AN ARTIFICIAL NEURAL NETWORK DESIGN FOR DETERMINATION OF HASHIMOTO'S THYROIDITIS SUB-GROUPS

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Abstract: In this study, an artificial neural network was developed for estimating Hashimoto's Thyroiditis sub-groups. Medical analysis and measurements from 75 patients were used to determine the parameters most effective on disease sub-groups. The study used statistical analyses and an artificial neural network that was trained by the determined parameters. The neural network had four inputs: thyroid stimulating hormone, free thyroxine (fT4), right lobe size (RLS), and $RLS^2 - fT4^4$, and two outputs for three groups: euthyroid, subclinical, and clinical. After training, the network was tested with data collected from 30 patients. Results show that, overall, the neural network estimated the sub-groups with 90% accuracy. Hence, the study showed that determination of Hashimoto's Thyroiditis sub-groups can be made via designed artificial neural network.

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Introduction

Hashimoto's thyroiditis (HT), one of the most common autoimmune disease, was described over a century ago as a pronounced lymphoid goiter affecting approximately 2% of the population and being 20 times more prevalent in women than men. An autoimmune disease is a disorder in which the body's immune system attacks the body's own cells and organs. Normally, the immune system protects the body from infection by identifying and destroying bacteria, viruses, and other potentially harmful foreign substances. In HT, the immune system attacks the thyroid gland, causing inflammation, and hinders the thyroid gland in producing balancing hormones (Omitek, Burda, & Wojcik, 2013; Caturegli, Remigis, & Rose, 2014).

Thyroid hormones regulate metabolism and affect almost all organs in the body. Hashimoto's disease often leads to reduced thyroid function, or hypothyroidism. Hypothyroidism is a disorder that occurs when the thyroid fails to make enough thyroid hormone for the body's needs (Ozyılmaz & Yıldırım, 2002). The thyroid produces two thyroid hormones, triiodothyronine (T3) and thyroxine (T4). Triiodothyronine is the active hormone and is derived from T4. Thyroid-stimulating hormone (TSH), which is produced by the pituitary gland in the brain, regulates thyroid hormone production (Omitek, Burda, & Wojcik, 2013; Caturegli, Remigis, & Rose, 2014; Ozyılmaz & Yıldırım, 2002; Health Information, 2016). The diagnosis of HT is based on the indication of excursive antibodies to thyroid antigens and reduced echogenicity on thyroid sonogram in a patient with proper clinical features. Diagnosis begins with a physical exam and medical history. A goiter, nodules, or growths may be found during a physical exam, and symptoms may suggest hypothyroidism. Health care providers will then perform blood tests to confirm the diagnosis. Diagnostic blood tests may include the TSH test, T4 test, and anti-thyroid and anti-body tests, as well as common methods to diagnose HT, including ultrasound and computational-tomography scans (Ozyılmaz & Yıldırım, 2002; Health Information, 2016).

Artificial neural networks (ANNs) are widely used in science and technology, with applications in various branches of engineering and medicine. Artificial neural networks have many advantages, such as, flexible modelling structure for large data sets and highly accurate results that supports clinical decision making. Artificial neural networks have been used in diagnosis of many diseases. In Omitek,

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Burda, and Wojcik (2013), diagnosis of Hashimoto's thyroiditis was carried out using ultrasound images of thyroid glands and ANN. In Caturegli, Remigis, and Rose (2014), determination of thyroid illnesses was carried out via ANN. In Er, Temurtas, and Tanrıkulu (2008), diagnosis of tuberculosis was performed by ANN with 95.08% accuracy. Castanho, Hernandes, De Re, Rautenberg, and Billis (2013) used an expert system for predicting the pathological stage of prostate cancer. In Takahashi, Hayashi, & Watanabe (2010), diagnosis of schizophrenia was carried out by ANN with 87.90% accuracy. In Kaya, Aktan, Akdoğan, and Koru (2015), diagnosis of anemia in children was performed using ANN with 90.00% accuracy.

The aim of this study is to diagnose (determine) Hashimoto's thyroiditis sub-groups via artificial neural networks. There is no exact therapy or medicine for treating the advanced stage of this disease. This study will help diagnosis early stages of the disease. In this way, patients could be monitored with imaging testing much earlier. A vital issue is to increase the effectiveness of treatment, so that diagnosis can be achieved as early as possible.

Data Analysis

The analyses, performed using SPSS software, identified the designated parameters from a total of eight (body mass index, waist measurement, hip measurement, TSH, fT3, fT4, right lobe size (RLS), or left lobe size) tested and measured in 75 Hashimoto's thyroiditis patients, that affected the disease sub-groups. Mode, mean, median, and table distribution graphs were obtained from univariate analyses. A regression analysis with a post-hoc test was performed to measure the relationship between two or more variables. This approach provided an opportunity to obtain both descriptive and inferential statistics. Calculations were based on 5% margin of error. Further hypothesis related to whether the data showed effects in the patients. The results of hypothesis testing were considered suitable for modeling. The t-test and chi-squared test were performed to establish the hypothesis. The t-test was performed for the comparison of paired samples and groups, with a variance test performed to examine the difference between groups. Since the data was homogeneously distributed, a Tukey's range test was performed. The results of the regression analysis, an analysis of variation (ANOVA), and coefficient values identified whether the model could be generated and, following this, a correlation analysis was performed.

Training Artificial Neural Networks

The Neural Network Toolbox of Matlab© R2013b was used to create, train, and test the artificial neural network. First, training and test data were normalized between −1 and 1. Then the training and test data along with the output data were assigned to variables. The network training function, TRAINLM, the learning function, LEARNGDM, and the mean squared error as the performance function were used.

Training and test data were transferred as input data, and the output of training data as target data to create the network and this was followed by training of the neural network. The training was achieved by a backpropagation method after setting the network properties and the training parameters. The network was tested with 30 data points collected from patients.

Results and Discussion

Table 1 shows the results of the t-Test, and Table 2 the results of the regression and ANOVA. According to the results of the coefficients table, obtained after the regression, the most important parameters affecting the disease sub-groups were TSH, fT4, and RLS.

Structure of Artificial Neural Networks

The network was developed to feed forward multilayer perceptron with a 3-layer structure. For selection of input parameters, various combinations were trialed for best performance. The results showed that the network was able to diagnose the disease with high accuracy. The network structure is shown in Figure 1. As a result of network training with the three parameters identified from the data analysis, i.e., TSH, fT4, and RLS, up to 80% accuracy was obtained. Because data of euthyroid and subclinical groups were closely related, effective determination could not be achieved. Therefore, various trials were performed with the power of input parameters and best accuracy (90%) was

obtained by squaring the value for the right lobe side and subtracting the value for free triiodothyronine to the power of four (equation: $RLS^2 - fT^4$). The trial results are shown in Table 4.

Table 1: t-Test statistics of data from 75 Hashimoto's thyroiditis patients

Parameters	Sex	N	Mean	Std. Deviation	Std. Error Mean
Waist	male	10	88.333	14.874	4.958
	female	65	81.774	10.968	1.393
Body Mass Index	male	10	25.760	4.805	1.519
	female	65	26.006	6.008	0.751
Hip	male	10	100.222	9.562	3.187
	female	65	102.564	10.275	1.305
TSH	male	10	45.363	58.636	18.542
	female	65	13.547	23.792	2.951
fT4	male	10	0.812	0.308	0.097
	female	65	0.906	0.198	0.024
fT3	male	10	2.677	0.992	0.330
	female	65	2.928	0.376	0.049
RLS	male	10	19.300	5.598	1.770
	female	65	16.359	2.026	0.253
LLS	male	10	50.300	6.783	2.145
	female	65	47.890	6.796	0.849

TSH: thyroid-stimulating hormone; fT4: free thyroxine; fT3: free triiodothyronine; RLS: right lobe side; LLS: left lobe side

Source: Authors

Table 2: Regression results for dependent variable, right lobe side, and predictors, thyroid-stimulating hormone, free thyroxine, and free triiodothyronine

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.202[a]	0.041	-0.007	1.92357

ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	9.431	3	3.144	0.850	0.472[a]
	Residual	222.006	60	3.700		
	Total	231.438	63			

Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	16.822	2.309		7.286	0.000
	TSH	0.009	0.012	0.136	0.742	0.461
	fT4	1.632	1.476	0.187	1.106	0.273
	fT3	-0.636	0.779	-0.157	-0.816	0.417

[a] Predictors: (Constant). TSH: thyroid-stimulating hormone; fT4: free thyroxine; fT3: free triiodothyronine

Source: Authors

Table 3: Tukey homogeneous subclinical sets

Body Mass Index			**Waist**		
		Subclinical set for alpha = 0.05			Subset for alpha = 0.05
Group	**N**	1	**Group**	**N**	1
euthyroid	25	25.172	euthyroid	25	81.652
clinical	25	25.556	clinical	25	83.000
subclinical	25	27.241	subclinical	25	83.125
Sig.		0.432	Sig.		0.903

fT4				**Hip**		
		Subclinical set for alpha = 0.05				Subset for alpha = 0.05
Group	**N**	1	2	**Group**	**N**	1
clinical	25	0.737		clinical	25	101.791
subclinical	25		0.918	euthyroid	25	102.000
euthyroid	25		1.020	subclinical	25	103.000
Sig.		1.00	0.134	Sig.		0.914

TSH				**fT3**		
		Subset for alpha = 0.05				Subset for alpha = 0.05
Group	**N**	1	2	**Group**	**N**	1
euthyroid	25	3.202		clinical	25	2.731
subclinical	25	6.791		subclinical	25	2.950
clinical	25	0.883	43.374	euthyroid	25	3.005
Sig.			1.000	Sig.		0.169

RLS: right lobe side; TSH: thyroid-stimulating hormone; fT4: free thyroxine; fT3: free triiodothyronine

Source: Authors

Table 4: Trial results of training artificial neural networks

Input Parameters: TSH, fT4, RLS			**Input Parameters:** TSH, fT4, RLS, $RLS^2 - fT4^2$		
	Accuracy (%)			**Accuracy (%)**	
Neurons	**TANSIG**	**LOGSIG**	**Neurons**	**TANSIG**	**LOGSIG**
20	80	73	20	83	70
50	83	70	50	83	77
60	83	80	60	83	80
70	60	70	70	77	70
80	73	67	80	77	67
100	70	60	100	70	67

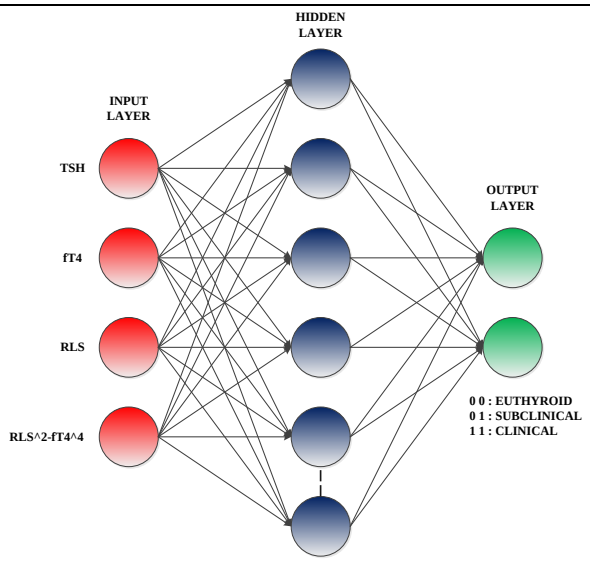
Input Parameters: TSH, fT4, RLS, $RLS^2 - fT4^4$			**Input Parameters:** TSH, fT4, RLS, $RLS^2 - fT4^6$		
	Accuracy (%)			**Accuracy (%)**	
Neurons	**TANSIG**	**LOGSIG**	**Neurons**	**TANSIG**	**LOGSIG**
20	63	63	20	60	60
50	86	77	50	80	77

60	90	83	60	83	80
70	80	77	70	73	67
80	80	73	80	70	60
100	57	70	100	73	60

RLS: right lobe side; TSH: thyroid-stimulating hormone; fT4: free thyroxine; fT3: free triiodothyronine

Source: Authors

Figure 1: Network structure



RLS: right lobe side; TSH: thyroid-stimulating hormone; fT4: free thyroxine; fT3: free triiodothyronine

Source: Authors

According to trial results, four of the inputs to the ANN were TSH, fT4, RLS, and $RLS^2 – fT4^4$, and two of the outputs were representative of euthyroid, subclinical, and clinical. There were 60 neurons in the hidden layer. Tangent-sigmoid were used as an activation function. The data for 45 of the 75 patients were used for training and another 30 for testing the neural network. Samples of the training and test data are shown in Table 5.

Table 5: Sample training and test data

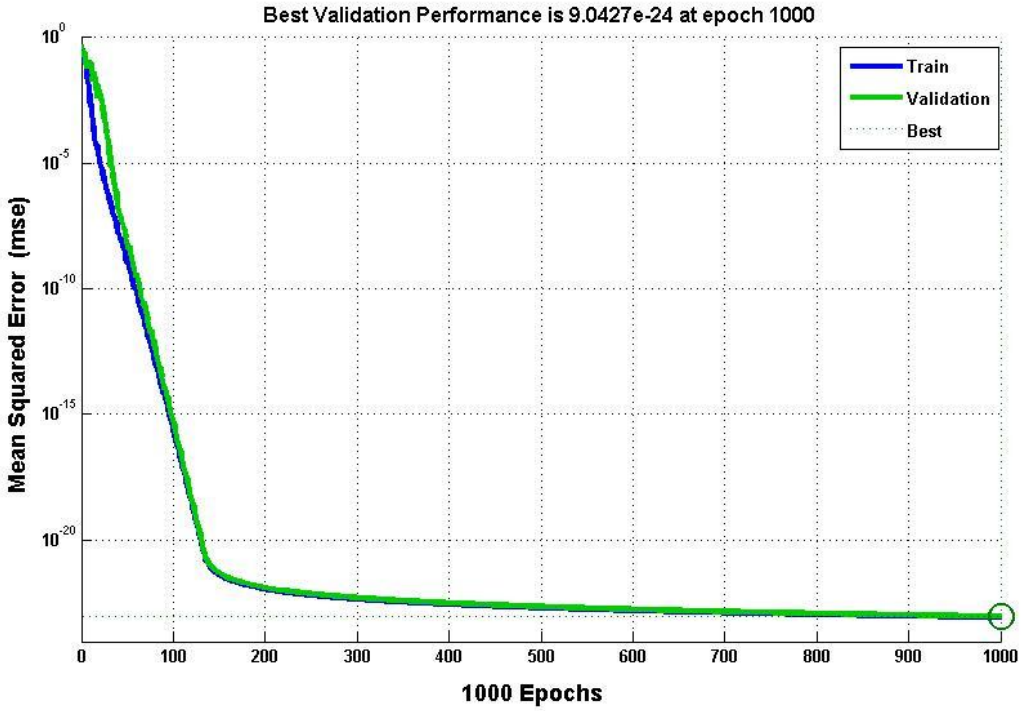
TSH mU/mL	**fT4** ng/dL	**RLS** mm	**$RLS^2 – fT4^4$**	**0 0: euthyroid 0 1: subclinical 1 1: clinical**	
5.80	0.91	15	224.3	0	1
20.00	0.80	12	143.5	1	1
1.76	1.20	19	358.9	0	0

RLS: right lobe side; TSH: thyroid-stimulating hormone; fT4: free thyroxine; fT3: free triiodothyronine

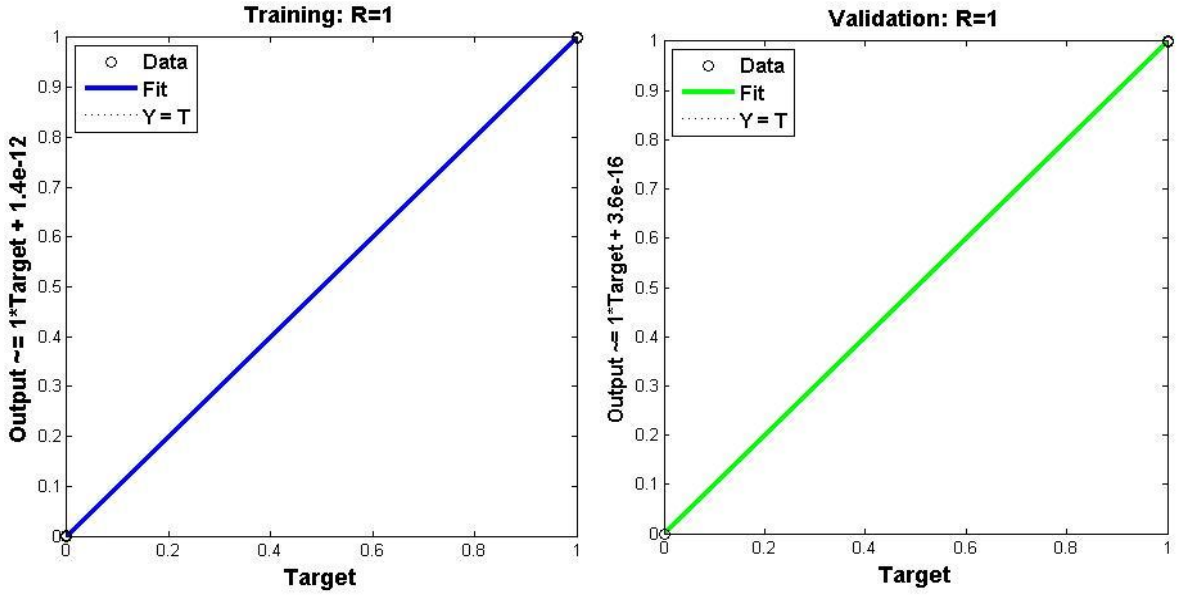
Source: Authors

Performance of the network and regression results plots are shown in Figure 2. Figure 2a shows the mean square error (MSE) reached 10^{-23} after epoch 600 and best validation performance was $9.0427e^{-24}$ at epoch 1000. In contrast, training and validation results were highly satisfactory, depending on the MSE (Figure 2b). This result indicated that the neural network was successfully trained.

Figure 2: Performance of learning (a) and regression results (b)



(a)



(b)

Source: Authors

Testing Artificial Neural Networks

Once the outputs of the network were compared with actual results, there were three incorrect outcomes found. A comparison of the artificial network outputs with actual doctor's (or 'real') values is shown in Table 4. The binary numbers '0, 0' indicated the euthyroid sub-group, '0, 1' the subclinical sub-group, and '1, 1' the clinical sub-group.

Table 4: Test results, comparison of the artificial network outputs with actual (or 'real')

Patient	Real Value		Network Output		Accuracy (%)	Patient	Real Value		Network Output		Accuracy (%)
P1	0	0	0	0	100	**P16**	0	1	0	1	100
P2	0	0	0	0	100	**P17**	1	1	1	1	100
P3	0	1	0	1	100	**P18**	1	1	1	1	100
P4	1	1	1	1	100	**P19**	0	0	0	0	100
P5	1	1	1	1	100	**P20**	0	1	0	1	100
P6	0	1	0	1	100	**P21**	0	0	0	1	0
P7	0	0	0	0	100	**P22**	0	1	0	0	0
P8	0	0	0	0	100	**P23**	1	1	1	1	100
P9	1	1	1	1	100	**P24**	1	1	1	1	100
P10	0	1	0	1	100	**P25**	0	0	0	0	100
P11	0	0	0	0	100	**P26**	0	1	0	1	100
P12	1	1	1	1	100	**P27**	0	0	0	1	0
P13	0	1	0	1	100	**P28**	0	1	0	1	100
P14	1	1	1	1	100	**P29**	0	1	0	1	100
P15	0	0	0	0	100	**P30**	1	1	1	1	100
Total accuracy of the artificial neural network:											**90**

Source: Authors

For 27 of 30 cases, outputs of the network and decisions of the doctor were in agreeance, and total accuracy of the artificial neural network was 90% (Table 4). Incorrect predictions emerged in the euthyroid and subclinical groups, while the clinical group was estimated with 100% accuracy.

Conclusion

This paper describes an artificial neural network that was developed to determine Hashimoto's thyroiditis sub-groups. Medical analyses and measurements, from 75 patients, were used to determine the most influential parameters on the disease sub-groups. The study used statistical analyses and a neural network that was trained by the determined parameters. In the test, outputs of the network were compared to the decisions of the doctor. The reason for the outcome was that euthyroid and subclinical sub groups were closely related. We consider the developed artificial neural network model adequate for use in helping doctors determine Hashimoto's thyroiditis sub-groups.

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