Machine learning for medical applications

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Abstract. Machine learning has been well applied and recognized as an effective tool to handle a wide range of real situations, including medical applications. In this scenario, it can help to alleviate problems typically suffered by researchers in this field, such as saving time for practitioners and providing unbiased results. This tutorial is concerned with the use of machine learning techniques to solve different medical problems. We provide a survey of recent methods developed or applied to this context, together with a review of novel contributions to the ESANN 2016 special session on Machine learning for medical applications.

1   Introduction

Machine learning (ML) has been an active research area in the last decades finding success in many different applications, among them in medical problems. ML is capable of automating manual processes carried out by practitioners, which are usually time-consuming and subjective. Therefore, the use of machine learning can save time for practitioners and provide unbiased, repeatable results. Additionally, the large dimensionality of data in medicine together with the common reduced sample size of pathological cases makes indispensable the use of advanced machine learning techniques for clinical interpretation and analysis.

The detection and interpretation of pathological conditions usually require a large of number of experts available, desirably showing a broad experience in the topic. However, the number of experts is sometimes not enough, and other problems may appear such as disagreement among experts [1]. Therefore, in a field which requires human experts with a high level of expertise and able to maintain a high degree of concentration —and even so, it is very prone

to errors—, machine learning techniques can help improve diagnostic accuracy and standardization among clinicians, and for development of computer-based decision support tools that model expert behavior.

Moreover, with the recent advent of Big Data, the explosion in data available for analysis is as evident in healthcare as anywhere else. Private and public insurers, healthcare providers, particularly hospitals, physician groups and laboratories, and government agencies are able to generate far more digital information than ever before. In such a situation, the research community can take advantage of machine learning techniques and their ability to tackle millions of examples at a time, as well as helping in other issues such as human interpretability, lack of data availability, or unbalanced data.

Machine learning comprises a wide set of techniques that can be helpful in medical applications. *Classification* is perhaps the most famous one, since it corresponds to a task that occurs frequently in everyday life. For example, when having to classify medical patients into suffering a certain illness, or risk of acquiring it. Popular classification techniques usually applied in medical problems are neural networks, support vector machines, decision trees or Bayesian learners, among others. Classification can be also viewed as one form of prediction, with the restriction that the value to be predicted is a discrete class. However, there are situations in which the goal is to provide a numerical prediction, which is known as *regression*. Another popular category of machine learning is called *clustering*, which consists in examining the available data to find groups of examples that are similar in some way. Since these groups are not known beforehand, it is considered an unsupervised task, useful when we do not know a priori the different types of patients that we are dealing with, for instance. Other ML techniques that are gaining increasing attention in the last few years by the medical community are those related with *dimensionality reduction*. This kind of techniques are useful to find the important characteristics of the patients, or in the classification of the so-called DNA microarray data, in which it has been demonstrated that most genes measured in a DNA microarray experiment are not relevant for an accurate classification among different classes of the problem. Dimensionality reduction techniques soon became indispensable, not only to remove redundant of irrelevant features, but also to help biologists identify the underlying mechanism that relates gene expression to diseases.

2   The need for machine learning in medical applications

Machine learning is an area of Artificial Intelligence that appears from the evolution of pattern recognition, probability theory, optimization and statistics, and whose purpose is allowing computer programs to learn from data, building a model to recognize common patterns, devise data-driven predictions and being able to take knowing, smart decisions based on these. Learning from data encircles certain difficulties, since data sets are frequently characterized by [2]:

- Incompleteness, as frequently there are missing values.

- Incorrectness, most of the times there is random or even systematic noise in the data, perhaps due to sensor errors.

- Inexactness, because sometimes the selection of parameters is not adequate or complete for a certain task, or redundant data is present.

- Sparseness, as there might be very few or non-representable patient records available.

All these problems are quite common in medical applications, requiring from machine learning adequate tools for researchers to fight them. A variety of these techniques, including artificial neural networks, Bayesian networks, support vector machines, and decision trees, have been widely applied to the development of diagnostic and predictive models, resulting in effective and accurate decision making tools. Besides these characteristics of medical datasets, and more acutely during the last years, there has been a dramatic increase in medical data being collected, due to new detection methods, new techniques and new diagnostic modalities being developed. This fact adds complexity to the already complicated, high-dimensional and heterogeneous data types and systems to be analyzed by the clinicians, giving rise to an even greater potential impact and need of machine learning in the field, as analytical solutions are impossible, and human-generated, rule-based heuristics intractable. For this reasons, diagnostic, prognostic and clustering approaches have been constantly appearing during the last years in different medical areas [3, 4, 5].

Another important aspect is related with the preparation of medical data. Data samples are the basic food for machine learning methods. Each sample is described by several features, each one of this consisting of different types of values. It is advisable to have information about the specific type of data being used, as this will allow for the selection of adequate tools and techniques for the analysis. As said above, the quality of the data is an important issue, and draw the preprocessing techniques [6] that perhaps should be used (as it is the case in most medical applications) in order to facilitate or even make it possible the application of ML techniques. Some data quality issues are mentioned before (noise, outliers, missing or duplicate data, etc.), for which several preprocessing techniques are available. Furthermore, in medical applications is well-known the need for dimensionality reduction, as some datasets have unmanageable high input dimension for ML algorithms, such as the case of microarrays or genetic datasets previously mentioned. From these reduction methods, specifically feature selection and feature extraction techniques are the most common in medical applications. If preprocessing is needed in ML in medicine, as the data is frequently noisy, incomplete, etc., there is even more gaining reducing dimensionality when the datasets have a large number of features [7], as it is the case in many clinical applications. Besides, feature selection can eliminate irrelevant features, reduce noise and frequently achieves more robust learning models due to the involvement of fewer features. Many applications of dimensionality reduction techniques can be found in the medical area, specifically some of them are presented in this special session [8, 9, 10, 11].

The use of machine learning techniques in the clinical field constitutes a crucial step in a growing trend towards more personalized, predictive medicine. At a more fundamental level, it is also evident that machine learning can also help to improve our basic understanding of the mechanisms under the development of several sickness and disorders. A successful implementation of machine learning techniques can greatly avail integration of more sophisticated computer-based systems in healthcare, an important area not only technologically but also socially, as during the last years healthcare costs have constantly increased, professionals and practitioners are overloaded with patients and also with new knowledge and techniques that should be trained, governments are increasingly relying on private healthcare companies, and thus crescent numbers of citizens are excluded from healthcare systems. Machine learning might be, why not, a new way that permits the reduction of health costs while increasing the quality of assistance to an exhausted healthcare system, paving the way ironically for a more humanized medical care.

3 Recent contributions

Machine learning has been an active research area finding success in many different medical problems, as can be found in the literature [12, 13, 14]. Proof of this are the recent advances in this field, which allow to automatize manual processes carried out by practitioners, saving time for them and providing unbiased results. A brief review on the recent contributions is subsequently presented, according to the set of techniques mentioned in the Introduction: classification, regression, clustering, and dimensionality reduction.

Classification problems are very common in medicine, in order to detect or diagnose a disease, or even to determine its severity. In this context, different classical machine learning algorithms have been considered, including for example random forests for the classification of Alzheimer's disease [15], support vector machines (SVM) for glaucoma screening [16], or the well-known k-nearest neighbor (kNN) classifier for retinal hemorrhage detection in fundus images [17]. Additionally, new learning techniques have been specifically developed to solve different clinical problems. Among them, the path-adaptive sparse approximation (PASA) method [18] was designed to classify lung images into one of the five tissue categories, or new learning-based techniques were presented in [19] to measure disease progression in patients with multiple sclerosis.

Classification techniques have been used not only to support the diagnosis of different diseases, but also to analyze clinical information in the form of text or reports. For example, a novel regular expression discovery (RED) algorithm was presented in [20] to classify regular expressions used in clinical environments, or a novel framework was proposed in [21] to automatically capture relations from narrative text included in pathology reports.

When the goal is to provide numeral prediction, instead of discrete classes, regression techniques are used. Adaptive kernel regression was used, for example, to the definition of a spatiotemporal atlas of the brain [22], whilst regression

forests were applied to the detection and localization of anatomical structures in computer tomography (CT) scans [23]. Another example is the automatic segmentation of bones in radiographs, which is useful for disease diagnosis, pre-operative planning, and treatment analysis. Two fully automatic methods were proposed to perform this task [24, 25], using regression voting systems based on random forests. Logistic regression was used to create predictive models which can be used to identify disease risk associations using data from electronic medical record databases [26], and it was combined with the kNN algorithm to predict patients' registration on transplant waiting lists [27].

Clustering is also popular in medical problems, and several works use it in different contexts. Magnetic resonance imaging (MRI) is frequently used to analyze brain diseases, and different approaches are based on clustering. For example, a new method is proposed in [28] to predict the subjects' behavior during a scanning session, and an algorithm to segment high angular resolution diffusion MRI into multiple regions is presented in [29]. Histopathology images are used in [30] to detect abnormal patterns associated to cancer tissues by means of classification, segmentation and clustering. And for medical images in general, efficient clustering algorithms are presented in [31] based on fuzzy c-means and non-Euclidean distance measures.

Dimensionality reduction techniques should be finally highlighted due to their increasing popularity in the last years. They became indispensable mainly because of the large dimensionality of data and the reduced number of pathological samples. Therefore, both feature extraction and feature selection methods were applied to different problems in medicine. For example, feature selection methods were successfully applied to eliminate redundant information and select the optimal subset of features [32, 17], analyze the contribution of different features to the classification procedure [33], reduce costs such as the processing time [34, 35], or even to understand the underlying causes of inter-expert variability [1]. Regarding feature extraction, it is worth mentioning the use of different techniques such as principal component analysis (PCA) or linear discriminant analysis (LDA) to improve image classification [36, 37].

4   Contributions to the special session

The special session *Machine Learning for Medical Applications* has received research works from different groups, presenting approaches to deal with image and signal analysis, feature extraction and selection, recognition and classification, and microarrays. Each accepted paper is briefly introduced in the following.

The observation of electroencephalographic (EEG) signals allows to detect arousals, a common cause of fragmented sleep. In this context, a model based on signal processing and machine learning is presented in [38] to automatically detect arousals. The authors proposed a set of relevant features extracted from the EEG signals, as well as a machine learning model obtained from a combination of individual models. The experiments conducted on real patients reported positive results, with an error of 13%.

The microglial cells' states are indicative of what is occurring in the central nervous system, and so they are associated with different neuronal diseases. A first approach for an automatic classification of the state of microglial cells into three classes is presented in [39]. It uses stacked denoising autoencoders, a type of deep neural networks, and was validated on a 45-image dataset. Taking into account the cells' morphology and the variability among experts, promising results are provided by this preliminary approach with an accuracy around 64%.

In the field of neuro-oncology, a machine learning-based approach is proposed in [40] to discriminate brain glioblastomas from single brain metastases. The analysis approach uses well-established methods for feature extraction and classification, including a collection of different learning algorithms. Besides diagnostic classification, the method could be also used as a guide for surgery planning since it provides enough information to create a map descriptor.

The diagnose of lung cancer can be achieved by categorizing lung nodules into benign or malignant. A computer-aided diagnosis system, which makes this classification automatically, is presented in [11]. It includes feature extraction techniques from chest computerized tomographies (CT) and feature selection methods to define an optimal subset of features. Additionally, the authors used several classifiers in order to evaluate the different feature subsets. The method provides a good performance with an AUC value over 96%.

The bag-of-steps feature generation method is applied in a novelty way for predicting rehabilitation periods [41]. This approach is based on the bag-of-words methodology used in text recognition and computer vision, and here describes the features of a rehabilitation session. Using this information, a predictive model is created to distinguish between patients with different rehabilitation patterns. The results obtained are promising, with an accuracy over 80%.

Brain tumor segmentation in magnetic resonance imaging (MRI) is the focus of attention in [42]. The authors presented an application of the successive projection algorithm (SPA) for initialization of non-negative matrix factorization (NMF) in multiparametric MRI, and compare it with random initialization. The experimentation demonstrated that the quality of tumor segmentation is statistically similar in both methods, whilst their proposal is more efficient and results obtained are reproducible, a relevant property in the medical domain.

The degree of redness in the bulbar conjunctiva, known as hyperemia, can serve as an early indicator of dry eye syndrome. Different features can be extracted from eye images in order to estimate the level of hyperemia, and following classified by means of machine learning algorithms. In [10], a methodology based on feature selection methods (filters and wrappers) is used to analyze the influence of different features when determining the hyperemia level. The results demonstrated the effectiveness of feature selection in this clinical domain.

DNA microarray classification is a challenging issue in the field of machine learning, mainly because there is a mismatch between the high gene dimension and the small sample size. Three different contributions of this special session are focused on this interesting topic. In [9], the authors proposed an ensemble feature selection method based on combining rankings of features. Aggregation

methods are used to combine the individual rankings, and the final subset of features is selected using the inverse of Fisher discriminant ratio as data complexity measure. Their proposal provides good results on seven DNA microarray datasets, using the SVM as classifier. Other application to microarrays can be found in [43], where a new learning algorithm for one-layer neural networks based on a singular value decomposition is presented. This approach, in which a system of linear equations is used to obtain the optimal parameters of the model, provides a fast learning algorithm for high dimensional problems, as is the case of microarray datasets. The experimental results demonstrated the adequacy of this method, by providing improvements in CPU time with no significant loss of accuracy. Class imbalance is another property of this type of data and, for this reason, the authors of [44] proposed to analyze the usefulness of data complexity measures to evaluate the SMOTE algorithm. More specifically, its behavior has been analyzed before and after applying feature gene selection.

The large amount of variables and the imbalance between classes are typical problems in the assessment of mortality in patients with cardiovascular disease risk factors. This topic has been considered in [45], whose authors have analyzed the behavior of different machine learning methods to solve this problem. The aim of the study was to determine the most suitable methodology to predict mortality, and so they considered different variable selection techniques, class balancing methods and classifiers.

In [8], the problem of selecting genes differentially expressed with some phenotype of interest (POI) in large genomic datasets has been addressed. The proposed approach uses spatiotemporal ICA as a previous step in the use of matrix factorization, and combines information from different spatiotemporal parameter values to improve the set of selected genes. The experimental results demonstrated that the method allows to significantly increase the proportion of genes related to the POI in the final selection.

Brain-computer interface (BCI) is also a common topic in machine learning applied to medical problems, and an approach for unsupervised BCI classification is presented in [46]. Not having enough training data to build a robust classification model for a specific subject is a typical problem in this scenario, and it was addressed by the authors using a subject selection algorithm combined with Riemannian geometry. This work presents an effective solution to a frequent challenge with good results.

One of the most usual morbidities associated to diabetes is diabetic retinopathy, which can be properly controlled by screening programs. In [47], random forests are used to build a classifier which may determine whether a diabetic patient is likely to develop retinopathy. This learning model can be used in a decision support tool to help practitioners in the determination of the best screening periodicity for each patient.

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