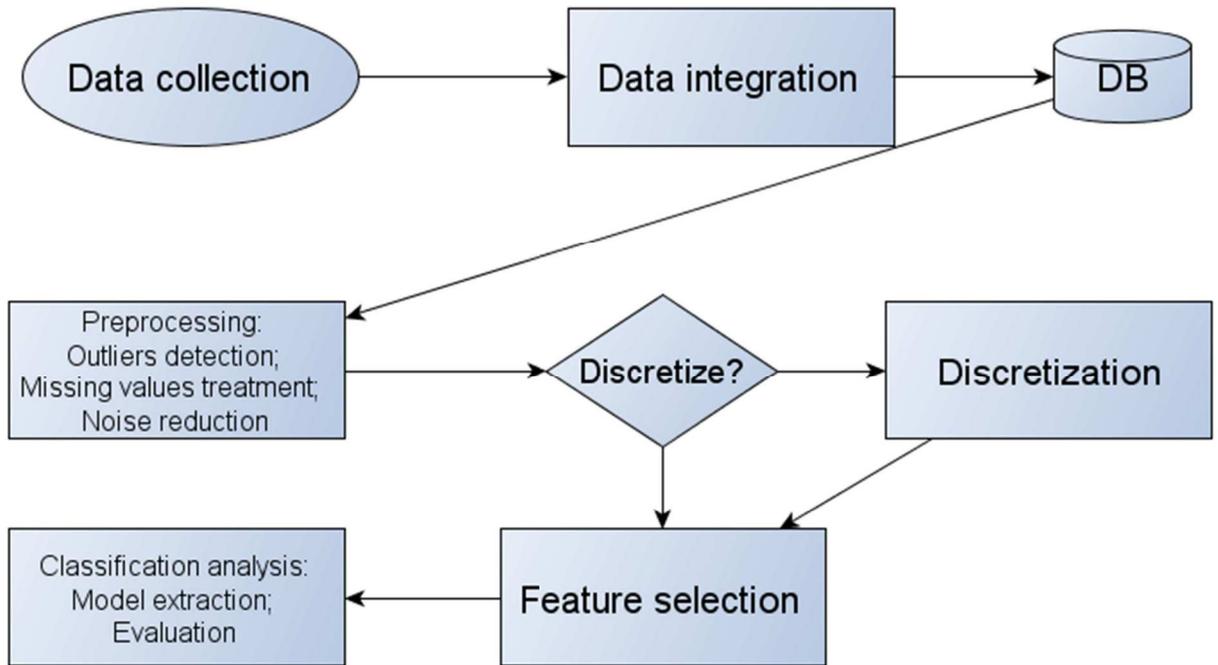

Fig. 1 Flow chart of the clinical data mining process

A clinical data set is composed of a number of patient samples (records) each one associated with its trials (variables). These data can be represented as in a matrix depicted in table I.

TABLE I CLINICAL DATA MATRIX

Patient	Patient$_1$	…	Patient$_n$
Class	Healthy	…	Diseased
trial$_1$	value$_{(1,1)}$	…	value$_{(1,n)}$
trial$_2$	value$_{(2,1)}$	…	value$_{(2,n)}$
…	…	…	…
trial$_n$	value$_{(n,1)}$	…	value$_{(n,n)}$

A. Data collection and integration

The first step in a clinical data mining study is the collection of the different electronic health patient records from the considered sources, e.g. hospitals, ambulatories, labs, etc. The data set is frequently composed from disparate health care facilities by non IT staff. The trials

5

values and names are inserted manually in spreadsheets or copied from hard copy archives. Often the IT systems (if available) are not integrated and every health care facility uses his own data format. Clinical data sets are therefore very noisy, missing values and outliers are frequent due to wrong measures and mixed variables types (textual - numeric). The integration of this data is very challenging, but is often necessary for the analysis of a representative patient set associated to a disease in order to perform a valuable knowledge extraction. A common integration technique is to join all the patient records on common trials names, considering all the non-common trials as complementary. A problem may occur when the trials names are different in the diverse sets. This problem may be solved with the creation of ontologies or trials names standardization, see for example the "Logical Observation Identifiers Names and Codes (LOINC): a universal code system for identifying laboratory and clinical observations" (http://loinc.org) and the Health Level Seven International organization (http://www.hl7.org). Last but not least in the clinical data domain the privacy issues are very important to respect. The patient confidential information, as names, has not to be shared among the analysts. So a private numeric identifier has to be assigned to the patient by the source structure and be stored in a non-accessible encrypted data base. The quality of data collection is a necessary, but not sufficient condition, for good analysis results. It is therefore suggested to plan and invest heavily on these steps, e.g. with integrated IT systems and adequate training for medical staff.

B. Data analysis: Preprocessing and missing values

Cleaning the clinical data with an adequate preprocessing step is always necessary when dealing with multiple sources. The knowledge extraction is aided by this important step. The investigator could start to apply the classical statistical measures on every trial present in the data set, e.g. mean, standard deviation, minimum, maximum, number of missing values, modal value and attribute type. According to these measures the analyst is able to filter the trials that present high noise. It is recommended:

- to exclude the trials with a high number of missing values, e.g. more than 20%;
- to fill the remaining missing values with the class mean [7];
- to detect the outliers by mean - standard deviation - minimum - maximum values analysis and records removal;
- to correct the mixed attributes types.

Alternative methods for processing the missing values are reported in [6]. The methods are frequently tailored in replacing them with statistical artifacts:

- most common attribute value;
- assignment of all possible attribute values;
- removal of records with unknown attribute values;
- event-covering method;
- insertion of special values.

The authors in [7] suggest to fill the missing values of numeric variables (trials) with the class mean and of categorical with the modal value. The investigator needs to implement ad-hoc preprocessing programs and procedures fitted on the analyzed clinical data.

C. Data analysis: Discretization

The discretization is suggested by the presence of data of mixed nature (numerical, categorical, logical) or by the presence of numerical variables, when using tree based or logic based classification algorithms. Discretization is a procedure that converts numeric variables in categorical by the definition of intervals. The discretization step determines a number of

cutpoints in the range of values of the considered variable and defines a set of intervals in which the variable can be. Clinical data sets are often large matrices of real and integer values, which represent the patients trials measures. These data is often not optimally accepted as input by some classification algorithms, like logic data mining and trees, and a conversion in the discrete domain is necessary to improve their performance. A binarization is suggested, i.e. transform the data set composed of real numbers in binary. Define cutpoints for each variable by intervals identification and convert it into a new discrete one. Apply then a binary conversion of the variables in order to let the data be treatable in a logic framework. Following methods are suggested for applying a discretization and binarization of the data: [8] and [9]. Other effective approaches are available on www.keel.es. Also the well-known data mining software Weka [10] provides a large collection of discretization procedures.

D. Data analysis: Noise reduction

After the preprocessing phase (II-B), that provides a major cleaning of the data, advanced noise reduction techniques could be necessary in very noisy clinical data sets. An effective noise reduction technique in logic frameworks is described in [11], where a logic data mining software is enriched with special cleaning procedures. These procedures operate at discretization (II-C), feature selection (II-E), and classification model extraction (II-F) levels. In addition, the authors in [12] provide an extensive list of noise removal techniques.

E. Data analysis: Feature selection

Feature selection aims at selecting the candidate variables (trials) that are able to distinguish the different classes in the data set. Another main goal is the reduction of the data by filtering out the irrelevant and redundant variables, and by extracting only high informative ones. These variables are then considered as input to the real knowledge extraction algorithm, that is so able to work better, faster and effectively [13]. The classification problem becomes tractable and only informative variables are considered to extract the model. The authors of [14], [15], [16] and [17] provide a comprehensive review of feature selection algorithms and describe the main computational steps. The importance of feature selection in clinical domains is highlighted, as the data sets are often composed by a large number of trials (100 - 1000) associated to every patient sample that belongs to a given class.

F. Data analysis: Classification

Classification is the action of assigning an unknown object into a predefined class after examining its characteristics [2]. The classical example from medicine is distinguishing diseased patients from healthy ones. Automatic classification is known as supervised learning: Unknown objects are automatically assigned to a class by analyzing their attributes (variables, trials) using a classification model computed from objects with a known class (training set). Each object is a record of the data set and is composed by a tuple $(\mathbf{x}, c)$, where x is the attribute set and c is the class. A formulation of the classification problem is reported in [7]. Given t objects $\{x_1, \ldots, x_t\}$ whose class is known, build a function and use it to classify new objects, whose class is unknown. This function is called also classifier and is defined as c' : R^n → {1, ..., m}.. The goal is to have c'(x) = c(x) and for each x, the predicted class should be the correct class. A classification function is learned from (or fitted to) a training data and applied to a test data. This process is called supervised learning. Systematic approaches able to build a classification model by analyzing the training set are called classification methods. Currently many classification methods are present in the literature; the most suited for clinical data mining are the following:

1) *Support Vector Machines*: Support Vector Machines (SVM) [18], [19] have high classification performance when classifying data sets composed of numeric variables. The

classification task is considered a two class distinction problem (in case of more classes a one class versus all the other approach is performed) and the two classes are represented in two n dimensional vectors. The Support Vector Machine builds the best separating hyperplane, which maximizes the margin (defined as the minimum distance between the hyperplane and the closest point in each class) between the two vectors. The main feature of this method is its ability to efficiently project the data into a higher dimension with very rich non-linear transformations. SVM generally perform very well on clinical patient trials data, as the most attributes are numeric. The main disadvantage is that no clear and human interpretable classification model is given as output to the analyst and so no real knowledge is transmitted.

2) *Nearest Neighbor classifiers*: Nearest Neighbor classifiers are classifiers that consider the closest similarity between the unknown object in the test set and the training set and perform so the class assignment. To compute the similarity they often use Euclidean distance. Given a training set with known class object, a new object is assigned to a class by computing the closest neighbors of the training set. Also in this case, no real descriptive model of the data is computed and only the classification assignments are provided to the analyst.

3) *Classification Trees*: Classification trees (or decision trees) are mathematical structures composed of nodes and edges. Each node represents a predicate, associated to the objects in the data set, each edge a binary decision. The class labels are on the leaves of the trees. A path from the root to the leave is a set of decision on the objects values that leads to a classification of an object. One of the best performing classification tree method is C4.5 [21], as it is based on the minimization of the class entropy between each node. Classification trees provide a clear human interpretable model that is extracted by following the paths from the root to each leaves (classes).

4) *Logic Data Mining*: Logic Data Mining is often referred to as rule based classification or classification with logic formulas. The characteristic of this method is the extraction of logic formulas ("if-then rules") in disjunctive or conjunctive normal form as classification model. The logic rules are evaluated on the objects to perform classification. The most powerful methods for logic data mining are DMB [14], [24], RIPPER [22], LSQUARE [23], LAD [25], RIDOR [26], and PART [27]. The evident advantage of rule based classification is the data model, in terms of logic formulas, that is compact and human interpretable. This last fact is very valuable in clinical data mining, as a human interpretable classification model could aid the medical doctor to identify the trials values that are characteristic for a certain disease.

3. Results and discussion

The following section provides to the reader a real case of clinical data mining. A collection of classification algorithms and methods are used to process an integrated data set of patient records trials. These trials are in different formats and type (real, integer, binary, categorical). Final goals of the experimentation is to define a work-flow and to extract a diagnostic model for the identification of dementia. The model should ideally be human interpretable and able to distinguish successfully the various classes of patients present in the data set. A new diagnostic model, in terms of logic classification formulas, is found by analyzing the patients clinical variables of following classes: *Demented, Depressed, Mild Cognitive Impairment (MCI), Psicotic, Uncertain and Control.*

A. The data set

More than 4,000 patients' psychometric and blood tests, imaging and other clinical data collected in several Geriatrics and Alzheimer's departments in Italy [28] compose the data set. The data is collected in the framework of the ReGAl project in 36 health-care facilities from Italy under supervision of Perugia University. Every facility had its own collection procedures and formats and a prior quality control is performed on a central unity. The data set comprises demographic characteristics, medical history, pharmacological treatments, clinical and neurological examination, psychometric tests, laboratory blood tests, imaging (MRI and CT). The total number of patients is 4,728 each one with 722 trials (variables).

Approximately 30% of missing values are present in the trials. 367 numeric, 318 ordinal and 37 of mixed type variables (attributes, trials) are present. The variables represent demographic characteristics, medical history, pharmacological treatments, clinical and neurological examination, psychometric tests, laboratory blood tests, imaging and various other clinical patient trials. Six different classes are assigned to the patients by domain expert medical doctors: *Demented, Depressed, Mild Cognitive Impairment (MCI), Control, Psicotic and Uncertain.* Table II provides a summary of the data set composition and distribution [30].

TABLE IIIII THE DATA SET

class	# of patients	# of trials	% missing val
Demented	3110	722	29.45
Depressed	375	722	37.13
MCI	406	722	25.07
Control	365	722	30.41
Psicotic	49	722	31.77
Uncertain	423	722	31.48
Total	4728	722	30.88

B.   The data mining analysis

Several data mining methods and systems are considered for analyzing the previously described clinical data set in order to extract disease characteristic variables and ad-hoc classification models. A supervised classification approach is adopted, as the classes of the patients are present in the data set provided by an accurate diagnosis from domain expert medical doctors. This data forms the training set. Considering the training set the data mining methods select candidate variables for patient distinction (feature selection) and, based on these, compute the classification model. This model is then evaluated on the test set that may be composed of object with unknown class or object of known class, the latter is used for verification of the classification performances of the model.

1) *Preprocessing phase*: All the preprocessing procedure described in section II-B are implemented in scripts and software to effectively clean the data set. The variables that present a missing values ratio greater than 20% are discarded, the rest of missing values are filled with the class mean (or modal value in case of categorical variables), and the outliers are detected and removed. Special noise reduction procedures, like [11], are additionally adopted when using the DMB data mining system.

2) *Feature selection phase*: Feature selection present in the DMB system and described in [14] is performed in order to extract the characteristic clinical trials for every disease state present in the data set. DMB feature selection detects following representative features [30] for the disease classes drawn in figure 2. These variables are confirmed by multiple runs of the feature selection step by repetitively changing the random sampling sets of the data (80%).

Variables that discriminate between one class form the others			
Normal	**MCI**	**Dementia**	**Depression**
Albumin	Albumin	Albumin	Babcock_1
Anxiety_symptoms	Anxiety_symptoms	Babcock_1	CIRS_cognitive_psychiatric
Azotemia	Azotemia	CIRS_cognitive_psychiatric	CIRS_hypertension_artery
Babcock_1	Babcock_1	CIRS_hypertension_artery	CIRS_skeletal_muscle
CIRS_cognitive_psychiatric	CIRS_cognitive_psychiatric	CIRS_skeletal_muscle	Copy_drawing_corrected
CIRS_hypertension_artery	CIRS_hypertension_artery	Copy_drawing_corrected	Delayed_Recall_corrected
Copy_drawing_corrected	Copy_drawing_corrected		Diffused_hypodensity_CT
Cortical_CT	Cortical_CT	Frontal_horn_hypodensity_CT	FAS
Delayed_Recall_corrected	Delayed_Recall_corrected	How_lives_alone_not	How_lives_alone_not
ECG_patological	ECG_patological	How_long_Stop_drink	How_long_drink
How_lives_alone_not	How_lives_alone_not	IADL_Total	IADL_Total
IADL_Total	How_long_drink	MMSE_Total	Main_job
Main_job	IADL_Total	NPI_Depression	Marital_status
NPI_Depression	Main_job	Years_education	MMSE_Total
Token_test	NPI_Depression		NPI_Depression
	Token_test		Son_daughter_living
			Token_test

Fig. 2 Characterizing features for every disease

3) *Model extraction phase*: Final goal of the data mining analysis is to compute a reliable classification model of the patients, that is able to distinguish the various disease states present in the considered clinical data set. The model should contain the characteristic variables for each class of the patient samples. In noisy data sets this is a hard task and the model creation is more challenging. A relatively small number of variables is used to build the classification model. The patients belonging to the Demented class are the most easy to classify, Control patients are more difficult and classification is more time consuming and complex with MCI and Depressed subjects. Uncertainty in MCI and Depressed classes is due to different facts: loose criteria to define the MCI disease, compared to Dementia one; overlapping value intervals for similar variables in the MCI and Depressed classes [28]. Ruled based classifiers (RIPPER and DMB), classification trees (C4.5), classification functions (SVMs) and nearest neighbor classifiers (KNN) are considered and applied to classify the previously described clinical data set. Table III shows the classification accuracy of the different data mining methods [30] tested with 10-fold cross validation [7].

TABLE IVII CLASSIFICATION RESULTS IN %

method	settings	correct %	discretization	model
DMB	no settings	87.36	yes	yes
RIPPER	opt. run = 10	86.86	no	yes
C4.5	unpruned, minobj = 2	88.49	no	yes
SVM	polykernel = 1	90.31	yes	no
KNN	k = 1	78.27	yes	no

The results show that the systems were able to classify the data with a reasonable accuracy. The preprocessing steps play a key role in this process: without them the classification performances are very low (in the range of 60% of accuracy) and no clear classification model and patient distinction can be performed. When using SVN and KNN as classification

algorithms a discretization of the data is performed with the method of Fayyad et al. [29], these improves the correct classification rate in the range of 10%. When analyzing the classification accuracy of the methods it can be seen that SVM performs best, but, as stated before, it is not able to provide a human interpretable model to the investigator. DMB, RIPPER (logic data mining) and C4.5 (classification tree) have a slightly inferior accuracy, but output a classification model in terms of logic classification formulas. The model is a collection of "if-then rules", which consider a subset of clinical variables, that identify each class in the data. Figure 3 shows an example of classification model for the Mild Cognitive Impairment (MCI) state [30].

```
(MMSE_Totale >= 24) and (IADL_Punteggio_2 >= 16) and (Dilatazione_SottoCorticale_AtrofiaTAC <= 0) and
(Fluidita_Verbale_Categorie_Corretto >= 12.25) and (etaprecisa >= 73.08) OR \\
(MMSE_Totale >= 24) and (IADL_Farmaci_1 >= 1) and (Hachinski_Score >= 4) and
(Fluidita_Verbale_Categorie_Corretto <= 10) and (Corni_Frontali_IpodensitaTAC <= 0) OR \\
(MMSE_Totale_Rettificato >= 22.5) and (Matrici_Corretto >= 34) and (Assurdita_Test_Verbali <= 13) and
(GB >= 4.9) OR \\
(MMSE_Totale_Rettificato >= 23.200001) and (IADL_Farmaci_1 >= 1) and
(Dati_Test_Base_Valutazione_Disturbi_ID_Utente <= 3) and (regione <= 6) and (Forgetting >= 4) OR \\
(MMSE_Totale_Rettificato >= 22) and (IADL_Spostamenti_2 >= 4) and (Depressione_Psichiatrico <= 0) and
(regione <= 2) and (CIRS_Comorbilita_Complessa >= 1) OR \\
(MMSE_Totale >= 23) and (Token_Test_Corretto >= 30) and (Raven_Test_Corretto >= 215) and
(Familiarita_Demenza <= 0) and (Richiamo_Immediato_Corretto <= 34) and (CIRS_Vascolare_Linfatico <= 1)
```

Fig. 3 Example of MCI classification model

With supervised classification methods, that provide a human interpretable model, the clinicians are able to highlight the characteristic variables for each disease present in the data set and to aid the medical doctors in a diagnosis - a potential new faster and cheaper diagnostic work-flow.

4. Conclusions

This work delineated the main guidelines for a clinical data analysis, focusing on the particular data mining application of classification. Classifying patient samples collected in different health-care facilities is a challenging task, that may be solved with ad-hoc data processing programs and consolidated supervised machine learning methods. These methods have been extensively described providing a possible work-flow for clinical data analysis. A full and automatic knowledge discovery process was performed on a large data set of real clinical data collected in Italy. With a robust preprocessing and cleaning, reliable classification results and models have been achieved, providing to medical doctors and clinicians new insights of the different diseases present in the data set. These models could finally aid the medical staff to accelerate the diagnosis process (by analyzing only the individuated trials) and to formulate the diagnosis more effectively.

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