

Artificial Neural Network Based ‘Continuous Feedback Loop’ Platform to Support Multicenter Cardiac Clinical Trials

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Abstract

Multicenter clinical trials are complex that traditional rigid concepts of data acquisition and analysis algorithms may culminate in poor trial design, incomplete protocols, unidentified variables and absence of feedback modification. This provides no flexibility to accommodate new, useful and informative predictors during the course of the trial. Thus most of the trials will realize the limitations by the end of the study period. This fact motivated the development of a suite of decision support tools utilizing an artificial neural network (ANN) based platform. We conceptualize an ANN based platform for supporting large clinical trials based on a continuous feedback loop mechanism to enable restructuring the data acquisition, data analysis and may identify novel hidden clinical correlations and findings thus significantly improving the efficiency of the trial outcomes.

1. Introduction

Interventions in cardiovascular medicine require rigorous proof of effect. Currently the gold standard for evaluating new drugs or device therapy is randomized controlled trials that often involve multicenter design enrolling large numbers of subjects. The design of such trials needs to be ingrained with principles of lack of bias which make the progress of patient invisible to the investigators. Adverse events remain the only manifest effect of possible worsening of a critical parameter in clinical trials. Endpoints usually take the shape of statistical values generated via hard statistical analysis.

Traditional rigid concepts of data acquisition and analysis algorithms may culminate in poor trial design, incomplete protocols, unidentified variables and absence of feedback modification even by existing standards. Such design provides no flexibility to accommodate new, useful and informative predictors during the course of the trial and perhaps will realize the design limitations only by the end of a pre-specified study period. Adaptive flexible clinical trial designs, where the interim analysis

is used to drive the future course of the trial is pivotal in such situations. Food and Drug Administration has recently shown warm response to adaptive trials [1].

Pharmaceutical Research and Manufacturers of America workgroup identified areas like dose finding, seamless Phase II/III trials designs, and sample size re-estimation that may be benefited by adaptive trial design [2]. However, unblinded interim analysis can lead to disappointments for both the investigators and study participants as 30% of trials are said to stop early because of appearance of benefits [3].

This brings the necessity and development of other supporting tools and we propose an automated decision support system utilizing Artificial Neural Network (ANN). ANN is a highly interconnected network of a large number of simple processing units and can be described as a network of weighted additive values with nonlinear transfer function [4]. Our model utilizes a feedback loop design based on the generated data to continuously modify the future direction of the trial.

2. Methods

The process of clinical trials starts by collection of the baseline data from the subjects participating in the trial who are subsequently assigned to the study groups by randomization which often involves stratification. Some of the variables that need to be balanced between the study groups will be given emphasis.

2.1. Principal component analysis and Multi layer perceptron

Our design proposes to use Principal Component Analysis (PCA) to conduct exploratory data analysis to identify additional stratification variables at this point.[5] The key concept underlying PCA is the singular value decomposition of the correlation matrix ‘R’. PCA is a simple, non-parametric method for extracting relevant information from data by identifying patterns (relationships) among the variables and reducing the dimensionality of the data set without any significant loss

of information. The PCA is to find the components s_1, s_2, \dots, s_n so that they can explain the maximum amount of variance possibly from nonlinearly transformed components. PCA can be defined in an intuitive way using a recursive formulation. Define the direction of the first principal component, say \mathbf{W}_1 , by

$$\mathbf{W}_1 = \arg \max_{\|\mathbf{w}\|=1} E\{(\mathbf{w}^T \mathbf{x})^2\}$$

Where \mathbf{W}_1 is of the same dimension m as the random data vector \mathbf{X} . (All the vectors in this paper are column vectors). Thus the first principal component is the projection on the direction in which the variance of the projection is maximized. Having determined the first $k-1$ principal components, the k -th principal component is determined as the principal component of the residual:

$$\mathbf{W}_k = \arg \max_{\|\mathbf{w}\|=1} E\{[\mathbf{w}^T (\mathbf{x} - \sum_{i=1}^{k-1} \mathbf{w}_i \mathbf{w}_i^T \mathbf{x})]^2\}$$

The principal components are then given by $\mathbf{S}_i = \mathbf{w}_i^T \mathbf{x}$. In practice, the computation of the \mathbf{w}_i can be accomplished using the (sample) covariance matrix $E\{\mathbf{x}\mathbf{x}^T\} = \mathbf{C}$. The \mathbf{C} are the eigenvectors of the one that correspond to the 'n' largest eigen values of \mathbf{C} .

PCA can be performed even before the completion of the enrollment of the subjects. Once the enrolment is complete, the key variables among the factors identified can be used to build and run a multilayer perceptron model to redefine the prognostic model between the baseline and the randomization steps if time permits. This will enhance the 'quality' of enrolled subjects.

2.2. Artificial neural network clustering

The subjects are then administered the treatment. After a specified time, the subjects are again evaluated and the data will be collected at the end of the first cycle. Thereafter, the new data will be compared with the baseline data and further analysis will be performed to calculate compliance rate. This will identify whether any variables show a significant change in mean values by using logic similar to Hy's law in hepatotoxicity [6] and calculate change score for each variable. When significant change is detected, a flag will be raised and subsequently reported to the interim review committee.

After the first few cycles and once the post treatment data sets are collected, analysis will be performed, i.e. clustering these respondents into distinct subgroups using a clustering algorithm like 'K Means' or Kohonen or perhaps a hybrid method where clusters are created using an ANN based Kohonen Self Organizing Maps (SOM) and refining it using a K Means algorithm [7].

Kohonen SOM is a way of representing multi-

dimensional data in one or two dimensional spaces. This process, of reducing the dimensionality of vectors, is essentially a data compression technique known as vector quantization. In addition, the Kohonen technique creates a network that stores information in such a way that any topological relationships within the training set are maintained.

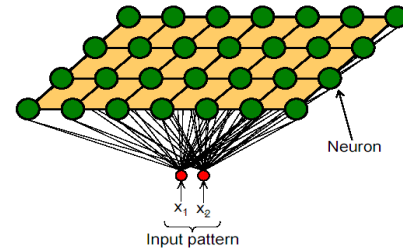


Figure 1. Kohonen Self-organising Map

The basic algorithm works as follows: 1. Initialize weights. 2. Repeat until convergence: 2a- Select next input pattern, 2b- Find Best Matching Unit, 2c- Update weights of winner and neighbours and 2d- Decrease learning rate & neighborhood size.

The clustering algorithm gives a set of K where we get the sub groups of patients who are behaving significantly different from each other. These subgroups are analyzed for additional outcomes or symptoms they exhibit and if the outcomes are serious, then it would raise a flag to alert the committee.

2.3. Classification tree

Once we have completed our clustering process and identified sub groups of patients who exhibit certain serious outcomes, a decision tree model capable of identifying the factors that cause these outcomes need to be built. Thereafter, these factors need to be included into the clinical trial design as well as be able to predict how likely a new patient will be going to exhibit the symptoms.

Decision tree algorithms essentially follow the greedy strategy of splitting the records based on an attribute test that optimizes certain criterion. The test condition depends on the attribute type (continuous, nominal or ordinal) or it could depend on the number of ways of splitting (binary or multi-way). In order to determine the best split, we need a measure of node impurity which could be the Gini Index, Entropy or Misclassification error. For example Gini Index for a given node t :

$$GINI(t) = 1 - \sum_j [p(j|t)]^2$$

where $p(j | t)$ is the relative frequency of class j at node t .
 Splitting stops when all the records belong to the same

Decision trees are inexpensive to construct, extremely fast at classifying unknown records, easy to interpret for

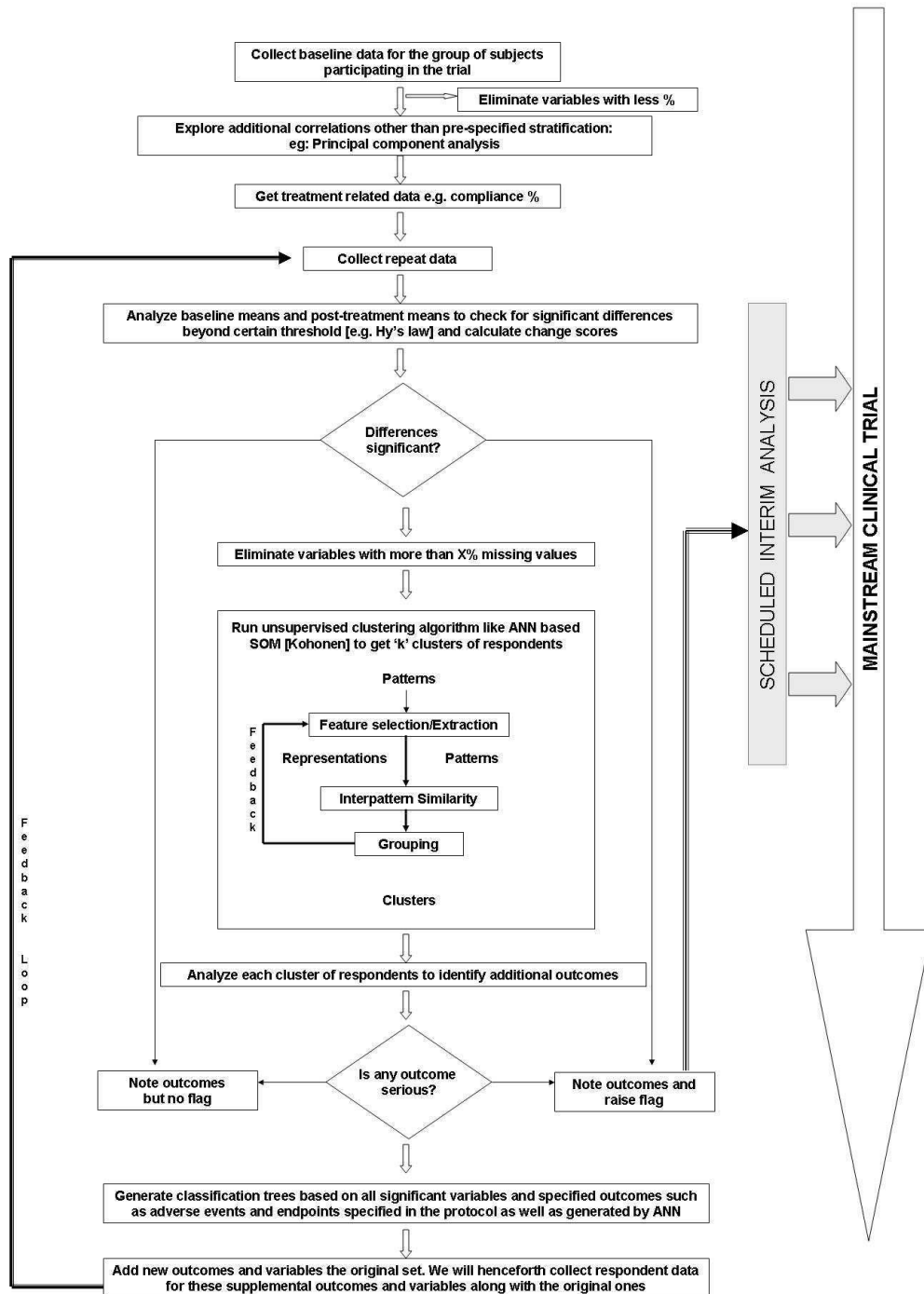


Fig 2. Flowchart of the ANN assisted interim data analysis and feedback to the mainstream clinical trial

class or when all the records have similar attribute values.

small-sized trees and accuracy is comparable to other

classification techniques for many simple data sets. Disadvantages include problems with sparse data and over fitting, even though pruning may address the latter issue to certain extent.

3. Results

An illustration of the first part of the framework could be done with an example of a study of HIV persons where wasting as a variable is stratified according to CD4 counts (CDC classification). However, as the prior treatment was not considered as a stratifier, the fact that these categories of treatment affected some clotting factors may have indicated a possibility of vascular problems with the new therapy instead of waiting for post-marketing information. The proposed PCA step would point to the need of additional stratifying variable.

The second step is to use some of these safety variables (e.g. fibrinogen levels in the study mentioned above) in the baseline and subsequent visits of the patients to model clusters. Unique groups start forming themselves using Kohonen maps. Clusters need to be correlated with not only the stratifying variables but also the other important variables including new treatment related variables like type of treatment, dosage, and compliance rates. If more compliant persons are clustered into warning levels of safety variables, then the study shall be subjected to an unblinded interim analysis at that level.

It is imprudent, if not unethical, to prematurely terminate a clinical trial poised to answer an important clinical question, particularly if it is near completion. Interim termination of nisoldipine arm in hypertensive patients in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial was later put into question by a 'private detective' who uncovered non-fatal MI events in the superior drug arm. In the 'Rosiglitazone Evaluated for Cardiovascular Outcomes' (RECORD) study for type 2 diabetes mellitus, one was intrigued to note that the study underwent an 'unplanned' interim analysis half way into the trial [8]. This was after another meta-analysis pointed out cardio-vascular side-effects for rosiglitazone.

4. Discussion and conclusions

The examples cited point to two issues. One is the necessity of being objective about the way unplanned interim analysis are ingrained into the trials by designing them adaptively. Secondly, the need for keeping the trials blinded without interference from 'feeling' of insecurity about the futility of the trial. The present method of interim analysis based on hard end-points seems to be cutting promising trials short and needs supplementation by a 'black box' method such as ANN.

The newly described model will provide several

advantages. The statistical significance of a clinical trial may be different from the clinical significance. This bias can be minimized as there is no overemphasis of statistical significance upon clinical significance. Additionally, intuitive migration from Phase 1-2 to Phase 3 is seamless; for eg: difference due to change in the population tested. The 'clinical quality' of enrolled subjects because of model fitting in initial stages is pivotal and can be achieved. Moreover, this model prevents unnecessary avoidable outcomes by identifying 'bad clusters'. Neural network is a black box and hence is not transparent to sponsor or investigators which is crucial in the integrity of the trial and its outcome. Such a model will provide a 'totality of information' of the subjects and factors affecting the outcome rather than a mere statistical end point. Here, the end points are not just pre-specified, but is evolved from an ANN based analysis driven warning system.

Our model incorporates a built in 'subgroup analysis' performed before the completion of the trial. It is performed 'on the fly' during the course of the trial thus amplifying the more relevant groups or sub groups for overall efficacy thus adding another dimension to Evidence Based Medicine.

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