Uses and opportunities for machine learning in hypertension research

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ABSTRACT

Background: Artificial intelligence (AI) promises to provide useful information to clinicians specializing in hypertension. Already, there are some significant AI applications on large validated data sets.

Methods and results: This review presents the use of AI to predict clinical outcomes in big data i.e. data with high volume, variety, veracity, velocity and value. Four examples are included in this review. In the first example, deep learning and support vector machine (SVM) predicted the occurrence of cardiovascular events with 56%–57% accuracy. In the second example, in a database of 378,256 patients, a neural network algorithm predicted the occurrence of cardiovascular events during 10 year follow up with sensitivity (68%) and specificity (71%). In the third example, a machine learning algorithm classified 1,504,437 patients on the presence or absence of hypertension with 51% sensitivity, 99% specificity and area under the curve 87%. In example four, wearable biosensors and portable devices were used in assessing a person’s risk of developing hypertension using photoplethysmography to separate persons who were at risk of developing hypertension with sensitivity higher than 80% and positive predictive value higher than 90%. The results of the above studies were adjusted for demographics and the traditional risk factors for atherosclerotic disease.

Conclusion: These examples describe the use of artificial intelligence methods in the field of hypertension.

1. Introduction

The growing availability of large volumes of biomedical data, some derived from novel sources, is starting to help clinical researchers gain valuable insights into medical conditions. For researchers in hypertension, these insights will offer opportunities to assess hypertension prevalence and risk, to diagnose and gauge the severity of hypertension, and to estimate the risks of subsequent complications, thus offering the opportunity for timely treatment [1–4]. Overall, these developments offer great opportunities to significantly improve clinical management and patient care.

As an example, many studies have been conducted using the Myocardial Infarction Data Acquisition System (MIDAS). MIDAS is a statewide database containing de-identified records of all cardiovascular disease hospitalizations in New Jersey since 1986. It contains over 17 million records corresponding to over 4 million patients with cardiovascular disease. Mining this database has led to important publications that has changed the way cardiovascular medicine is practiced as follows. Wellings et al. reported that the rate of admission for heart failure (HF) after discharge for a first myocardial infarction as well as all-cause death decreased markedly from 2000 to 2015 [5]. Using a Personalized Disease Network (PDN), Cabrera et al. described the development of complications in these patients and observed the prevalence of hypertension prior to the onset of cardiovascular diseases such as HF [6]. This is consistent
with the known fact that hypertension is a major risk factor for cardiovascular disease.

Many types of data are becoming available for biomedical research including data from (a) clinical trials, (b) databases such as MIDAS that have large numbers of observations, (c) diagnostic tests such as electrocardiograms and imaging, (d) wearable biosensors which have the potential to generate real time data, (e) genomics, transcriptomics and proteomics, which may have considerably more variables than observations. Also, there is the potential to integrate data from multiple possibly very different sources to gain broader insights.

Nevertheless, there are many challenges to generating truly meaningful and generalizable insights from these large amounts of diverse and complex data. These include issues of data quality and data volume; or, to use a term common in big data analysis, the “4Vs”: Volume, Variety, Velocity, and Veracity. Overcoming these issues is not trivial.

Many steps are involved when dealing with big data. The first step should always be an appraisal of whether the data are appropriate for the research objective, followed by an examination of the data via exploration and visualization techniques to assess heterogeneities in the data, imbalances of key variables, outlier detection, and other issues that could affect the validity and generalizability of any subsequent findings. For example, the information in MIDAS for vital status, age, gender and race was checked and found to be over 98.8% accurate [7]. This is a major consideration as unstructured electronic health records (EHR) and data drawn from multiple sources for other purposes could have quality issues as well as inconsistencies in variable definitions (e.g., changes in International Classification of Diseases (ICD) codes). In addition, prior to analysis, some structuring of the data may be necessary taking into consideration concepts such as statistical experimental design, matching, propensity scoring, calibration, normalization, and data projection. This first step is essential.

The data can then be analyzed. One approach is to apply familiar statistical models, such as those used in multiple linear regression, logistic regression and survival analysis. These methods can generate predictions together with a performance measure and an explanation of which factors most contribute to the prediction. However, the volume and complexity of the data may be such that alternative approaches designed for analysis of big data and artificial intelligence could be considered. This includes methods such as artificial neural networks, support vector machines (SVM) and deep learning. These methods employ complex algorithms which include ensembles of models interacting with each other and enable the study of complex associations which cannot easily be reduced to an equation. Since the algorithms are set to seek solutions over a broad domain without being provided explicit instructions of where to search, they are often able to provide better predictions than simpler schemes.

In the following sections, we will briefly describe the machine learning approach and give some examples in which it has been applied for hypertension research.

2. Methods: machine learning and deep learning

Machine learning is devoted to the methodology and algorithms for predictive modeling with the objective of making the best possible linear or non-linear predictions. In classical statistics, the emphasis was on statistical inference and predictive modeling and was just another element of the statistical analysis. Fig. 1 shows the intersections between machine learning, statistics and computer sciences/engineering (CS/E) in the context of data science. Statistics and biostatistics intersect with CS/E in the areas of machine learning and big data and only in part in bioinformatics. However, there are major parts of CS/E that are not part of data science.

Machine learning was initiated in the late 1970s by Breiman et al. who proposed the methodology of Classification and Regression Trees (CART) and later proposed the methods of Bagging and Random Forests [8–10]. Contributions from Computer Science came later in the 1990s, with Neural Networks, Boosting and Support Vector Machine (SVM) [11, 12]. These methods can be used to study the relationship between an outcome variable and several features that could potentially affect the outcome. For example, they could be used to predict the likelihood of a person with certain clinical features developing hypertension. Depending on the methods, it may be possible to also identify the main features that affect the outcome.

The main considerations in the analysis are balancing bias, variance and model complexity. Resampling or the use of a set-aside test set can be used to prevent overfitting which could be a major concern when fitting complex models such as these; overfitting occurs when a model is found to fit only the training data very well, but does not generalize to other data. Deep learning is a technique that was introduced recently as an updated version of neural networks. Deep learning is expected to become one of the most successful methods in terms of performance in predicting...
outcomes.

One of the most successful algorithms for deep learning is the Convolution Neural Net (CNN). The idea of a CNN is to apply a sequence of linear convolution filters to the set of predictors and to use the outcomes as inputs to Tensor Flow, the main neural net algorithm with several hidden layers (Fig. 2). To improve performance, the tensor flow algorithm will use a training set, a validation set, and a testing set and it will be configured with three hidden layers and it will be trained using thousands of optimizations called “epochs”. The outcomes of tensor flow will be class predictions if doing classification or predicted values if the response is continuous. The importance of each predictor can be assessed by comparing the performance of the model by including and excluding the predictor. These techniques could be used to identify subsets of patients with particular constellations of risk factors that lead to a higher risk of events.

Both support vector machines and deep learning methods can also be helpful in identifying risk factors leading to cardiovascular death or serious morbidity. The main idea is to use the concept of variable importance combined with penalized selection which produces an ordered list of important predictors [13].

Machine learning also includes methods for unsupervised learning. Thus, cluster analysis can be used to group or segment datasets into clusters of observations which are similar to one another based on a set of characteristics. The performance (the percent of correct predictions) in the testing set was 57% for deep learning and 56% for SVM. This performance is not unreasonable given the diversity and high variability of the data.

Example 2: Weng et al. conducted a prospective cohort study using routine clinical data of 378,256 patients from UK family practices [14]. The patients were free from cardiovascular disease at study onset and this data was used to predict whether or not the individuals in the study would have a cardiovascular event during the next 10 years. Among the patients, 24,970 had experienced cardiovascular events over the 10 years. Several different machine learning methods were used to analyze the data. Of these, a neural network algorithm had decent performance: high negative predictive value (NPV) (95.7%), good sensitivity (67.5%), good specificity (70.7%), but low positive predictive value (PPV) (18.4%). Age, gender, ethnicity, chronic kidney disease, mental illness, and atrial fibrillation were among those identified as major risk factors by this algorithm.

Example 3: Ye et al. used data from individual patient EHR extracted from the Maine Health Information Exchange network to develop a risk prediction model for incident essential hypertension within one year [15]. Retrospective (823,627, calendar year 2013) and prospective (680,810, calendar year 2014) cohorts were formed. A machine learning algorithm was used to generate an ensemble of classification trees and assign a predictive risk score to each individual. The model had good performance with 82.3% PPV, 94.9% NPV, 50.9% sensitivity, 98.8% specificity, 0.917 AUC in the retrospective cohort, and 0.870 AUC in an independent prospective cohort. Diabetes, lipid disorders, cardiovascular diseases, mental illness, clinical utilization indicators, and socioeconomic determinants were identified as major risk factors, with the very high-risk population comprised mainly of elderly individuals with multiple chronic conditions. They report that Maine has already deployed their real-time predictive analytic model.

Example 4: The potential of employing wearable biosensors and portable devices as a means of continuous monitoring of assessing a subject’s risk of developing hypertension is being explored. Liang et al. studied the possibility of using wearable biosensors which use photo-plethysmography (PGP) to assess hypertension [16,17]. They first applied statistical and machine learning tools to select 10 characteristics of the PPG signal, which were then used in four machine learning algorithms to separate hypertensive patients (systolic blood pressure (SBP) over 140 or diastolic blood pressure (DBP) over 100) from non-hypertensive subjects (SBP below 120 or DBP below 80) with high sensitivity (over 80%) and high PPV (over 90%). Separately, Tison et al. used a deep neural network to predict hypertension using heart rate and step count data obtained from off-the-shelf wearables with a PPG heart rate sensor and accelerometer; they found that they could predict hypertension in a validation set with high sensitivity (over 80%) and good specificity (over 60%) [18]. These studies indicate the potential of employing wearable biosensors and portable devices for regular monitoring of patients at risk for hypertension or complications thereof.

4. Discussion

Machine learning is beginning to have an impact on clinical research and practice in various ways. One way is by aiding effective clinical decision making through insights obtained from mining massive amounts of data, such as the MIDAS data mentioned above, and identifying complex patterns associated with hypertension and other clinical conditions. This was not possible to be done at a scale and speed now achieved by machine learning. Some of these findings could allow researchers to study the broad heterogeneity of pathophysiological factors and processes that interact and contribute to disease and thus could conceivably pave the way to a form of personalized treatment of diseases. At the other end of the spectrum, it could also allow epidemiologists and other researchers to study patterns of disease occurrence and gain a better understanding of what factors in patients’ lives influence their health and susceptibility to disease. This should, in turn, enable physicians as well as government bodies and community health organizations...
to recommend preventive measures and improve disease management and control.

Another way is by having a means to monitor patient behavior, such as through wearable sensors and other mobile communication devices. This will help clinicians track patient movement and behavioral patterns (perhaps even remotely in real time) and recognize early warning signs of the onset of potentially dangerous conditions. Also, in the case of patients at risk, this will allow physicians to assess compliance with clinical recommendations [17,19–21]. The information obtained from these devices could also be used for the design of clinical research. They could also be useful as a way to develop personalized intervention plans tailored to suit the complex clinical needs unique to individuals. Overall, these developments have the potential to radically change health care. A clinician practicing hypertension may benefit from reading this manuscript and the use of artificial intelligence methods by learning new associations that were unknown before the use of this technique and by learning the opportunity of using such techniques in future research. Artificial intelligence explores big data with high volume, variety, veracity, velocity and value. However, at the present time, there has been much enthusiasm, but little benefit in clinical practice mainly because clinical validation of the findings of artificial intelligence in different data sets is lacking. Also, predictive models change from year to year over time and that requires calibration of model performance. Data quality is critical.

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Declaration of Competing Interest

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CRediT authorship contribution statement

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