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PAPER

Prediction of lupus nephritis in patients with systemic lupus erythematosus using artificial neural networks

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Artificial neural networks are intelligent systems that have been successfully used for prediction in different medical fields. In this study, efficiency of neural networks for prediction of lupus nephritis in patients with systemic lupus erythematosus (SLE) was compared with a logistic regression model and clinicians' diagnosis. Overall accuracy, sensitivity and specificity of the optimal neural network were 68.69, 73.77 and 62.96%, respectively. Overall accuracy of neural network was greater than the other two methods (P-value < 0.05). The neural network was more specific in predicting lupus nephritis (P-value < 0.01), but there was no significant difference between sensitivities of the three methods. Sensitivities of all three methods were greater than their specificities. We concluded that neural networks are efficient in predicting lupus nephritis in SLE patients. *Lupus* (2002) **11,** 485–492.

Key words: artificial neural network; lupus nephritis; prediction; regression analysis

Introduction

Predicting disease complications and estimation of its prognosis are two important constituents of medical management. In recent years, new methods such as artificial neural networks and regression models have been proposed to improve the performance of physicians and surgeons in risk stratification of their patients, clinical decision-making and patient management. In this regard, neural networks have been used in different medical fields such as cardiology for predicting the probability of acute myocardial infarction,[1] emergency medicine for prediction of trauma outcomes and screening of high-risk patients,[2–5] surgery for determining the outcome and risk factors of operation,[6–12] oncology for cancer diagnosis, staging and survival analysis,[13–23] pediatrics for prediction of infantile morbidity and mortality[24] and more recently, in estimating for mortality rate and outcome prediction of disease complications.[25–30]

A few studies have compared the ability of neural networks for clinical prediction with linear, multivariate and logistic regression analyses in the aforementioned fields.[5,7,8,13,19,21,24,29] The accuracy of these methods has been compared with physicians' clinical diagnoses,[9,15,18,21,26] discriminant function analysis[10,25] and also some scoring systems.[12,16,17,28] In a study conducted by Esdaile *et al.*,[31] the accuracy of prediction of lupus nephritis outcome made by experienced clinicians was compared with a regression model. They assessed the performance of physicians and a statistically generated computer model (regression model) for prediction of short-term outcome (serum creatinine level at one year) and long-term outcome (renal insufficiency) of lupus nephritis.

Kidney involvement is one of the most serious complications of lupus. It has a major effect on morbidity and mortality. Earlier diagnosis of lupus nephritis leads to successful outcome and better treatment plan by which renal failure could be prevented.

In this study, we used an artificial neural network for prediction of lupus nephritis in systemic lupus erythematosus (SLE) patients and compared it with the results obtained from a regression model and experienced clinicians.

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There are different factors that are correlated with prognosis, predisposition and progression of lupus nephritis such as sex (male), age (youngsters), black race, chronicity index, initial hypertention, hyperlipidemia, elevated level of serum creatinine at the time of diagnosis, anti-dsDNA, antiphospholipid and anticardiolipin antibodies, thrombocytopenia, leukopenia, anemia, low serum complement, LE cell, genetic factors such as some HLA types (e.g., DR2, DQw1), Fc gamma RIIA alleles, familial clustering and environmental factors such as smoking and silica exposure.[32–51]

A number of factors mentioned here have been used (in accordance with the selection algorithm described in the method part) to achieve the prediction by different methods. The degree of confidence in prediction has been evaluated for these methods.

Methods

Data source

The medical charts of all the patients who had been admitted to Rasool Akram General Hospital (Tehran, Iran) from 1991 to 2000 and had been labeled as SLE were reviewed retrospectively. The data of 242 patients, who fullfiled the American College of Rheumatology (ACR) criteria for classification of SLE were collected.[52] We selected six items of criteria (arthritis, oral ulcers, seizure or psychosis, anti-dsDNA, coagulation abnormality, haematologic disorders) as a part of the predicting factors.

Diagnosis of lupus nephritis in the majority of cases had been confirmed by light microscopy of renal biopsy and had been classified according to WHO (World Health Organization) classification of lupus nephritis.[53] In some cases, lupus nephritis has been diagnosed clinically according to renal manifestations and also paraclinical findings (cellular casts, may be red cell, haemoglobin, granular, tubular or mixed in urine analysis, and persistent proteinuria greater than 0.5 g per day or greater than 3 + if quantitation not performed). Most of the cases (150 cases) had one or more missing data.

Methods of prediction

Artificial neural network (see Appendix). We designed several architectures of multi-layered perceptron neural network in Matlab 5.3 in order to obtain optimal architecture. In these structures, the numbers of input and hidden layer nodes and the numbers of hidden layers are different. Only one node was used at the output layer, which determined renal involvement by a binary code. Using a back-propagation algorithm for training the network, the desired output (existence or nonexistence of lupus nephritis) was compared with network output in each session of training and synaptic weights of the network altered according to this difference (by delta rule).[54] At the beginning of training, synaptic weights were determined randomly. Training of the network was stopped when minimal square error (MSE) in time decreased to below 4%. Over-trained trials (MSE $< 1\%$) and under-trained trials (MSE $> 10\%$) were eliminated. Under-training was produced due to local minima.[54] At the testing phase, the values more than 0.5 (threshold) in the network output were considered as 1 (renal involvement) and the values less than 0.5 were considered as 0 (no renal involvement). A three-layered neural network is shown in Figure 1.

As the majority of cases included missing data, evaluation of missing parameters was necessary. Three different methods were used for this aim. The simplest and the most inexact method was substituting missing parameters with random values in the acceptable range. In the next method, we used redundancy analysis in which a correlation matrix predicted missing data. Finally, the SPSS package was used for estimation of missing data.

In a number of neural networks that we designed, the input patterns were selected from all cases of data source (all cases with both corrected missing and non-missing data) during training and testing phases. However, in the rest of the designed networks, input patterns of training and testing phases included only cases which had complete data.

As the number of cases containing complete data was insufficient for training the network, we used the 'leave-one-out' method.[55] Using this method we

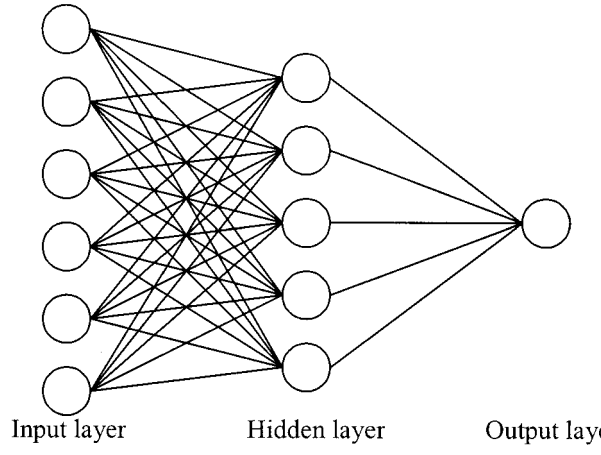

Figure 1 A three-layered fully interconnected neural network used in our article. Lines between nodes represent synaptic connections, which are initially determined by random values and then altered by delta learning rule of the backpropagation algorithm.

selected 95% of cases as training and 5% as testing patterns. After one session of training and testing, we substituted the test cases with other new cases, which had previously been used as training cases. This task continued until all the cases were used in the testing phase. Finally, the averages of correct percentages of predictions were calculated.

As the ratio of training cases to the number of input factors (the predisposing factors for lupus nephritis) was relatively low, the network could not be trained. Thus the most important predisposing factors (as the items of input layer) for prediction of lupus nephritis had to be selected. We used the following two methods for this selection:

(1) using the literature to determine the most important factors predisposing to and predicting the outcome of lupus nephritis; and
(2) using a statistical method (correlation coefficient) to determine the most significant predicting factors associated with existence of lupus nephritis for our cases.

The most recommended and common factors obtained by the above methods formed the fixed part of input layer in all of designed networks. The other input nodes were chosen by trial and error to achieve the best prediction result.

The list of all predisposing factors used in our article is illustrated in Table 1. Age and latency of SLE diagnosis were numerical variables and normalized between 0 and 1. Other factors were nominal and encoded to the network by a binary code.

Regression model. We used SPSS-10.0 for prediction of lupus nephritis by logistic regression model. Using the 'leave-one-out' method, 30 randomly selected cases were tested in each session of testing and the final averages of sensitivity, specificity and overall accuracy of the model were calculated. Arthritis and hypocomplementemia were selected as regressors from the list of covariates (11 factors in all) through the stepwise conditional method. Receiver operating characteristics (ROC) curves were used to determine the best positivity criterion for the model.

Table 1 Eleven clinical and paraclinical criteria used for prediction of lupus nephritis

1	Sex
2	Age
3	Arthritis
4	Oral ulcers
5	Seizure or psychosis
6	Anti-dsDNA
7	Anticardiolipin Ab or false-positive VDRL
8	Hypocomplementemia (C3 or C4 or CH50)
9	LE cell
10	Haematologic disorder (hemolytic anemia or leukopenia or lymphopenia or thrombocytopenia)
11	Time interval between onset of symptoms and SLE diagnosis

Experienced clinicians. Five specialists (four rheumathologists and one nephrologist) were requested to predict lupus nephritis for 20 randomly selected SLE cases. All the specialists working in a referral center for SLE patients had at least 5 years' experience in dealing with SLE patients complicated by nephritis. Information on the 11 factors (in Table 1) was given to each doctor. They also determined their own criteria for this prediction and ranked these criteria. Final performance of this method was obtained by averaging the percentages of correct responses.

Statistical analysis

Correlation between SLE-related clinical factors (nominal ones) and lupus nephritis for our patients was calculated by nominal-by-nominal phi and Cramer's V coefficient in SPSS. Correlation of age and latency of SLE diagnosis with lupus nephritis was achieved using the *t*-test.

Performances of the above-mentioned methods were expressed as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) indexes of these methods in prediction of lupus nephritis. Validity criteria of three methods were compared using χ^2 test.

Results

The optimal back propagation network had one hidden layer and included six input nodes, five hidden layer nodes and one output node. This architecture was designed only for input patterns contained non-missing data (115 cases). As the number of cases was low, we applied low numbers of nodes in the input layer. The optimal network had nine input nodes, six hidden nodes in one hidden layer and one output node when all cases (242 cases), including corrected missing and non-missing data, were used in the input.

Factors used in the input layer of the initial network were age, arthritis, anti-dsDNA, coagulation factors (anticardiolipin Ab or false-positive VDRL), hypocomplementemia and the time interval between onset of symptoms and SLE diagnosis. In the later network, sex, haematologic disorder and LE cell positivity were added to previous items.

Correlation coefficients between different nominal factors and lupus nephritis are shown in Figure 2.

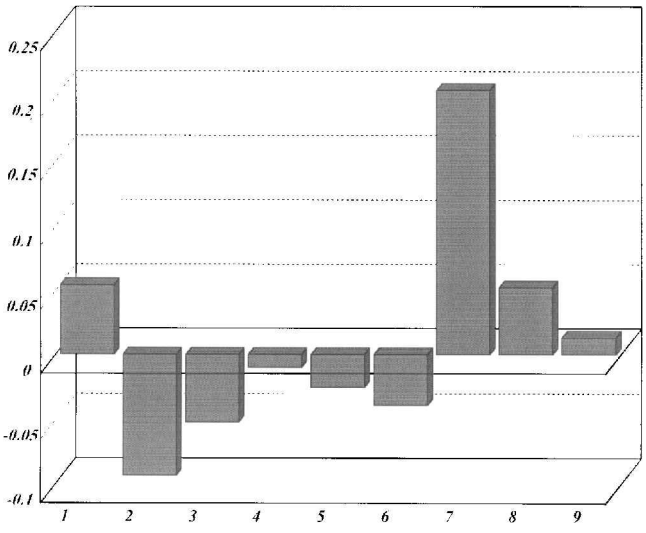

Figure 2 Correlation coefficients between different nominal factors and lupus nephritis. 1, Sex; 2, arthritis; 3, oral ulcers; 4, CNS lupus; 5, anti-dsDNA; 6, coagulation abnormality; 7, hypocomplementemia; 8, LE cell; 9, haematologic disorder.

Hypocomplementemia had a significant correlation with lupus nephritis (P-value < 0.01 using χ^2 test).

Seizure or psychosis and oral ulcers were not used according to our methods for selecting input factors. The LE cell had a good correlation with existence of lupus nephritis in our cases, but we ignored it in the former network due to its considerable missing data.

Age and latency of SLE diagnosis were numerical factors. Mean of ages in nephritis and non-nephritis groups had no significant difference, although nephritis in young (age < 20) and old (age > 40) patients was significantly more frequent than in middle-aged patients (P-value < 0.05 using t-test), but the number of outlier ages was few. Latency mean of SLE diagnosis in nephritis group was less than the non-nephritis group (P-value < 0.05 using t-test). The result indicated that SLE in nephritis group is more severe than other group, which leads to earlier diagnosis.

Performance of neural network in lupus nephritis prediction was calculated in the testing phase for the optimal designed network. The correct percentage (overall accuracy) of prediction was 68.69% using non-missing data and 65.28% using all data when the statistical regression method was used for estimation of missing data. Performance decreased to 60.43 and 55.17%, respectively, when redundancy analysis and random methods were used.

The neural network statistics for the validation set showed a sensitivity and specificity of 73.77 and 62.96%, respectively, in the condition of non-missing data prediction (6-5-1 perceptron network). Sensitivity and specificity of prediction for all data (9-6-1 perceptron network) were 67.78 and 61.29%, respectively.

PPV for 6-5-1 and 9-6-1 networks were 69.23 and 73.72%, respectively. NPV for 6-5-1 and 9-6-1 networks were 68 and 54.28%, respectively.

Logistic regression model sensitivity, specificity and overall accuracy were 73.17, 34.48 and 57.14%, respectively, when the cut-off value was 0.5 (in the model, the existence of lupus nephritis was determined by value 1 and its absence was determined by value 0). PPV and NPV of the model were 61.22 and 47.61%, respectively. Using the ROC curve, the best regression gave an area under the ROC curve of 0.538, a sensitivity of 84.6% and specificity of 38.5% (the positivity criterion was 0.4163).

The average of correct percentages in prediction (overall accuracy) for clinicians was 53.33%. Clinicians' sensitivity, specificity, PPV and NPV were 61.9, 33.33, 68.42 and 27.27%, respectively.

Overall accuracy of neural network was better than two other methods (P-value < 0.05 using χ^2 test). Comparison of three methods' specificity also showed an improvement for neural network (P-value < 0.01 using χ^2 test). Clinicians ranked their own important criteria for prediction of lupus nephritis (see Table 2). Figure 3 shows the comparative diagram for performances of prediction by different methods.

Discussion

Our results showed that the neural network had a good performance in prediction of lupus nephritis in SLE

Table 2 Ranking of criteria by clinicians for prediction of lupus nephritis in SLE patients

Clinician 1	*Clinician 2*	*Clinician 3*	*Clinician 4*	*Clinician 5*
1. Anti-dsDNA	1. Anti-dsDNA	1. Anti-dsDNA	1. Anti-dsDNA	1. Anti-dsDNA
2. Hypo-complementemia	2. Hypo-complementemia	2. Haematologic disorder	2. Hypo-complementemia	2. Latency of SLE diagnosis
3. Latency of SLE diagnosis	3. Latency of SLE diagnosis	3. Hypo-complementemia	3. Age	3. Hypo-complementemia
4. Haematologic disorder	4. LE cell	4. Age	4. Haematologic disorder	
			5. Sex	

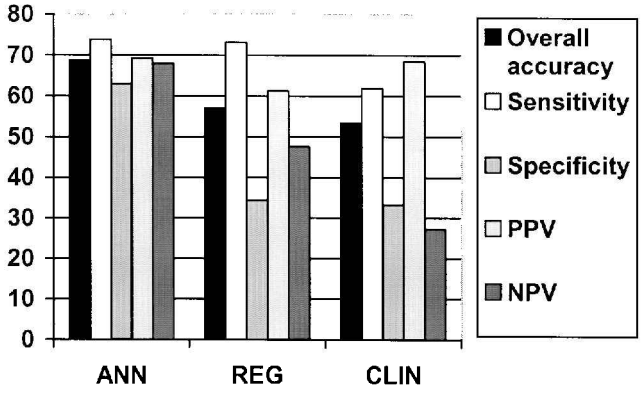

Figure 3 Comparative diagram for overall accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of optimal artificial neural network (ANN), logistic regression model (REG) and clinicians (CLIN).

patients. All validity criteria for neural network were better than regression model and clinicians' judgments. Specificities of the three methods were less than their sensitivities, hence these methods are probably more suitable for detecting those patients with a higher risk of developing lupus nephritis. In other words, indication for performing renal biopsy may be determined more exactly using the proposed methods in our article.

Although in our study the neural network showed less prediction error than the two other methods (regression model and experienced physicians), we assume that it should have an even better performance in clinical practice when prospective prediction can be done with minimal missing data.

Some cases had missing data; however, the neural network had a good performance when it used the corrected missing data. Such an intervention may prove to be useful and increase the value of the prediction.

In our study, cases with similar predicting factors occasionally had different renal outcomes. This phenomenon could be attributed to the multifactorial and very complex pathophysiology of SLE. This means that we should not be unreasonably optimistic about the performance of the neural network, unless more accurate parameters for predicting lupus nephritis are defined.

All cases of our study had one or more clinical evidences of renal involvement. In fact, clinical evidence of renal involvement had been the main reason for performing renal biopsy in the subgroup of patients who had biopsy-proven lupus nephritis. We were unable to detect a potential subset of patients with silent lupus nephritis (ie those with biopsy-proven renal involvement in the absence of any clinical renal manifestations[56,57]). Even if we could detect these patients, however, the predictive value of such differentiation would not be clear.

As shown in Table 2, predicting factors used by expert clinicians were similar. Such similarity could be observed in their ranking of predicting factors for lupus nephritis. The most relevant factors among the three methods used in our paper were similar.

Elevated serum creatinine and hypertension at the time of diagnosis and renal biopsy are good predictors of lupus nephritis. However, these factors have other clinical relationships with renal involvement independent of SLE, hence they were not used as inputs of the network. Proteinuria and cellular casts were two criteria for clinical diagnosis of nephritis in a subgroup of patients. As their data were used in the output layer, they could not be applied as predictors in the input layer of the network.

It seems that the complexity of the prediction could not be efficiently solved by classical methods and the newer methods are needed to achieve better performance for solving such a problem.

The artificial neural networks may prove to be more consistent in predicting outcomes in lupus patients than individual physicians. This possible advantage may even be more prominent when several factors affect the outcome. Lupus nephritis as an outcome endpoint is an outstanding example for such a situation. We propose that prediction of other important outcomes in SLE patients such as mortality and severe neurological complications could be determined by such a method. However, it should be noted that optimal training of artificial neural networks needs a relatively large group of patients with various characteristics. This requirement may limit the application of the artificial neural networks in rare diseases or outcomes.

We suggest improvement of the neural network's performance by the following means:

1. Using analog data coding instead of binary coding for complement provided that we could find homogeneity among values from different medical laboratories.
2. Using WHO classification for lupus nephritis or future renal function status to address more precisely the major concern of practitioners regarding lupus nephritis.
3. Another algorithm such as genetic algorithm may be used for the learning of neural network.

Further studies are needed to optimize the accuracy of artificial neural networks to predict lupus nephritis and define their role in clinical decision-making of SLE patients.

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References

1 Furlong JW, Dupuy ME, Heinsimer JA. Neural network analysis of serial cardiac enzyme data. A clinical application of artificial machine intelligence. *Am J Clin Pathol* 1991; **96**: 134 – 141.
2 Reinus WR, Kalman B, Kwasny S. Artificial neural networks for screening patients needing emergency cranial computed tomography scans in emergency departments. *Acad Radiol* 1995; **2**: 193 – 198.
3 Dombi GW, Nandi P, Saxe JM, Ledgerwood AM, Lucas CE. Prediction of rib fracture injury outcome by an artificial neural network. *J Trauma* 1995; **39**: 915 – 921.
4 Izenberg SD, Williams MD, Luterman A. Prediction of trauma mortality using a neural network. *Am Surg* 1997; **63**: 275 – 281.
5 Lang EW, Pitts LH, Damron SL, Rutledge R. Outcome after severe head injury: an analysis of prediction based upon comparison of neural network versus logistic regression analysis. *Neurol Res* 1997; **19**: 274 – 280.
6 Dvorchik I, Subotin M, Marsh W, McMichael J, Fung JJ. Performance of multi-layer feedforward neural networks to predict liver transplantation outcome. *Meth Inf Med* 1996; **35**: 12 – 18.
7 Jefferson MF, Pendleton N, Lucas SB, Horan MA. Comparison of a genetic algorithm neural network with logistic regression for predicting outcome after surgery for patients with nonsmall cell lung carcinoma. *Cancer* 1997; **79**: 1338 – 1342.
8 Dorsey SG, Waltz CF, Brosch L, Connerney I, Schweitzer EJ, Bartlett ST. A neural network model for predicting pancreas transplant graft outcome. *Diabetes Care* 1997; **20**: 1128 – 1133.
9 Abdolmaleki P, Movhead M, Taniguchi RI, Masuda K, Buadu LD. Evaluation of complications of kidney transplantation using artificial neural networks. *Nucl Med Commun* 1997; **18**: 623 – 630.
10 Grigsby J, Kramer RE, Schneiders JL, Gates JR, Brewster Smith W. Predicting outcome of anterior temporal lobectomy using simulated neural networks. *Epilepsia* 1998; **39**: 61 – 66.
11 Arie JE, Perrine K, Devinsky O, Doyle WK. Neural network analysis of preoperative variables and outcome in epilepsy surgery. *J Neurosurg* 1999; **90**: 998 – 1004.
12 Buzatu DA, Taylor KK, Peret DC, Darsey JA, Lang NP. The determination of cardiac surgical risk using artificial neural networks. *J Surg Res* 2001; **95**: 61 – 66.
13 Ravdin PM, Clark GM. A practical application of neural network analysis for predicting outcome of individual breast cancer patients. *Breast Cancer Res Treat* 1992; **22**: 285 – 293.
14 Burke HB. Artificial neural networks for cancer research: outcome prediction. *Sem Surg Oncol* 1994; **10**: 73 – 79.
15 Speight PM, Elliott AE, Jullien JA, Downer MC, Zakzrewska JM. The use of artificial intelligence to identify people at risk of oral cancer and precancer. *Br Dent J* 1995; **179**: 382 – 387.
16 Burke HB, Goodman PH, Rosen DB *et al*. Artificial neural networks improve the accuracy of cancer survival prediction. *Cancer* 1997; **79**: 857 – 862.
17 Naguib RN, Adams AE, Horne CH *et al*. Prediction of nodal metastasis and prognosis in breast cancer: a neural model. *Anticancer Res* 1997; **17**: 2735 – 2741.
18 Abdolmaleki P, Buadu LD, Murayama S *et al*. Neural network analysis of breast cancer from MRI findings. *Radiat Med* 1997; **15**: 283 – 293.
19 Timmerman D, Verrelst H, Bourne TH *et al*. Artificial neural network models for the preoperative discrimination between malignant and benign adnexal masses. *Ultrasound Obstet Gynecol* 1999; **13**: 17 – 25.
20 Ronco AL. Use of artificial neural networks in modeling associations of discriminant factors: towards an intelligent selective breast cancer screening. *Artif Intell Med* 1999; **16**: 299 – 309.
21 Orr RK. Use of an artificial neural network to quantitate risk of malignancy for abnormal mammograms. *Surgery* 2001; **129**: 459 – 466.
22 Ziada AM, Lisle TC, Snow PB, Levine RF, Miller G, Crawford ED. Impact of different variables on the outcome of patients with clinically confined prostate carcinoma. *Cancer* 2001; **91**(S8): 1653 – 1660.
23 Kok MR, van Der Schouw YT, Boon ME *et al*. Neural network-based screening (NNS) in cervical cytology: No need for the light microscope? *Diag Cytopathol* 2001; **24**: 426 – 434.
24 Ambalavanan N, Nelson KG, Alexander G, Johnson SE, Biasini F, Carlo WA. Prediction of neurologic morbidity in extremely low birth weight infants. *J Perinatal* 2000; **20**(8 Pt 1): 496 – 503.
25 Ortiz J, Ghefter CG, Silva CE, Sabbatini RM. One-year mortality prognosis in heart failure: a neural network approach based on echocardiographic data. *J Am Coll Cardiol* 1995; **26**: 1586 – 1593.
26 Bottaci L, Drew PJ, Hartley JE *et al*. Artificial neural networks applied to outcome prediction for colorectal cancer patients in separate institutions. *Lancet* 1997; **350**: 469 – 472.
27 Lundin J. Artificial neural networks in outcome prediction. *Ann Chir Gynaecol* 1998; **87**: 128 – 130.
28 Wong LS, Young JD. A comparison of ICU mortality prediction using the APACHE II scoring system and artificial neural networks. *Anaesthesia* 1999; **54**: 1048 – 1054.
29 Sonke GS, Heskes T, Verbeek AL, de la Rosette JJ, Kiemeney LA. Prediction of bladder outlet obstruction in men with lower urinary tract symptms using artificial neural networks. *J Urol* 2000; **163**: 300 – 305.
30 Turton EP, Scott DJ, Delbridge M, Snowden S, Kester RC. Ruptured abdominal aortic aneurysm: a novel method of outcome prediction using neural network technology. *Eur J Vasc Endovasc Surg* 2000; **19**: 184 – 189.
31 Esdaile JM, Mackenzie T, Barré P *et al*. Can experienced clinicians predict the outcome of lupus nephritis? *Lupus* **1**: 205 – 214.
32 Donadio JV Jr, Burgess JH, Holley KE. Membranous lupus nephropathy: a clinicopathologic study. *Medicine (Balt.)* 1977; **56**: 527 – 536.
33 Magil AB, Puterman ML, Ballon HS *et al*. Prognostic factors in diffuse proliferative lupus glomerulonephritis. *Kidney Int* 1988; **34**: 511 – 517.
34 Fronek Z, Timmerman LA, Alper CA *et al*. Major histocompatibility complex genes and susceptibility to systemic lupus erythematosus. *Arthrit Rheum* 1990; **33**: 1542 – 1553.
35 McCurdy DK, Lehman TJ, Bernstein B *et al*. Lupus nephritis: prognostic factors in children. *Pediatrics* 1992; **89**: 240 – 246.
36 Ward MM, Studenski S. Clinical prognostic factors in lupus nephritis. The importance of hypertension and smoking. *Arch Intern Med* 1992; **152**: 2082 – 2088.
37 Austin HA 3rd, Boumpas DT, Vaughan EM, Balow JE. Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. *Kidney Int* 1994; **45**: 544 – 550.
38 Austin HA 3rd, Boumpas DT, Vaughan EM, Balow JE. High-risk features of lupus nephritis: importance of race and clinical and histological factors in 166 patients. *Nephrol Dial Transplant* 1995; **10**: 1620 – 1628.
39 Salmon JE, Millard S, Schachter LA *et al*. Fc gamma RIIA alleles are heritable risk factors for lupus nephritis in African Americans. *J Clin Invest* 1996; **97**: 1348 – 1354.
40 Freedman BI, Wilson CH, Spray BJ, Tuttle AB, Olorenshaw IM, Kammer GM. Familial clustering of end-stage renal disease in blacks with lupus nephritis. *Am J Kidney Dis* 1997; **29**: 729 – 732.
41 Thumboo J, Fong KY, Chia HP *et al*. Clinical predictors of nephritis in systemic lupus erythematosus. *Ann Acad Med Singapore* 1998; **27**: 16 – 20.
42 Bhandari S, Harnden P, Brownjohn AM, Turney JH. Association of anticardiolipin antibodies with intraglomerular thrombi and renal dysfunction in lupus nephritis. *Q J Med* 1998; **91**: 401 – 409.
43 Marini R, Costallat LT. Young age at onset, renal involvement, and arterial hypertension are of adverse prognostic significanse in juvenile systemic lupus erythematosus. *Rev Rheum Engl Edn* 1999; **66**: 303 – 309.
44 Huong DL, Papo T, Beaufils H *et al*. Renal involvement in systemic lupus erythematosus. A study of 180 patients from a single center. *Medicine (Balt.)* 1999; **78**: 148 – 166.
45 Blatt NB, Glick GD. Anti-DNA autoantibodies and systemic lupus erythematosus. *Pharmac Ther* 1999; **83**: 125 – 139.
46 Lim CS, Chin HJ, Jung YC *et al*. Prognostic factors of diffuse proliferative lupus nephritis. *Clin Nephrol* 1999; **52**: 139 – 147.
47 Abraham MA, Korula A, Jayakrishnan K, John GT, Thomas PP, Jacob CK. Prognostic factors in diffuse proliferative lupus nephritis. *J Assoc Physicians India* 1999; **47**: 862 – 865.
48 Hopkinson ND, Jenkinson C, Muir KR, Doherty M, Powell RJ. Racial group, socioeconomic status, and the development of persistent proteinuria in systemic lupus erythematosus. *Ann Rheum Dis* 2000; **59**: 116 – 119.

49 Gamba G, Quintanilla L, del Bosque MD, Chew-Wong A, Correa-Rotter R. Clinical course and prognostic factors in lupus nephropathy. *Rev Invest Clin* 2000; **52**: 397–405 (Abstract).
50 Hogan SL, Satterly KK, Dooley MA, Nachman PH, Jennette JC, Falk RJ. Glomerular Disease Collaborative Network. Silica exposure in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and lupus nephritis. *J Am Soc Nephrol* 2001; **12**: 134–142.
51 Font J, Ramos-Casals M, Cervera R *et al*. Cardiovascular risk factors and the long-term outcome of lupus nephritis. *Q J Med* 2001; **94**: 19–26.
52 Tan EM, Cohen AS, Fries JF *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthrit Rheum* 1982; **25**: 1271–1277.
53 Churg J, Bernstein J, Glassock RJ. Lupus nephritis. In: Churg J, Bernstein J, Glassock RJ. *Renal Diseases—Classification and Atlas of Glomerular Diseases*. Igaku-Shoin: New York, 1996, p 151.
54 Rummelhart DE, McLelland JC. *Parallel Distributed Processing*. MIT Press, Cambridge, MA, 1986.
55 Finne P, Finne R, Auvinen A *et al*. Predicting the outcome of prostate biopsy in screen-positive men by a multilayer perceptron network. *Urology* 2000; **56**: 418–422.
56 Bennett WM, Bardana EJ, Norman DJ, Houghton DC. Natural history of 'silent' lupus nephritis. *Am J Kidney Dis* 1982; **1**: 359–363.
57 Font J, Torras A, Cervera R, Darnell A, Revert L, Ingelmo M. Silent renal disease in systemic lupus erythematosus. *Clin Nephrol* 1987; **27**: 283–288.

Appendix: Basic introduction to artificial neural networks

An artificial neural network (ANN) is an information-processing paradigm inspired by parallel information processing in the mammalian brain. Artificial neural networks are collections of mathematical models that emulate some of the observed properties of biological nervous systems. They are composed of a large number of highly interconnected processing elements that are analogous to neurons and are tied together with weighted connections that are analogous to synapses.

Learning in biological systems involves adjustments to the synaptic connections that exist between the neurons. This is true of ANNs as well. Learning typically occurs by example through training, or exposure to a set of input/output data, where the training algorithm iteratively adjusts the connection weights (synapses). These connection weights store the knowledge necessary to solve specific problems.

ANNs are applied to an increasing number of real-world problems of considerable complexity. They are good pattern recognition engines and robust classifiers, with the ability to generalize in making decisions about imprecise input data. They offer ideal solutions to a variety of classification problems as well as functional prediction and system modeling where the physical processes are not understood or are highly complex. The advantage of ANNs lies in their resilience against distortions in the input data and their capability of learning. They are often good at solving problems that are too complex for conventional technologies (eg problems that do not have an algorithmic solution or for which an algorithmic solution is too complex to be found), and are often well suited to problems that people are good at solving, but for which traditional methods are not.

There are multitudes of different types of ANNs. Some of the more popular include the multilayer perceptron, which is generally trained with the back-propagation of error algorithm. ANNs can be implemented in software or in specialized hardware. The backpropagation neural network has been used in this article and implemented in software.

A typical backpropagation neural network is organized in layers. Layers are made up of a number of interconnected nodes (analogous to neurons). Patterns are presented to the network *via* the input layer, which communicates to one or more hidden layers where the actual processing is done *via* a system of weighted connections. The hidden layers then link to an output layer where the answer is output (see Figure 1).

The delta rule is often utilized as a learning rule by backpropagation neural networks. With the delta rule learning is a supervised process that occurs with each cycle or epoch (ie, each time the network is presented with a new input pattern) through a forward activation flow of outputs, and the backwards error propagation of weight adjustments. More simply, when a neural network is initially presented with a pattern it makes a random guess as to what it might be. It then sees how far its answer (network output) was from the actual one (desired output) and makes an appropriate adjustment to its connection weights according to calculated error.

The error is calculated as the difference between the desired output and the network output. We want to minimize the sum of these errors. If the answer of each node in the output layer and its desired output are showed by $N(k)$ and $D(k)$, respectively, then minimal square error (MSE) for outputs of all nodes (Q) is defined as:

$$\sum_{k=1}^{Q}(N(k)-D(k))^2 = \min$$

Error calculation and weight adjustment performed for all input patterns are repeated several times because neural network analysis often requires a large number of individual runs to determine the best solution.

Once a neural network is trained to a satisfactory level it may be used as an analytical tool on other data. To test this, the user no longer specifies any training runs and instead allows the network to work in forward propagation mode only. New inputs are presented to the input pattern where they filter into and are processed by the middle layers as though training were taking place; however, at this point the output is retained and no backpropagation occurs. The output of a forward propagation run is the predicted model for the data, which can then be used for further analysis and interpretation.

It is also possible to over-train a neural network (MSE $< 1\%$ in this article), which means that the network has been trained exactly to respond to only one type of input; which is much like rote memorization. If this should happen then learning can no longer occur. In real-world applications this situation is not very useful.

Under-training occurs when the problem could not be solved or the network reach a virtual minimum of error named local minima during training. In this article under-training was specified by MSE $> 10\%$.

Further information can be found at: www.emsl.pnl.gov:2080/proj/neuron/neural/what.html