Model of Cholera Forecasting Using Artificial Neural Network in Chabahar City, Iran

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Abstract

Background: Cholera as an endemic disease remains a health issue in Iran despite decrease in incidence. Since forecasting epidemic diseases provides appropriate preventive actions in disease spread, different forecasting methods including artificial neural networks have been developed to study parameters involved in incidence and spread of epidemic diseases such as cholera.

Objectives: In this study, cholera in rural area of Chabahar, Iran was investigated to achieve a proper forecasting model.

Materials and Methods: Data of cholera was gathered from 465 villages, of which 104 reported cholera during ten years period of study. Logistic regression modeling and correlate bivariate were used to determine risk factors and achieve possible predictive model one-hidden-layer perception neural network with backpropagation training algorithm and the sigmoid activation function was trained and tested between the two groups of infected and non-infected villages after preprocessing. For determining validity of prediction, the ROC diagram was used. The study variables included climate conditions and geographical parameters.

Results: After determining significant variables of cholera incidence, the described artificial neural network model was capable of forecasting cholera event among villages of test group with accuracy up to 80%. The highest accuracy was achieved when model was trained with variables that were significant in statistical analysis describing that the two methods confirm the result of each other.

Conclusions: Application of artificial neural networking assists forecasting cholera for adopting protective measures. For a more accurate prediction, comprehensive information is required including data on hygienic, social and demographic parameters.

Keywords: Cholera, Iran, Forecasting, Statistical Model, Neural Network

1. Background

Cholera remains a major health risk despite global institutional attention. In 2012, a total of 245393 cholera cases were reported leading to 3043 deaths. In Asia, 27 deaths from 7367 cases were reported among 12 countries with highest mortalities in Iraq. While in Asia, the main proportion of cases is due to *Vibrio cholerae*, most cases elsewhere are caused by acute watery diarrhea (1). It is estimated that among actual cholera cases worldwide, only 1% are formally stated (2). Underreporting might be due to limitations in surveillance systems, fear of travel related and trade related sanctions (1). In Iran, the last epidemic of 2011 involved 1187 cases and 12 deaths (3). Despite advances in treatment plans, due to continuous worldwide incidence, cholera is globally considered a hazard to public health.

Persistence of cholera incidence has been shown to be correlated with unsanitary living conditions (4). According to the WHO protocols, cholera as an international hazard has to be reported if two of the following four concerns are prominent; a severe impact on public health, peculiar or unexpected outbreak, fear of considerable international spread and a significant risk of international restriction on trade and travel (5).

Dissemination of cholera is strongly correlated with lack of proper management in environmental and health issues. Aquatic environment is vital for survival of *V. cholerae*. The spread of cholera is unavoidable when adequate environmental conditions such as temperature, salinity and availability of nutrients exist. In the absence of human intervention, *V. cholerae* grows and spreads for long time; otherwise, metabolically active state shifts to a dormant state. Specific alterations with-

in climate conditions influence the spread of some infectious diseases, among which incidence of *V. cholerae* is highly encouraged by contamination of water and food supplies. *V. cholerae* is highly persistent in foods, especially when contaminated after preparation. Cooking and heating to some extent eliminates bacteria from the food (2).

When initiation and spread of infectious diseases such as cholera are predicted with reliable modeling, expert human, pharmaceutical and logistic resources can be employed for successful preventive actions within the prone locations (6).

Artificial neural networks are used for nonlinear statistical modeling, specifically as alternatives to logistic regression that is widely used in development of models of disease spread and prediction of epidemic outcomes and subsequent preventive actions (7).

Such models are capable of pattern recognition when ambiguity and/or intense variability occur within input data and expert knowledge cannot be easily served. Hence, for environmental and biological evaluations containing such data, application of artificial neural networks allows a proper elucidation of data and nonlinear forecast analysis of variables. Examples include categorizing quality of river water and automatic identification of phytoplankton (8), prediction of sea surface temperatures (9) and identifying excess deaths due to cholera (10). Artificial neural network modeling may contribute to management of diseases, which in some conditions spread by abnormal patterns of environmental parameters.

Artificial neural networks were used to study cholera mortality during epidemic of 1993-1994 in Brazilian state of Ceara through a network of two neurons in the input layer, twelve in the hidden layer, one in the output layer and one in the memory layer, and by backpropagation, with 0.01 learning rate and 0.9 momentums. Results indicated good prediction ability of artificial neural network, especially in the initial period (10).

2. Objectives

In this study, we developed a multilayer perception artificial neural network to achieve a model to predict cholera event within villages of Chabahar District, a south-eastern district of Iran among the regions with the highest cholera incidences nationwide. Data of geographic parameters were processed using geographic information system (GIS) and used as inputs of statistical analysis and neural network models (11).

The incidence of disease was studied based on climate and geographic variables. Such parameters including temperature, humidity, rainfall, altitude and distances of villages from district health center, rural health centers, eastern national border, the nearest river and subterranean canal, were considered as input data for prediction models.

3. Materials and Methods

3.1. Study Population

The incidence of cholera was investigated during 1997 - 2006 among rural regions of district of Chabahar, a free economic zone and coastal resort of Oman Sea on the southeast of Iran bordering Pakistan on east that has continuously been prone to cholera outbreak. All 465 villages of Chabahar were included in the study, among which 104 were listed with cholera incidence within the period of study.

3.2. Data Collection

Data of cases during 1997 - 2006 were acquired from the line list of Nag and Eltor cholera disease reported to the center for disease control, Iran ministry of health and medical education through the surveillance system. The diagnosis of disease was assured after clinical examination of fecal samples with initial syndromes similar to those of cholera.

Data of temperature, humidity and rainfall as monthly average for each year were collected from Iran meteorology organization. Geographical parameters included elevation and distances of villages from district health center, rural health centers, national eastern border, the nearest river and subterranean canal. Using geographic information systems, these parameters were quantified through geographical layers as discussed in previous article (11).

The incidence of cholera was binary coded, with "one" allocated for villages with cholera incidence and "zero" for those without cholera. The number of cholera cases per 100 persons was similar among villages.

3.3. Data Processing

To determine cholera risk factors, statistical analysis was performed using SPSS software (IBM, New York) accompanied by neural network modeling for prediction of cholera spread.

3.3.1. Logistic Regression Modeling and Correlate Bivariate

Statistical analysis was performed to investigate correlation between cholera spread and variables of study. Since the histograms of independent and dependent variables were not normally distributed, the cholera incidence among villages was binary coded. Using SPSS version 11.5, binary logistic regression and correlate bivariate performed with 95% confidence interval to model influence of climate and geographical parameters in cholera incidence in 10 years period of study (11).

3.3.2. Artificial Neural Network Modeling

Two categories of input variables were considered in predictions. All variables of the study and variables that

were statistically significant in cholera incidence were based on logistic modeling (Table 1). To predict cholera event, a multilayer perceptron architecture containing input, hidden and output layers with backpropagation training algorithm, sigmoid activation function with 0.01 learning rate and 0.7 momentum was trained and tested with different variables (Table 2). The climate variables were introduced as both monthly averaged and seasonally averaged. The output parameter was cholera incidence as monthly and seasonally averaged. The number of neurons of the hidden layer was according to the input and output layers.

To obtain validated results, the input data was normalized by subtraction of mean value of each data column and division of results by standard deviation. After pre-processing, data was divided into training and test categories. This was performed to analyze the ability of network in prediction of test group after network training. Within the training group, data of 365 villages and in test group those of 100 villages were collected. The number of neurons in each layer was different based on monthly or seasonally weather data, inputting all variables or only statistically significant variables in logistic regression model.

The output tag was a binary code in which the cholera incidence was either one or zero. Since the applied activation function (sigmoid) generates outputs in the (0,1) range, these outputs have to be converted to binary tags and then compared to desired ones during the test phase. This conversion can simply performed through rounding the outputs; i.e. the outputs smaller than 0.5 are converted to zero and the ones larger than 0.5 rounded to 1. If the resultant code is the same as the tag code, the prediction is considered as true. The ratio of true distinctions in test data to all test data is introduced as accuracy of prediction. In the current study, comparison measurement was based on proper decrease of error and accuracy of prediction in test villages (12).

Due to successful applications in data classifications, multi-layer perceptrons (MLP) are well known forms of feed forward artificial neural networks. The process of supervised learning for a MLP with input data and target, requires usage of an objective function to evaluate deviation of the predicted output, from the observed data and assessment for the convergence toward an optimal set of results. There are several MLP training algorithms, from which the backpropagation (BP) algorithm is commonly well-known (13).

Backpropagation, as one of the most prominent developments in artificial neural networking, is a systematic method for training multilayer artificial neural networks (Figure 1). It reveals generalization of least mean squares (LMS) algorithm to multiple layer networks and nonlinear differentiable transfer functions (14).

MLP is initiated with random weight matrices with elements in the range of (0, 0.01). Training is performed for several iterations until the weight matrices converge. In

each iteration, the weight matrices of MLP are updated according to backpropagation algorithm. The outputs of layers are then calculated as:

$$(1) \qquad a_{i+1}^t = f_{i+1}\left(W_i^t a_i^t + b_{i+1}\right) i = 1,\ldots,m-1$$

where

$$a_{i+1}^t$$

is the output of layer i + 1 at iteration t, m is the number of layers in the network, f_{i+1} indicates the transfer functions of layer i + 1,

$$W_i^{t+1}$$

is the weight matrix that connects the ith layer to $i+1^{th}$ layer at t^{th} iteration and b_{i+1} describes the bias of layer i + 1. The transfer functions used in this study is tan-sigmoid function described as

$$f(s) = 2/\left(1 + e^{-2.s}\right)$$

for input and hidden layer and linear (f(s) = s) for the output layer. The training data includes N observations and their corresponding labels, which are used in training phase to adjust weight matrices of the neural network. After training phase, neural network is tested with another set of data, including M observations and corresponding labels. These labels are compared to those estimated by neural network to assess the training efficacy (12).

3.4. Validity of Prediction of Neural Network

To evaluate optimized prediction of the neural network, receiving operator characteristic (ROC) diagrams were used. Usage of ROC curve is one of the most suitable methods of assessing the value of a test by defining an appropriate decision threshold (15).

When the ROC diagram is considered, the Y axis describes the true positive (sensitivity) value and the X axis indicates false positive (1-specificity) value for each possible prediction. The prediction value is selected to categorize the extent of correct detection of cholera occurrence through optimum verification of the input parameters when the adopted model is taken into account (16, 17).

When the test cases are classified, four categories are distinguished (17); true positives (TP) as correctly classified positive cases, true negatives (TN) as correctly classified negative cases, false positives (FP) as incorrectly classified negative cases and false negatives (FN) as incorrectly clas-

sified negative cases. Then "true positive fraction" (TPF) and "false positive fraction" (FPF) are defined as follows:

$$\text{(2)} \qquad \text{TPF} = \frac{\text{TP}}{\text{TP+FN}}$$

$$\text{(3)} \qquad \text{FPF} = \frac{\text{FP}}{\text{TN+FP}}$$

Within the ROC diagram, the northwest zone is favored since the true positive (TP) rate is higher and the false positive (FP) rate is lower (18).

4. Results

4.1. Risk Factors of Cholera Incidence

A total of 286 cases were registered with cholera in 104 of 465 villages in Chabahar during 1997 - 2006. Several factors were found to be significantly correlated with cholera incidence in Chabahar rural area (P < 0.05) (Table 1). Villages with higher temperature and humidity, lower rainfall, shorter distances to border and rural health center and longer distance to the district health center were at higher risk of disease incidence, among which humidity with odds ratio of 1.12 had the highest impact.

4.2. Prediction of Cholera Incidence by Artificial Neural Network

Neural network was trained with variables of data related to 365 villages and tested with those of 100 villages. The best result (true positive on y axis and false positive on x axis) was achieved when the model was trained with statistically significant variables including temperature, humidity, rainfall, distance of villages to national border and distance of villages to rural and district health centers.

Table 2 indicates seven most important methods describing layer topology, results of training, estimate of network, sensitivity and accuracy of prediction.

4.3. Optimized Prediction of the Neural Network Using ROC

To determine a network with best specification for prediction of cholera event, ROC diagrams were analyzed with allocation of true and false positive values. Figure 2 shows ROC diagram of an optimized network with 39 neurons in input layer, 20 neurons in hidden layer and 4 neurons in output layer (as indicated by row 4 in Table 2). Such network has been trained by variables of distances of villages to frontier, health center and district health center, monthly average temperature, humidity and total rainfall data in input layer and seasonally cholera event in the output layer.

4.4. Accuracy of Prediction

Figure 3A and B show error of root mean square (ERMS) and accuracy percentage of prediction for the neural network with the best prediction (row 4 in Table 2). The ERMS parameteris extensively used for evaluating the ability of the model for prediction by quantifying how the predicted and true conditional performances are close; commonly it is considered the only criterion (19, 20). Results showed that the network predicted cholera disease event up to 80% accuracy in 100 monitored villages (test group).

The sensitivity (accuracy of disease prediction) of the network in villages was 44.4% and the specificity (accuracy of prediction of lack of illness) was 90.24%. This means that neural network model after training could specify 44.4% of villages with cholera cases and 90.24% of villages without cholera cases in test group.

Table 1. Relation Between Cholera Event (binary) and Climate Condition/Geographical Variables by Correlate Bivariate

Variables	Pearson Correlation	Sig. (2-Tailed)
Temperature	0.052 [a]	< 0.000
Rainfall	−0.048 [a]	< 0.000
Humidity	0.094 [a]	< 0.000
Elevation	0.007	0.589
Village distance to river	−0.002	0.893
Village distance to subterranean canal	−0.022	0.108
Village distance to frontier	−0.047 [a]	< 0.000
Village distance to district health center	−0.055 [a]	< 0.000
Village distance to health center	−0.034 [b]	0.011
Mutual impact of temperature, humidity and rainfall	0.092 [a]	< 0.000

[a]Correlation is significant at the 0.01 level.
[b]Correlation is significant at the 0.05 level.

Table 2. Specification and Results of Neural Network Testing with Different Variables and Number of Neurons

Input Variables	Output Variables	Hidden Layer Neuron	Input Layer Neuron	Output Layer Neuron	Root Mean Square Error (RMSE)	Accuracy [a]	Sensitivity [a]	Specificity [a]
All variables (monthly [b]**)**	Monthly cholera event	20	42	12	0.1088	74	44.44	82.92
All variables (monthly [b]**)**	Seasonal cholera event	20	42	4	0.1126	75	50	84.14
Significant variables in logistic regression model (monthly [b]**)**	Monthly cholera event	20	39	12	0.1172	78	16.66	91.46
Significant variables in logistic regression model (monthly [b]**)**	Seasonal cholera event	20	39	4	0.1478	80	44.44	90.24
All variables (seasonally [c]**)**	Seasonal cholera event	12	18	4	0.1536	75	44.44	85.37
Significant variables in logistic regression model (seasonally [c]**)**	Seasonal cholera event	10	15	4	0.1947	79	22.77	95.12
Significant variables in logistic regression model (monthly-from climate, only humidity [b]**)**	Seasonal cholera event	10	15	4	0.2029	80	16.66	95.13

[a]Values unit is percent.
[b]Monthly average of weather variables in villages.
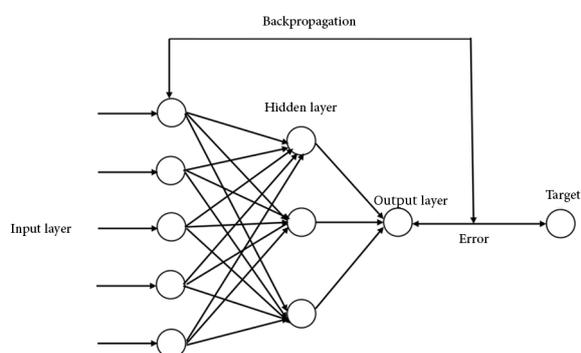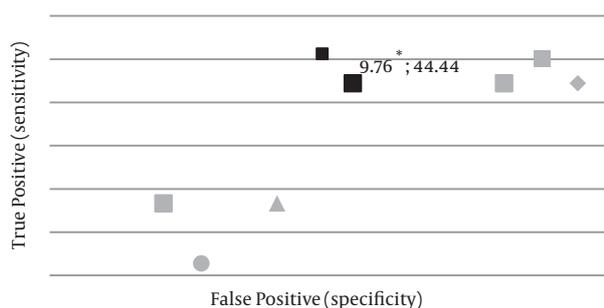[c]Seasonally average of weather variables in villages.

Figure 1. A Schematic Description of the Backpropagation Algorithm with 5 Neurons in the Input Layer, 3 in the Hidden Layer and 1 in the Output Layer

Figure 2. ROC Diagram for Determining Network with Best Specification for Prediction of Cholera Event

*Best prediction point.

Figure 3. A, Error of Root Mean Square (ERMS) vs. Number of Iteration. B, Accuracy Percentage vs. Number of Iterations

5. Discussion

In this study, cholera incidence was analyzed in Chabahar rural area, a coastal district located in southeast of Iran by determining risk factors through logistic regression and Correlate bivariate and developing prediction model by artificial neural network. Statistical modeling results described that cholera event was significantly related to climate factors, especially humidity (average 67%). In one study on linear correlation of *V. cholerae* with humidity in West Bengal using time series modeling and carrying different levels of humidity percentage in the analysis, a highly significant association was found between humidity and *V. cholerae* infection over 13 years (21). There was a significant association between the incidence of cholera and lack of rainfall (annual average 796 mm) as well. It might be due to drought that made people use stagnant water from seasonal river pounds and wells with lower depths, which had higher risk of contamination. In Bangladesh, there was a peak of cholera occurrence by low rainfall in spring and by high rainfall at the end of monsoon using
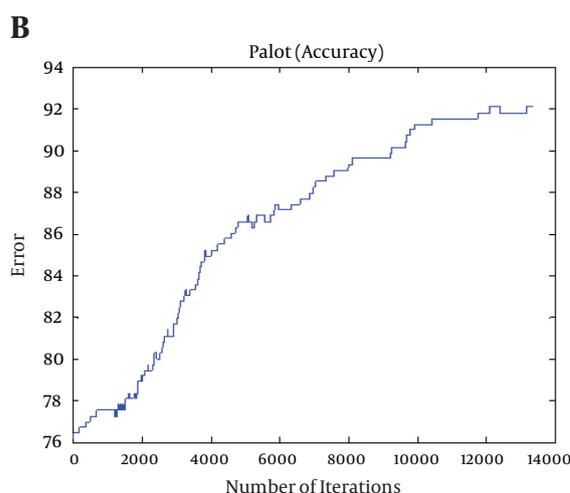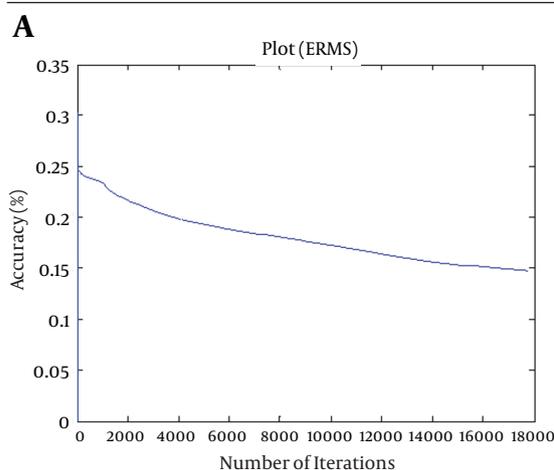
Poisson regression modeling (22). In several African nations, cholera incidence has happened mainly followed by drought or flooding as well (23). In a work investigating quantitative evidence for the influence of climate on cholera, low rainfall was shown to be related to the first cholera peak through alterations in water supply and social behavior toward sanitary measures (24). Additionally, cholera spread has been shown to be under influence of high temperature concurrent with elevated PH and plankton bloom (25). Our study showed higher temperature (average 27 degree centigrade) had a significant effect on the incidence of cholera. Therefore, the influence of climate conditions in cholera incidence has been well emphasized.

Reduction of disease hazard can be achieved by appropriate predictive measures among regions and communities at risk (5). A proper intervention necessitates synergetic approaches of prevention and awareness based on an efficient surveillance system to limit the cholera outbreak and control the disease burden in endemic regions (9).

Modeling by artificial neural networks revealed prediction ability of cholera event up to 80%, with 44.4% sensitivity and 90.24% specificity. Since the neural network identified 44.4% of villages with risk of cholera after training, it seems wise to take preventive measures in all the villages, unless the network can increase its sensitivity by being trained with comprehensive factors affecting the event of cholera.

The best prediction was achieved when trained by significant variables in statistical model. Hence, statistical analysis is a proper tool for determining variables for training neural network. However, neural networks lean on their potential for non-linear analysis of data for detection and prediction of the disease outbreak (26).

Climate changes cause new challenges for control of infectious diseases in human societies. This necessitates efficient prediction tools to take proper actions in disease incidences. Severe infectious diseases such as cholera and acute diarrhea, as well as malaria, dengue and other infections carried by vectors, are highly sensitive to climate conditions, especially temperature and rainfall. Alterations in global and local scales of such parameters threaten worldwide public health and controlling measures adopted in recent decades (27)

Considering geographical and climate features, especially when climate conditions are globally under change, it is of great importance to seek convenient algorithms to predict the spread of such diseases based on climate conditions. Artificial neural networks are proper tools for climate modeling and weather prediction (28). They are increasingly used to predict and detect specific events in bio-systems, especially for detection of various diseases being beneficial for medical intervention (26).

The accuracy of prediction significantly depends on availability of data for all possible variables. Here, lack of data on some hygienic, social and demographic indicators in Chabahar district has been one of the limitations of prediction. Such indicators include sanitary measures, sources of drinking water, situation of hygiene in restaurants and other food providers, population density, birth rate and literacy in different geographical regions. Adding additional hygienic, social and demographic variables would enhance the potential of model to predict more accurately, which remains a motivating field of survey.

5.1. Conclusions

In this study, the relation between cholera incidence in Chabahar and variables of study were statistically evaluated and a designed artificial neural network model was capable of predicting cholera event up to 80%. Our results showed that neural networks are promising tools for prediction of such infectious diseases to adopt preventive actions on time and reduce fatalities and limit undesirable social outcomes. However, due to limitations of our dataset with this neural network, sensitivity of prediction is not high enough. For achieving a more reliable prediction, comprehensive data is necessary and inclusion of influential hygienic, social and demographic parameters is recommended.

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Footnote

Authors' Contribution: Literature review, data collection, analysis and drafting: Zahra Pezeshki; editing and preparation: Mohammad Tafazzoli-Shadpour; technical advice for neural network, preparing data in GIS for using in neural network and cholera disease in order: Isar Nejadgholi, Ali Mansourian and Mohammad Rahbar; study design and interpretation: all authors.

References

1. World Health Organization. Cholera, 2012. *Wkly Epidemiol Rec.* 2013;**88**(31):321–34. [PubMed: 23980290]
2. Mandell GL, Bennet JE, Dolin R. *Principals and Practice of Infectious Diseases.* Seventh ed. London: Churchill Livingstone; 2011. pp. 2777–83.
3. Ministry of health and medical education. A review of cholera condition in Islamic Republic of Iran. Tehran;. 2011.
4. World Health Organization. *Cholera calibration. Fact sheet, N. 107.* WHO Web Site; 2011. Available from: http://www.who.int/mediacentre/factsheets/fs107/en/.
5. World Health Organization. *International health regulation.* 2nd ed. Geneva: World Health Organization; 2005. pp. 40–1.
6. Akanda AS, Jutla AS, Gute DM, Evans T, Islam S. *Reinforcing cholera intervention through prediction-aided prevention calibration.* WHO Web Site; 2012. Available from: http://www.who.int/bulletin/volumes/90/3/11-092189/en/.
7. Tu JV. Advantages and disadvantages of using artificial neural networks versus logistic regression for predicting medical outcomes. *J Clin Epidemiol.* 1996;**49**(11):1225–31. [PubMed: 8892489]
8. Helmer R, Hespanhol I, Supply W, Council SC, World Health Organization. *Water pollution control: a guide to the use of water quality management principles.* London: E & FN Spon; 1997. p. 17.
9. Wu A, Hsieh WW, Tang B. Neural network forecasts of the tropical Pacific sea surface temperatures. *Neural Netw.* 2006;**19**(2):145–54. doi: 10.1016/j.neunet.2006.01.004. [PubMed: 16527455]
10. Penna ML. [Use of an artificial neural network for detecting excess deaths due to cholera in Ceara, Brazil]. *Rev Saude Publica.* 2004;**38**(3):351–7. doi: 10.1590/S0034-89102004000300003. [PubMed: 15243663]
11. Pezeshki Z, Tafazzoli-Shadpour M, Mansourian A, Eshrati B, Omidi E, Nejadqoli I. Model of cholera dissemination using geographic information systems and fuzzy clustering means: case study, Chabahar, Iran. *Public Health.* 2012;**126**(10):881–7. doi: 10.1016/j.puhe.2012.07.002. [PubMed: 22884859]
12. Nejadgholi I, Seyyedsalehi SA. Nonlinear normalization of input patterns to speaker variability in speech recognition neural networks. *Neural Comput Appl.* 2009;**18**(1):45–55. doi: 10.1007/s00521-007-0151-5.
13. Silva LM, Marques de Sa J, Alexandre LA. Data classification with multilayer perceptrons using a generalized error function. *Neural Netw.* 2008;**21**(9):1302–10. doi: 10.1016/j.neunet.2008.04.004. [PubMed: 18572384]
14. Yilmaz B, Cunedioglu U. Source localization of focal ventricular arrhythmias using linear estimation, correlation, and backpropagation networks. *Comput Biol Med.* 2007;**37**(10):1437–45. doi:

10.1016/j.compbiomed.2007.01.008. [PubMed: 17346691]

15. Ubeyli ED. Implementing eigenvector methods/probabilistic neural networks for analysis of EEG signals. *Neural Netw.* 2008;**21**(9):1410–7. doi: 10.1016/j.neunet.2008.08.005. [PubMed: 18815008]

16. Subasi A, Alkan A, Koklukaya E, Kiymik MK. Wavelet neural network classification of EEG signals by using AR model with MLE preprocessing. *Neural Netw.* 2005;**18**(7):985–97. doi: 10.1016/j.neunet.2005.01.006. [PubMed: 15921885]

17. Mazurowski MA, Habas PA, Zurada JM, Lo JY, Baker JA, Tourassi GD. Training neural network classifiers for medical decision making: the effects of imbalanced datasets on classification performance. *Neural Netw.* 2008;**21**(2-3):427–36. doi: 10.1016/j.neunet.2007.12.031. [PubMed: 18272329]

18. Fawcett T. ROC graphs: Notes and practical considerations for researchers. *Mach learn.* 2004;**31**:1–38.

19. Faber NM. Estimating the uncertainty in estimates of root mean square error of prediction: application to determining the size of an adequate test set in multivariate calibration. *Chemometrics and Intelligent Laboratory Systems.* 1999;**49**(1):79–89. doi: 10.1016/s0169-7439(99)00027-1.

20. Sahiner B, Chan HP, Hadjiiski L. Classifier performance estimation under the constraint of a finite sample size: resampling schemes applied to neural network classifiers. *Neural Netw.* 2008;**21**(2-3):476–83. doi: 10.1016/j.neunet.2007.12.012. [PubMed: 18234468]

21. Rajendran K, Sumi A, Bhattachariya MK, Manna B, Sur D, Kobayashi N, et al. Influence of relative humidity in Vibrio cholerae infection: a time series model. *Indian J Med Res.* 2011;**133**:138–45. [PubMed: 21415487]

22. Hashizume M, Faruque AS, Wagatsuma Y, Hayashi T, Armstrong B. Cholera in Bangladesh: climatic components of seasonal variation. *Epidemiology.* 2010;**21**(5):706–10. doi: 10.1097/EDE.0b013e3181e5b053. [PubMed: 20562706]

23. World Health Organization. *Fourth emergency and humanitarian action annual review.* WHO Web Site 2008. Available from: http://www.afro.who.int/en/clusters-a-programmes/ard/emergency-and-humanitarian-action/eha-publications.html.

24. Pascual M, Bouma MJ, Dobson AP. Cholera and climate: revisiting the quantitative evidence. *Microbes and Infect.* 2002;**4**(2):237–45. doi: 10.1128/cmr.15.4.757-770.2002. [PubMed: 11880057]

25. Lipp EK, Huq A, Colwell RR. Effects of global climate on infectious disease: the cholera model. *Clin Microbiol Rev.* 2002;**15**(4):757–70. [PubMed: 12364378]

26. Lisboa PJG. A review of evidence of health benefit from artificial neural networks in medical intervention. *Neural Networks.* 2002;**15**(1):11–39. doi: 10.1016/S0893-6080(01)00111-3. [PubMed: 11958484]

27. World Health Organization. *Protecting health from climate change: Reportfor World Health Day 2008.* WHO Web Site; 2008. Available from: http://www.who.int/world-health-day/toolkit/report_web.pdf.

28. Krasnopolsky VM, Fox-Rabinovitz MS. Complex hybrid models combining deterministic and machine learning components for numerical climate modeling and weather prediction. *Neural Netw.* 2006;**19**(2):122–34. doi: 10.1016/j.neunet.2006.01.002. [PubMed: 16527454]