Author's response to reviews

Title: Artificial neural network models for prediction of cardiovascular autonomic dysfunction in general Chinese population

Authors:

Juanmei Liu (juanmeiliu80@163.com)
Zi-Hui Tang (albert.tang@163.com)
Fangfang Zeng (zengfangfang85@163.com)
Linuo Zhou (dr.zhoulinuo@gmail.com)

Version: 2 Date: 29 April 2013

Author's response to reviews: see over
Li Nuo Zhou M.D., Ph.D.,
Departments of Endocrinology and Metabolism,
Huashan Hospital of Fudan University
Building 0#, No. 12 Wulumuqi Xi Road,
Shanghai, 200040, China

30-Apr, 2013

James Sorace M.D., Editor-in-Chief
Baltimore VA Medical Center, USA

Dear Prof. James Sorace

Please find the enclosed revision of original manuscript (998687879131542) entitled “Artificial neural network models for prediction of cardiovascular autonomic dysfunction in general Chinese population” by Juanmei Liu et al. We would like to submit this manuscript for consideration of publication in BMC Medical Informatics and Decision Making. The submitted form of the manuscript has been read and approved by all the authors with no conflict of interest. The work has not been published or submitted elsewhere.

We are grateful to all reviewers for their time and effort in helping us improve and clarify our manuscript. The revised manuscript has benefited greatly from consideration and incorporation of the reviewers’ comments.

The paper conforms to the Journal’s requirements for a structured abstract and word limits. We highlighted any changes using gray background.

As follows, we would like to detail our point-to-point response to the reviewers’ comments in our revision. The corresponding revised parts were also shaded.
Reviewer's report
Reviewer: Ednaiko Pizzolato
Reviewer's report:
The paper describes the use of now standard machine learning and statistic techniques to assess the presence of cardiovascular autonomic dysfunction in the Chinese population. The paper reads very well and is well sound. I would only make a discretionary revision for suggestion. The authors used the K-S tests to assess normality assumptions, but they could also have used the Anderson-Darlington or Shapiro-Wilk tests which may have more power. Aside of that, I would say the paper is nice and reports some relevant results on its field, which may be important for the studied population.

Thank you for your comments. According to these comments, necessary analysis has been done. And similar results have been found.

Reviewer's report
Reviewer: Turgay IBRIKCI
Reviewer's report:
Major:
1-The manuscript definitely needs to rewrite by native speaker again.

Necessary correction has been done. Thank you for this comment.

2-The structure of the manuscript is little bit messy, because the discussion section has the "Introduction" materials.

We appreciated this comment. Redundancy or tedious sentences have been deleted. Necessary sentence have been saved to summarize this study (please see the section of Discussion paragraph 1).

3-The conclusion section has very strong statement as a conclusion statement that says "The performances of the ANN model (the manuscript just compared 5 ANN models) with high value predicted CA dysfunction". But, the manuscript did not compare other models. So, it is difficult to say that statement.

Many thanks for this comment. For prediction and diagnostic test studies, if the area under the receiver-operating curve for a prediction model ranged from 0.70 to 0.90, the model was considered as high prediction value, and if the area was more than 0.9, the model was considered as very high prediction value. In this study, the mean area under the receiver-operating curve was 0.762 (95% CI 0.732–0.793) for prediction using artificial neural network approach. So we have a conclusion that the performances of the ANN model with high value predicted CA dysfunction. Thank you again.

4-The manuscript gives 5 ANN models but does not explain any details about these models.

Thank you so much for your comment. We are sorry for not clarifying details of 5 ANN models.
Actually, throughout the section of Materials and methods and Results, we described in formation for 5 ANN as the following: "The ANN applied in this study was a standard feed-forward, back-propagation neural network with three layers consisted of an input layer, a hidden layer, and an output layer. The input layer contained 14 input neurons, the hidden layer contained 18 neurons, and the output layer contained 1 output neuron (Figure 1). During the training, the learning rate and momentum for network training were set to 0.20 and 0.9, respectively. A validation dataset was developed to avoid an over-fitting ANN model. In general, one-fourth of the patients were randomly selected from the exploratory set. The training was run until a minimum average square error (MSE) of <0.001 or an increasing MSE was found in the validation dataset. For developing a prediction model, five exploratory sets were generated using a computerized random calculator. Each exploratory set consisted of more than 1500 individuals. Every trained ANN included 14 input nodes, 18 layer nodes, and 1 output node (Figure 1). For training ANN, 101–112 echoes were performed and the MSE ranged from 0.12–0.13. Five validation sets were developed, all of which consisted of more than 500 subjects. The area under ROC curve ranged from 0.738–0.789 (Table 3). At the respective optimal cutoff points, when applied to the validation sets, the sensitivity and specificity of the ANN models were 67.7–82.1% and 64.7–70.4%, respectively. The positive and negative predictive values ranged from 30.1–37.3% and 89.8–94.0%, respectively." Because ANN is a black-box model, the relationships between input nodes and output nodes cannot be clearly described. Two matrices can be considered as save relevant information, which may not be shown in this paper. Thank you again.

5-The abstract section says that the database has 2092 patients, but page 9 line18 says that there are 2077 patients for ANN models. The manuscript needs to recalculate statistical parameters again because of this patient's information.

Thank you so much for your suggestion! A total of 15 individuals with 14 risk factors to develop ANN model had missing data. FPG and IR had 5 missing data, respectively. TG and FPG had 2 missing data, respectively. PH duration has 1 missing data. Because we mentioned missing data (accounted for less than 1% of total sample) in this paper (please see page9, line 17), we would like to not revising relevant sentence. Thank you.

Reviewer’s report
Reviewer: Eloy Irioyen

Comments for Authors:
1. In the Introduction section, second paragraph, the ANN are presented as "ANNs employ nonlinear mathematical models to mimic the human brain's own problem-solving process, by using previously solved examples to build a system of "neurons" that makes new decisions, classifications, and forecasts." This is not a complete information about ANN. There exist ANN used as dynamical system s. Moreover, some ANN training methods are unsupervised. Try to extend this information into the Introduction section.

We appreciated very much this comment. Necessary correction has been done. We added the sentence of "According to learning paradigms, each corresponding to a particular abstract learning task, these
are supervised learning, unsupervised learning and reinforcement learning.” Please the section of Introduction (please see page 3, line 19-21).

2. In the Artificial neural network models, first paragraph: To divide data sets in both, examples for training and validation, is better using methods which explore all the space and guarantee the representativeness of the parameter space.

Many thanks for this comment. Using methods which explore all the space can guarantee the representativeness of the parameter space. However, in practice, we divided training set to training and validation set which can prevent ANN models from over-fitting. In this study, the training was run until a minimum average square error (MSE) of <0.001 or an increasing MSE was found in the validation dataset.

3. In the Artificial neural network models, second paragraph: In ANN training exist another methods as Levenberg-Marquardt. Please, explore these possibilities.

Thank you so much for this comment. The Levenberg-Marquardt (LM) algorithm is a robust method for approximating a function. The LM algorithm provides a numerical solution to the problem of minimizing a (generally non-linear) function, over a space of parameters for the function. Its a popular alternative to the Gauss-Newton method of finding the minimum of a function. However, the LM is very sensitive to the initial network weights. Also, it does not consider outliers in the data, what may lead to over-fitting noise. Also, it does not consider outliers in the data, what may lead to over-fitting noise. A learning algorithm used in training artificial neural networks employs a form of gradient descent. M atlab software function: trainedx. The algorithm of trainedx was more slow convergence than LM algorithms. In this study, we do not need rapid convergence algorithms, but need an algorithm suitable to control over-fitting. We balanced advantages and disadvantages of the two learning algorithms to select traditional neural network learning algorithms to avoid rapid convergence to reduce over-fitting.

4. The Study Population section is well defined, with enough detail.

Thank you for your comment.

5. The Definition section has a good definition of Diabetes in China, which marks Chinese off clearly from other ethnic.

Many thanks for this comment.

Thank you very much for your time and effort to handle the manuscript!

Sincerely,

Linuo Zhou, M.D., Ph.D., Professor
Director, Department of Endocrinology and Metabolism
Professor of Internal Medicine, University of Fudan
Department of Endocrinology and Metabolism, Huashan Hospital
Shanghai, China
Phone: 0086-021-52888143
Email: drzhoulino@gmail.com