A Declaratory Model of Generalized Regression Neural Network (GRNN) for Estimating Sleep Apnea Index in the Elderly Suffering from Sleep Disturbance

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Abstract: *Objective*: The main objective of this paper is to present a novel model for classifying senior patients into different apnea/hypopnea index (AHI) categories based on their clinical variables.

Methods and Materials: The proposed model is a generalized regression neural network (GRNN). Three important variables were first selected from the original 30 clinical variables. The GRNN was trained using 75 patients that were randomly selected from the total117 patients. The remaining 42 patients were used for testing GRNN model. The design parameter of the network, i.e., the spread of the radial basis function, was empirically optimized. To alleviate the model complexity, the original AHI values were dichotomized into two different groups, i.e., AHI>13 and AHI<=13. The use of GRNN for this application appear fairly novel, notwithstanding that there is a host of literatures on predicting obstructive sleep apnea (OSA) syndrome from demographic or other easy means to assess clinical variables.

Results: The proposed model has sensitivity and specificity of 95.7% and 50.0%, respectively, for the training cases, while 88.0% and 52.9%, respectively, for the testing cases.

Conclusion: The proposed neural network model has outperformed existing classification approaches in terms of classification accuracy and generalization, thus it can be potentially used in clinical applications, which would lead to a reduction of the necessity of in-laboratory nocturnal sleep studies.

Keywords: AHI, sleep apnea, elderly, GRNN, ROC.

INTRODUCTION

Sleep disordered breathing (SRBD) is present in 4% of men and 2% of women above 40 years of age. However, less than 3% of patients with SRBD syndrome are diagnosed due to lack of awareness of the disease among health care practitioners and patients. Polysomnography (PSG) has been used as a golden standard for diagnosing SRBD; however, this test is available only in selected centers [1-5].

Studies on using neural network techniques for prediction of OSA are fairly sparse until recent years. In 2005, Fontenla *et al.* [6] presented a novel approach for sleep apnea classification. Their goal was to classify each apnea in one of three basic types: obstructive, central and mixed [6].

More recently, Liu *et al.* in 2007 [7, 8] developed an innovative signal classification method capable of differentiating subjects with sleep disorders which cause excessive daytime sleepiness (EDS) from normal control subjects who do not have a sleep disorder. The aim of their study was to develop an artificial neural network to predict sleep disordered breathing in the elderly.

CLINICAL SUBJECTS AND MATERIALS

The data were collected during the period from 1 January 2002 to 31 January 2003 at the Sleep Medicine Center, Changhua Christian Medical Centre, Taiwan. While patients' confidentiality was maintained, accessing to patients' records was approved by the ethics committee of Changhua Christian Medical Centre. Among the subjects who underwent nocturnal polysomnography (PSG), no patients with heart failure and chronic obstructive lung disease were admitted. Also the data belonged to subjects who were younger than 65 years were excluded. As a result, the clinical data included a total of 124 elderly aged from 65 to 88.5 years. Out of the 124 subjects, a total of 117 subjects had both weight and height, from which body mass index (BMI) was calculated. Apnea/hypopnea index (AHI), defined as the number of events of apnea/hypoxia per hour of sleep, was measured from PSG, which documented the objective sleep criteria. Although PSG has been the golden standard for the diagnosis of obstructive sleep apnea syndrome (OSAS), it is highly invasive, time-consuming, and expensive.

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The ratio of females/males in this data is 1: 1.7. The mean age of male subjects is 71.6 ± 4.47 years, while that of females is 72.3 ± 5.47 years. All subjects have chief complaints of sleeping disturbance.

The reasons for selecting this elderly age group are as follow: First, this field is a rather understudied entity, especially in sleep research on such an age group mentioned in this article. Indeed, all patients are vulnerable, but it is so much as those who are elderly. Thus, the difficulty of sleep study is due to the problems faced in obtaining volunteers as well as the possible philosophical and theological under-tones that people in general associate with 'they do sleep when they are at the end stage of their life'. Moreover, there is as well the misconception of sleep study on 'those who haven't many years left anyhow' in general. Next, there are more than half of community-living people aged 65 year and over experience sleep disturbances. Third, sleep onset is often reported to be more difficult and nighttime awakenings more prevalent in the elderly.

The datum source of clinical subjects includes this author's own study of 124 elderly aged from 65 to 88.5 years. Predominantly, the data of the total sleep time (TST), except that related to body height and its distribution, have been reported elsewhere [9].

Nocturnal In-Laboratory Polysomnography

Nocturnal polysomnography (PSG) (Alice 4 Sleep Diagnostic System, Respironics, Carlsbad, CA._USA) was done from about 9:30 pm to 6:30am next morning in the sleep laboratory. The following parameters were measured and recorded by the PSG: (i) chest and abdominal wall motion by uncalibrated respiratory inductance plethysmography; (ii) heart rate by ECG; (iii) inspired and end-tidal carbon dioxide pressure ($PETCO_2$), sampled at the nose or mouth at a rate of 60 mL/min by mass spectrometry (model 1100 Medical Gas Analyzer, Perkin Elmer; Pomona, Calif.) or by capnography (model 1000 Capnograph, Nellcor, Hayward, Calif. USA); (iv) combined oral nasal air flow, sampled with a three-pronged thermistor placed at the upper lip; (v) arterial oxygen saturation by pulse oximetry (model N 200, Nellcor, Hayward, Calif., USA); (vi) oximeter pulse wave form; (vii) electro-oculogram; (viii) EEG in overnight PSG; (ix) chin electromyogram; (x) actigraphy (placed on the hand); and (xi) microphone placed over the neck to monitor snoring. The transducers and lead wires permitted normal positional changes during sleep. Bedtime and awakening time were at each subject's discretion; the PSG was terminated after the final wakening.

Clinical Classification of Obstructive Sleep Apnea Syndrome

Apnea was defined as a decrease in airflow of ≥ 90% for a minimum of 10 seconds. Hypopnea was defined as ≥ 30% decrease in airflow and desaturations required a ≥ 3% decrease in oxygen saturation for a minimum of 10 seconds. The apnea hypopnea index (AHI) was calculated as the sum of apneas and hypopneas divided by nocturnal hours of sleep.

Based on the protocol of American Academy of Sleep Medicine Task Force (1999) [11]. The degree in severity of sleep apnea is defined in Table **1**.

Table 1: Degrees of Severity of Sleep Apnea (Elevated AHI)

Sleep variables with Apnea (changes of AHI)	The Degree
Apnea (AHI<5)	Zero degree
Apnea (AHI 5~15)	first degree,
Apnea (AHI 15~30)	second degree,
Apnea (AHI>30)	third degree,

In terms of the staging of sleep, it follows Rechtschaffen *et al*'s. criteria (1963) [12].

The METHOD Description

Generalized regression neural network (GRNN) is a special type of neural networks. And GRNN is a universal approximator that can approximate a continuous function to an arbitrary accuracy, given a sufficient number of neurons [14]. Comparing to conventional multilayer perceptron networks, GRNN has several advantages, including 1) it can accurately approximate functions from sparse and noisy data; 2) it can converge to the conditional mean surface with increasing the number of data samples; 3) it only has one design parameter (i.e., spread factor); and 4) it is easy to train. It is these unique advantages associated with GRNN that make this author to choose GRNN as a model for predicting OSA syndrome.

In this study, a brief description of the method is as following: the single design parameter, i.e., spread factor of GRNN is obtained via empirical optimization. The input variables to the GRNN model are also

empirically determined based on their classification performance. The three variables finally selected for this model are BMI, neck circumference (NC), and nocturnal total sleep time (TST). It is worth pointing out that TST values used in our model are dichotomized into two levels, <=6 hours and > 6 hours, before input to the model. It is also interesting to note that including age inputs to our model does not improve our model performance. (A figure of ROC to be followed).

To alleviate the model's complexity, the original AHI values (the dependent variable of our model) were also dichotomized into two different groups, i.e., AHI>13 and AHI<=13. That is, the GRNN model is designed to perform a 2-class classification.

RESULTS

The 117 cases are randomly split into two disjoint subsets: 75 cases for training, whereas 42 cases for testing (validation).

To evaluate the goodness of the GRNN model, following performance metrics are used in this study: 1) Accuracy; 2) Sensitivity/specificity; 3) PPV/NPV; Kappa statistics; and 4) AUC, the area under curve of ROC**.**

GRNN Performance

Figure **1** shows the ROC curves of the GRNN model for both the training and testing sets, respectively. For the training set, the area under curve (AUC) of the ROC is 0.8405 with 95% confidence interval from 0.8304 to 0.8506. For the testing set, the AUC calculated for this ROC is 0.751 with 95% confidence intervals between 0.728, and 0.77.

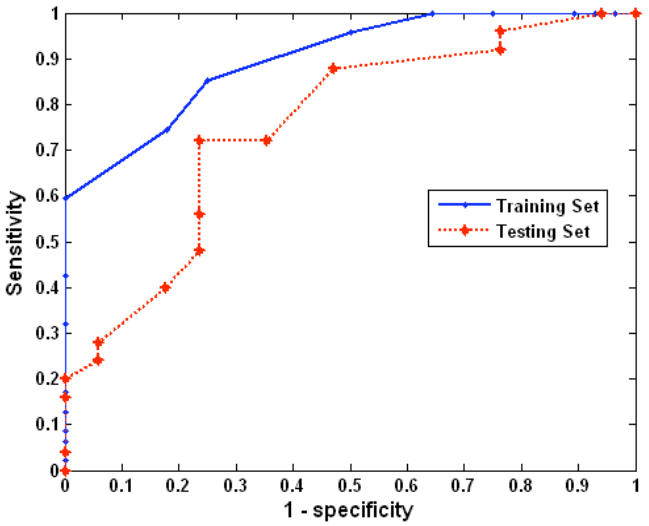

Figure 1: ROC curve for the training set.

Given the fact that the desired requirements for sensitivity and specificity are unknown, we choose the decision threshold for GRNN model to be 0.4, which gives the sensitivity and specificity of 95.7% and 50%, respectively, for training set. The confusion matrices corresponding to the decision threshold of 0.4 are given in Table **2**, from which other performance measures are derived. Those performance measures are summarized in Table **3**.

Table 2: Confusion Matrix of the Training and Testing Sets

(a)

		Predicted	
		AHI<=13	**AHI>13**
Truth	AHI<=13	14	14
	AHI>13	2	45

(b)

		Predicted	
		AHI<=13	**AHI>13**
Truth	AHI<=13	9	8
	AHI>13	3	22

Table 3: Summary of Performance Metrics of GRNN Model

Performance metrics	Training set	Testing set
Accuracy	0.787	0.738
Sensitivity	0.957	0.880
Specificity	0.500	0.529
Positive predictive value	0.763	0.733
Negative predictive value	0.875	0.750
Kappa	0.501	0.430
(95% CI)	*[0.302, 0.700]*	*[0.154, 0.705]*
AUC	0.8405	0.751
(95% CI)	*[0.830, 0.851]*	*[0.728, 0.774]*

Legend: By looking at the Table **3**, it can help to identify subjects with moderate to severe degree OSAHS (the second and third degrees) who need PSG badly, but were misclassified as AHI <=13 by the model, with a rate of 12%. Among the total five (two in the training set whereas three in the testing set) being misclassified as AHI <=13, there were merely one with AHI >25, whereas the other >40. The rest of three were all had AHI < 18 per hour.

From Table **2** one can observe the followings. Using this model, for the 47 subjects whose AHI measured from the nocturnal sleep study with in-laboratory PSG is greater than 13, 45 were correctly classified, whereas 2 was misclassified as AHI being less than or equal 13. Out of 42 testing subjects, there are 25

Table 4: Misclassified Cases

Sex	Age	High	weight	BMI	NC	Latency	TST	Snore	RDI/T
For training set									
F	64.85	150	48.2	21.42	34	12	351	534	17.6
F	72.96	150	54.3	24.13	35	8	247.5	0	16.2
For testing set									
F	72.53	164	57.5	21.38	34.5	6.5	315	674	40.4
F	69.88	159	53.1	21.00	35	22.5	295	752	14.2
M	66.72	145.5	54	25.51	34	38.5	227.5	1399	25.5

subjects whose AHI is greater than 13. For those 25 subjects, our model correctly classifies 22 of them while misclassifies 3, which gives the sensitivity of 88.0%. Similarly, for the 17 subjects whose AHI is less than or equal to 13, our model correctly classifies 9 and misclassifies 8, which yields the specificity 52.9%.

Characteristics of the two misclassified subjects are listed in Table **4**, from which one can see that both subjects are women and their AHIs are 17.6 and 16.2, respectively. Characteristics of the three subjects whose AHI is greater than 13 but misclassified as AHI being less than 13 are also listed in Table **4**.

The un-weighed likelihood ratios for the training set are 1.914 and 0.086 for conventional positive and negative, respectively. The un-weighed likelihood ratios for the testing set are 1.868 and 0.227 for conventional positive and negative, respectively.

Comparison with the Results of other Regression Models

To demonstrate performance superiority of GRNN model proposed in this study, two other models, that is, linear regression and logistic regression are developed for the same data and the results are compared and shown in Tables **5a** and **5b** for the training and testing sets, respectively. From Table **5**, one can clearly see that GRNN model performs significantly better than both linear and logistic regression models do.

Comparison with Results of other Studies

To better appreciate this model's performance, results from this model are further compared with those from other studies (See Table **6**). While all three other studies show relatively lower sensitivity (ranging from 74% to 85%), this study has higher sensitivity (88% and 95.7% for testing and training respectively). It is worth noting that the comparison among different studies is rather difficult. Hence, linear and logistic regressions are taken, but not other nonlinear model than logistic. Because logistic regression predicts the probability of particular outcomes [31].

Logistic regression is an alternative to Fisher's [32] 1936 method, linear discriminant analysis [31]. If the assumptions of linear discriminant analysis hold,

Table 5a: Comparison among Different Models – Training Set

Performance metrics	Linear regression	Logistic regression	GRNN
Accuracy	0.667	0.667	0.787
Sensitivity	0.809	0.809	0.957
Specificity	0.429	0.429	0.500
Positive predictive value	0.704	0.704	0.763
Negative predictive value	0.571	0.571	0.875
Kappa	0.250	0.250	0.501
(95% CI)	*[0.026, 0.474]*	*[0.026, 0.474]*	*[0.302, 0.700]*
AUC	0.628	0.636	0.841
(95% CI)	*[0.613, 0.642]*	*[0.622, 0.651]*	*[0.830, 0.851]*

Table 5b: Comparison among Different Models – Testing Set

Performance metrics	Linear regression	Logistic regression	GRNN
Accuracy	0.667	0.690	0.738
Sensitivity	0.800	0.800	0.880
Specificity	0.471	0.529	0.529
Positive predictive value	0.690	0.714	0.733
Negative predictive value	0.615	0.643	0.750
Kappa	0.028	0.339	0.430
(95% CI)	*[-0.011,0.574]*	*[0.05, 0.628]*	*[0.154, 0.705]*
AUC	0.617	0.614	0.751
(95% CI)	*[0.590,0.643]*	*[0.588, 0.641]*	*[0.728, 0.774]*

application of Bayes' rule to reverse the conditioning results in the logistic model, so if linear discriminant assumptions are true, logistic regression assumptions must hold. The converse is not true, so the logistic model has fewer assumptions than discriminant analysis and makes no assumption on the distribution of the independent variables.

Comments on Sensitivity and Specificity

It is well understood that designing a diagnostic system to achieve both high sensitivity and specificity is almost impossible in real-world applications. Thus striking a best trade-off between the two is the most practical solution. Obviously choosing such trade-off between sensitivity and specificity is problem-dependent. That is, there are no such thing as good numbers for sensitivity and specificity. For instance, for diagnosing clinically significant ankle fractures, the Ottawa Ankle Rule had a specificity of only 50% but a sensitivity of 100%. Henceforth, not all patients will meet the decision rule criteria, but in their cases of those who do, the necessity for an ankle radiograph can be disregarded. The Ottawa Ankle Rule has a diagnostic gray zone of about 70%, but in the field testing, it is estimated that the rule has reduced the necessity for ankle radiography by 30% (Siell *et al.*) [20].

For another clinical example, due to the severe morbidity associated with Obesity Hypoventilation Syndrome (OHS), some researchers selected a highly sensitive threshold of serum bicarbonate level. A threshold of 27 mEq/l had a sensitivity of 92% and a specificity of 50%. Merely 3% of patients with a serum bicarbonate level< 27 mEq/l had hypercapnia compared to 50% with a serum bicarbonate ≥27 mEq/l. In their conclusion, OHS is common in severe OSA. A normal serum bicarbonate level excludes hypercapnia and an elevated serum bicarbonate level should prompt clinicians to measure arterial blood gases [21, 22].

There are several other instances in the literature of sleep medicine. For example, an Italian version of the Epworth sleepiness scale (ESS) is an easy-to-use form useful for preliminary screening of daytime sleepiness level in specialist settings. Noticeably, the (ESS) cut-off scores associated with the best sensitivity and specificity were set to be 12 and 17. For the 5-min

Table 6: The Comparison among Various Studies

	FEIN *et al.*	Kapuniai *et al.*	Crocker *et al.*	This study (Training group) n=75	This study (Testing group) n=42
Method	#	#	Logistic regression	GRNN	GRNN
Sensitivity	74%	78"%	85%	95.7%	88.0%
Specificity	93%	67%	61%	50.0%	52.9%
AHI predicted	>=10	>10	>15	>13	>13
Probability cutoff-point	NA	NA	>= 0.15	>=0.40	>=0.40

[#]According to the original respective authors, their methods were based on derivation from ascribing a point value to a number of clinical characteristics that have been indicative for OSAS.

multiple sleep latency test (MSLT) cut-off, sensitivities were 87% and 47% for cut-off scores of 12 and 17 respectively, and specificities of 39% and 74%. For the 8-min MSLT cut-off, sensitivities were 84% and 49%, and specificities of 50% and 88% [22].

In this paper, our model achieves the sensitivity of 95.7% and specificity of 50.0 % for the training set, while 88.0%, and 52.9%, respectively, for the testing set. Specificity of equal or greater than 50% while sensitivity is higher than 85% indicates that our model developed in this paper is reasonable. Our sensitivity and specificity results are based on the decision threshold of 0.40, which can be tuned if costs associated with false positive and false negative errors are known.

DISCUSSION

It is true that *the widely recognized definition of sleep apnea has the round numbers of AHI cutoff = 5, 10, and 15. Conversely, in this study,* data did indicate that using AHI of 13 as cutoff is better than using 15. A brief review of the following mechanisms may help to understand the issues that we shall advance latter on.

The reason why we selected AHI cutoff of 13 events per hours is as follows:

While the accepted AHI cutoffs for defining OSA severity is somewhat arbitrary, as suggested by the author and others, an AHI cutoff of 13 instead of 15 events per hour seems 'unusual'. Nevertheless, this was used merely based on our previous clinical experience.

Furthermore, our selection of the criterion is clinically and not statistically. What is the actual clinical meaning of the two events represented by a cutoff of 13 (more precisely, 13.21) and not 15 is as follows.

Clinically, we do observe a better sleep efficiency (%) for those patients whose AHI were< 13.21 but not for those whose AHI > 13.21 (p=0.05). On the contrary, when we use AHI cutoff of 15, there is no difference between AHI <15 and > 15 these two groups. It can thus be stated that the employing of AHI cutoff of 13 is based on clinical finding of sleep efficiency (%) The employing of AHI cutoff 13 is not based on this GRNN modeling alone in this study.

OSA was defined by a polysomnographical AHI cutoff that has been considered by investigators to be clinically important. The cutoff of 13 for AHI does fall into the current definition of sleep apnea. Although the value was derived from the ROC, its clinical significance was particularly for symptomatic elderly patients. In this model, with AHI = 13 is obvious for the reason as follows. The cutoff value of 13 for AHI falls into the upper range of mild sleep apnea. In addition, there are the clinical significances of any particular cut off points between AHI 10 and 20 9. In fact, AHI=15 has never been the absolute and sole point of cutoff.

It all dependents on the nature of disease, and other clinical factors involved along with the setup of the device used in the measurement. For example, if the cutoff value of estimated AHI set at 17, instead of 15, there was optimal for the differentiation between patients with or without sleep related breathing disorder using the Lifescreen Apnea software from Holter ECG as an accurate, specific and sensitive method for the detection and classification of obstructive and mixed SRBD [19]. According to their estimated AHI, 50 (68%) patients were correctly diagnosed. The ROC analysis showed high accuracy of SRBD detection using Est. AHI: AUC – 0.91 with sensitivity – 91.2%, specificity – 87.5%, PPV – 88.6%, and NPV – 88.9%.

Cost Effectiveness Assessment of this Model

As shown in the section of RESULTS, with the decision threshold of 0.40, our GRNN model achieves the sensitivity of 95.7% and specificity of 50.0 % for the training set, as well as 88.0%, and 52.9% respectively. If a PSG sleep study were performed only in subjects for whom the model predicted an AHI > 13, the number of PSG required for the 42 subjects in our testing set would have been decreased from 25 to 22, a 12% (3/22) reduction in the number of PSG taken. To assess true cost effectiveness of our model, a cost-benefit analysis on the numbers of false positive and false negative case is needed, which can take into account the impact of quality of life on the subject (patient) and the family, and the financial impact on the community. In this model, the specificity attained of >=50% when sensitivity is high (>=88.0%), it is definitely indicative that the methodology used in this model is geared up for prime time.

It is important to remind readers that the study conducted in this paper here is not a CPAP treatment study, even though it is indeed a statistically nonparametric group undergoing medically diagnostic PSG. Nevertheless, this author intends to develop the study into a CPAP treatment study in the near future, with an aim in cost–effective purpose and as well

looking forward in seeking potential saving economically.

With this model, it can determine that if a clinical subject with complaints of poor sleep, if also with an AHI around the level of 13 and requires a CPAP treatment, whoever clinical subject may lead to an earlier therapeutic action without the need of going through a diagnostic PSG test.

LIMITATIONS OF STUDY

Some clinical variables, such as TST, used in this model for estimating AHI may require some more other device in order to measure the sleep time as accurate as possible.

Sleep latency, which has been removed from being as an initial input with a comparison, data of the total sleep time is somewhat easier to obtain and then measure than those of sleep latency. For example, devices such monitors using web-camera together with a home personal computer (PC) can serve the purpose. They are not expensive. For TST, the measurement with a web camera with a PC is quite cost-effective.

As compared to the portable home monitoring for OSA, the disadvantages follow. Generally, the set-up to be used at the examinees' homes using portable recording with an ambulatory system recording nasal/oral airflow (thermistor) measurement without electroencephalogram (EEG) or nasal airway pressure or pleural pressure measurements. By contrast, it is most important to note that in this context, the recording system that are described here for the ambulatory monitoring system indeed lacks the ability to detect any upper airway resistance.

On the other hand, the moderate specificity depicted in our model may suggest that when we use this model, the chance of co-applying other expensive extra tests is not indicated.

Although the expense of these additional screening, web-camera and P C, may not be disregarded, the expense of setting up a web-camera with the P C is really minimal, since often home P C is preexisting.

Using TST as a variable in this model is meaningful for the reason as follows. First of all, TST has been one of the 'good' (friendly) variables selected by the algorism used in this model. Nevertheless, one might still argue that it might be 'meaningless to use a PSG variable such a TST to predict OSA'. At first glance, such a statement sounds 'plausible'. However, it is neither logical nor acceptable. Unlike other sleep medicine variables, TST is one of the few that can be measured easily and precisely if only with a web-camera and a home P C at home instead of being at the Sleep Medicine Laboratory. Second, whoever believes that PSG and actigraphy, other than PSG, are the only two precise ways in obtaining a record of an individual's TST; such an assumption may be misleading. Third, TST, unlike sleep latency, can be used as an easily obtainable clinical datum.

CONCLUSION

This paper has its declaratory character. Hence, in conclusion, the variables of generalization of GRNN model over the general population in sleep medicine is possible.

It all depends on the various combinations of influences among variables of age, gender, weight, and BMI. They may attribute an entire spectrum of significant explanatory power for the AHI, above and beyond what has been explained by the clinical samples in the current study.

ABBREVIATIONS

AHI = apnea/hypopnea index

AUC = area under curve

BMI = body mass index

ROC = receiver operator characteristics

ANN = artificial neural network

GRNN = generalized regression neural network

NC = neck circumference

NN = neural network

OSA = obstructive sleep apnea

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