

Evaluation of Total Antioxidant Capacity (TAS) by Using Fuzzy Logic

ABSTRACT

Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Further, some reactive oxidative species act as cellular messengers in redox signaling. Thus, oxidative stress can cause disruptions in normal mechanisms of cellular signaling. Oxidative stress is suspected to be important in neurodegenerative diseases including ALS, Parkinson's disease, Alzheimer's disease, Huntington's disease, and Multiple sclerosis. Indirect evidence via monitoring biomarkers such as reactive oxygen species, and reactive nitrogen species production, antioxidant defense indicates oxidative damage may be involved in the pathogenesis of these diseases, while cumulative oxidative stress with disrupted mitochondrial respiration and mitochondrial damage are related with Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases.

Levels of total antioxidant capacity (TAS) reflect the total effect all antioxidants found in plasma and body fluids. Antioxidants such as albumin, uric acid, ascorbic acid, vitamin E and bilirubin are molecules forming the main contribution to the total antioxidant capacity. In this study, we tried to determine total antioxidant capacity of patients using systolic, diastolic blood pressure and age values of patient.

Keywords: Total antioxidant capacity (TAS), fuzzy logic, ANFIS, systolic and diastolic blood pressure.

1.Introduction

An antioxidant is a molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons or hydrogen from a substance to an oxidizing agent. Oxidation reactions can produce free radicals. In turn, these radicals can start chain reactions. When the chain reaction occurs in a cell, it can cause damage or death to the cell. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions. They do this by being oxidized themselves, so antioxidants are often reducing agents such as thiols, ascorbic acid, or polyphenols (Sies 1997).

Although oxidation reactions are crucial for life, they can also be damaging; plants and animals maintain complex systems of multiple types of antioxidants, such as glutathione, vitamin C, vitamin A, and vitamin E as well as enzymes such

as catalase, superoxide dismutase and various peroxidases. Insufficient levels of antioxidants, or inhibition of the antioxidant enzymes, cause oxidative stress and may damage or kill cells. Oxidative stress is damage to cell structure and cell function by overly reactive oxygen-containing molecules and chronic excessive inflammation. Oxidative stress seems to play a significant role in many human diseases, including cancers. The use of antioxidants in pharmacology is intensively studied, particularly as treatments for stroke and neurodegenerative diseases. For these reasons, oxidative stress can be considered to be both the cause and the consequence of some diseases.

Oxidative stress is the superiority of reactive oxygen structures (ROS) to antioxidant structures eliminates them. If these structures increase in the organism, it can damage main cellular structures such as protein, lipids and DNA. Oxidative stress can disrupt normal cellular signaling mechanisms. Oxidative stress can lead to many diseases in human such as cancers (Hallwell 2007), Parkinson's and Alzheimer's disease (Valko et al. 2007, Pohanka 2013), atherosclerotic disease (Li et al. 2014), autism (James et al. 2004), chronic fatigue syndrome (Kennedy et al. 2005). Epilepsy is also one of these diseases. There are findings showing that oxidative and nitrosative stress has a role in the pathogenesis of epilepsy (Chang and Yu 2010). Today's findings suggest that epileptogenesis causing from a structural process is mediated by oxidative stress which resulted in the change of the structure of cellular protein, membrane lipids and the nucleic acid (Aguiar et al. 2012). Many studies also have shown that monotherapy or combined antiepileptic therapy increase oxidative stress. Detection of anti-epileptic that does not increase oxidative stress or increase minimum is important to treat the disease.

There are several markers to show oxidative stress in the body. A portion of these markers have oxidant and the other portions of these markers have antioxidant properties. It can be taken knowledge about oxidative stress level with the measurement of these oxidant-antioxidant markers. However, measurement of one or more of these markers does not provide information about the total oxidative stress (Varoglu et al. 2010) (13). Levels of total antioxidant capacity (serum) (TAS) reflect the total effect all antioxidants found in plasma and body fluids. Antioxidants such as albumin, uric acid, ascorbic acid, vitamin E and bilirubin are molecules forming the main contribution to the total antioxidant capacity. Total oxidant status (TOS) reflects total effects of oxidants in plasma and body fluids. Oxidative stress index (OSI) found by proportioning of TOS levels to TAS level is a parameter indicating the direction of the body's oxidant-antioxidant balance (Erel 2004, Miller et al. 1993). (14, 15).

The interaction between doctors and engineers, and computer engineers and other engineers opened the unprecedented opportunities almost in every field. This has just possible because of the emergence of interdisciplinary technologies during past few years. The advancements in computer technology are playing a key role in development of medical diagnostic systems with demand for development of more intelligent and knowledge based systems. The medical practitioners are also employing computerized technologies to assist in diagnosis and access

the related information. They differ in diagnosis and opinions because medical diagnosis is full of uncertainty. Fuzzy logic provides the solution for dealing with these uncertainties. Fuzzy techniques provide decision support and expert systems with powerful reasoning capabilities in the form of approximate reasoning. Fuzzy logic provides powerful framework for combination of evidences and deduction of consequences based on knowledge stored in knowledge base. Fuzzy logic which is one of the soft computing techniques can render precise from what is imprecise (Skchi et al. 2012).

Fuzzy logic is widely used so in medicine such as Poongodi et al.(2011) used fuzzy logic to predict cancer. Yilmaz and Ayan (2013) also studied cancer risk analysis by fuzzy logic. Patel et al.(2012) formed a decision support system for the diagnosis of Asthma severity using fuzzy logic, and Kumar and Kaur (2013) also detected heart diseases using fuzzy logic. Sikchi et al. (2012) designed a fuzzy expert system to diagnosis of cardiac diseases. Balanica et al. (2011) performed evaluation of breast cancer risk by fuzzy logic. Malathi and Santra (2013) also studied to diagnosis of lung cancer using neuro fuzzy logic. Doudu et al. (2014) designated (architected) an algorithm to detect malaria diagnosis using fuzzy logic for treatment in Ghana.

The purpose of this paper is to propose a generic technique for diagnostic decisions. The particular focus is on calculating of total antioxidant capacity by employing the fuzzy logic.

Why use fuzzy logic?

The fuzzy logic method was preferred to current mathematical models due to its ability for modeling the obscurity in the related problem, ability to work with lower cost and easy application, higher mechanical intelligence level, ability to solve new problems by using the experience of the model within the framework of the rules defined in the model, flexible structure, compatibility for solving the insufficiently defined problems, and use of intuitive methods instead of a specific algorithm.

This study makes risk analysis for taking measures, unlike in diagnosis. Because of that, the reasons for choosing fuzzy logic in contrast to other systems are grounded on the lack of a flexible structure of other systems, operation for accurate data, and production of accurate results. Here is a list of general observations about fuzzy logic:

- Fuzzy logic is conceptually easy to understand and is a more intuitive approach. The mathematical concepts behind fuzzy reasoning are very simple.
- Fuzzy logic is flexible.
- Fuzzy logic is tolerant of imprecise data.
- Fuzzy logic can model nonlinear functions of arbitrary complexity.

- 114 • Fuzzy logic can be built on top of the experience of experts.
- 115 • Fuzzy logic is based on natural language. Because fuzzy logic is built on the
- 116 structures of qualitative description used in everyday language, fuzzy logic is easy to
- 117 use.

118 The last statement is perhaps the most important one and deserves more discussion. Natural
 119 language, which is used by ordinary people on a daily basis, has been shaped by thousands of
 120 years of human history to be convenient and efficient. Sentences written in ordinary language
 121 represent a triumph of efficient communication.

122

123 **Adaptive Network based Fuzzy Inference Systems (ANFIS)**

124 Adaptive Network based Fuzzy Inference Systems (ANFIS) are feed-forward adaptive
 125 networks which are functionally equivalent to fuzzy inference systems. The basic idea of
 126 ANFIS can be described as follows: A fuzzy inference system is typically designed by
 127 defining linguistic input and output variables as well as an inference rule base. However, the
 128 resulting system is just an initial guess for an adequate model. Hence, its premise and
 129 consequent parameters have to be tuned based on the given data in order to optimize the
 130 system performance. In ANFIS this step is based on a supervised learning algorithm (Jyh-
 131 Shing 1993).

132 All types of fuzzy inference systems shown in Figure 1 can be subjected to such a procedure.
 133 However, the complexity of the problem depends on the type of reasoning in the consequent
 134 part even if the results of all three types would not change significantly for the same data set.
 135 Therefore, in this section, Type-3 ANFIS is explained which is least complex and hence used
 136 for the prediction of the geoid heights. For simplicity, assume that the fuzzy inference system
 137 under consideration has two inputs x and y and one output f . Additionally, suppose that the
 138 rule base contains two fuzzy *if-then* rules of Takagi and Sugeno's type (Takagi and Sugeno
 139 1983) as

140 Rule 1: If x is A_1 and y is B_1 ; then $f_1 = p_1x + q_1y + r_1$.

141 Rule 2: If x is A_2 and y is B_2 ; then $f_2 = p_2x + q_2y + r_2$.

142 Related ANFIS architecture is shown in Figure 1.

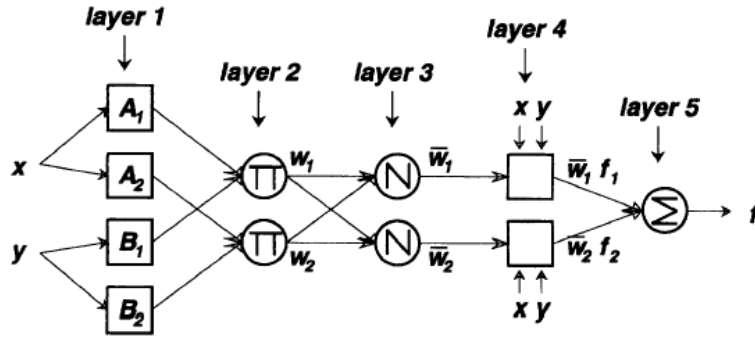


Figure 1: A simple two inputs and a single output of ANFIS structure

Note that the node functions in the same layer are of the same function family (all circles without parameters or square nodes with parameters) (Akyılmaz et al. 2003).

The functions of each layer can be described as below.

Layer 1: Every node i in this layer is a square node with a node function

$$\begin{aligned} O_{1,i} &= \mu_{A_i}(x) & i=1,2 \\ O_{1,i} &= \mu_{B_{i-2}}(y) & i=3,4 \end{aligned} \quad (1)$$

Where, x and y are the input to node i , and A_i is the linguistic label (small, medium, large, etc.) associated with this node function. In other words, $O_{1,i}$ is the membership function of A_i and it specifies the degree to which the given x satisfies the quantifier A_i . Usually, the membership function $\mu_{A_i}(x)$ is chosen to be bell-shaped with the maximum value equal to 1 and the minimum value equal to 0 such as, e.g., the generalized bell function (Figure. 2)

$$\mu_{A_i}(x) = \frac{1}{1 + \left[\left(\frac{x - c_i}{a_i} \right)^2 \right]^{b_i}} \quad i=1,2 \quad (2)$$

where, $\{a_i, b_i, c_i\}$ is the parameter set. As the values of these parameters change, the bell-shaped functions vary accordingly. Thus various membership functions on linguistic label A_i are defined. In fact, any continuous and piecewise differentiable functions, such as commonly used trapezoidal or triangular-shaped membership functions can also be considered as qualified candidates for node functions in this layer. Parameters in this layer are called “premise parameters” (Hines 1997).

Layer 2: Every node in this layer is a circle node, which performs a fuzzy intersection operation on the incoming signals from the first layer and sends the result to the next layer.

For instance,

$$O_{2,i} = w_i = \mu_{A_i}(x) \cdot \mu_{B_i}(y) \quad i=1,2 \quad (3)$$

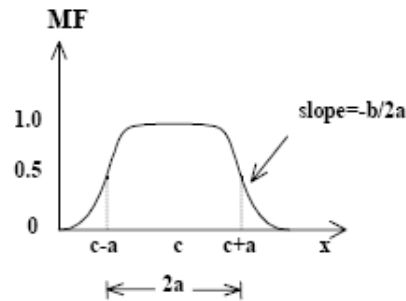


Figure 2: Meanings of the parameters in the generalized bell membership function

The left equation shows fuzzy intersection by the algebraic product, the second one the minimum intersection as they are called. Both variants are consistent extensions of intersection in classical set theory. Please note that each node output represents the firing strength of a rule.

Layer 3: Every node in this layer is a circle node such that the i -th node calculates the ratio of the i -th rule's firing strength to the sum of all rules' firing strengths as

$$O_{3,i} = \bar{w}_i = \frac{w_i}{w_1 + w_2} \quad i=1,2 \quad (4)$$

Outputs of this layer can be called normalized firing strengths.

Layer 4: Every node in this layer is a square node with a node function that calculates the output for corresponding rules weighted by its normalized firing strength such that

$$O_{4,i} = \bar{w}_i f_i = \bar{w}_i (p_i x + q_i y + r_i) \quad i=1,2 \quad (5)$$

where $\bar{w}_i$ is the output of the previous layer (layer 3), and $\{p_i, q_i, r_i\}$ is the set of parameters which are called "consequent parameters" (Jhy-Shing 1995).

Layer 5: The single node in this layer is a circle node that computes the overall output by using the weighted average defuzzification method as

$$O_{s,i} = f = \sum_i \bar{w}_i f_i = \frac{\sum_i w_i f_i}{\sum_i w_i} \quad (6)$$

i=1,2

Figure 3 shows an example of fuzzy partitioning of the input space in case of two inputs. Each of them is represented by three membership functions. So the input space is partitioned into nine fuzzy subspaces thus leading to nine fuzzy *if-then* rules in the ANFIS.

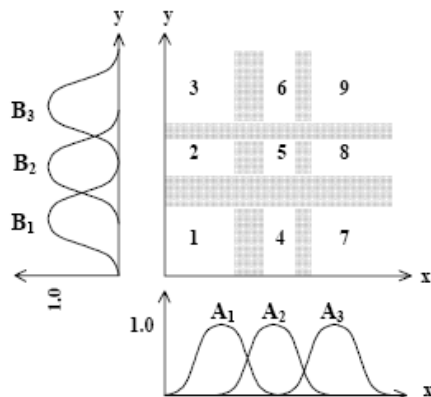


Figure 3: Corresponding fuzzy subspaces for a two-input Type-3 ANFIS with 9 rules

5. USED DATA and RESULTS

A total of 172 patients' Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) age and TAS values are used to form fuzzy models. Of them 140 patients' values are selected as model data to construct fuzzy models and 32 of them are used as test data to check whether fuzzy models are suitable or not. Statistical values about model and test data can be seen in Table 1.

Table 1: Summary of model and data used in the fuzzy models

	Model Data				Test Data			
	SBP	DBP	Age	TAS	SBP	DBP	Age	TAS
Maximum	220	120	89	1.15	200	100	83	1.01
Minimum	70	50	34	0.56	90	60	42	0.63
Average	135	82	62	0.82	127	78	59	0.83

In this study, 8 different fuzzy models are constructed to calculate patients' TAS values. In the models there are three inputs and one output. Input variables are Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and age of patients and output is TAS values of patients. Input variables are divided into two or three subsets in the models to find best fuzzy model. For example models M232 means first input variable SBP divided into 2 subsets,

second input variable DBP divided into 3 subsets and lastly third input variable age divide into 2 subsets. As the number of subsets increases, the number of parameters to determine increases in Sugeno type of fuzzy model. For example 48 linear and 14 non - linear parameters are to be determined. Therefore, input variables can be divided up to 3 because of small number of data we have. Gauss2 membership function is used in the model which gives the best results according to the previous research (Yilmaz and Arslan 2008).

Different fuzzy models are constructed to obtain better (or best) results. Therefore 8 different fuzzy models are formed. These are M222, M232, M223, M233, M322, M323, M332 and, M333. The performance of the Fuzzy models was tested at the 140 model data and 50 test data. The differences between measured TAS and the Fuzzy model results at both model and test data are summarised in Table 2.

Table 2: Minimum and maximum error and RMSE of fuzzy models on both model and test data.

Fuzzy Model	Model Data			Test Data		
	Max. Error	Min. Error	RMSE	Max. Error	Min. Error	RMSE
M222	-0.285	0.240	0.113	-0.173	0.308	0.122
M232	-0.290	0.235	0.102	-0.232	0.915	0.194
M223	-0.310	0.247	0.104	-0.289	1.321	0.267
M233	-0.273	0.248	0.093	-2.704	0.277	0.526
M322	-0.282	0.248	0.104	-0.180	1.381	0.329
M323	-0.272	0.267	0.091	-1.744	0.751	0.482
M332	-0.219	0.318	0.089	-0.186	2.889	0.628
M333	-0.230	0.274	0.073	-3.677	5.331	1.294

If we look at the Table 2, the best fuzzy model is M222 because RMSE values (which is calculated with $\sqrt{\sum \frac{vv}{n}}$, where v = error and n = number of points) of both model and test data are small and close enough to each other. This indicates that this model is valid. On the other hand fuzzy model M333 is gives the lowest RMSE value of the eight fuzzy models which is 0.073, contrary it also gives the highest RMSE value at the test data which is 1.294. This leads to fuzzy model M333 is not a good model. There is overfitting in this model which fuzzy model copies the model data however when the test data used, model gives enormous error such as -3.677 minimum and 5.331 maximum error values in the model. When the number of subsets increases in the fuzzy model, the difference between RMSE value of model and test data is increasing. This means that fuzzy models cannot be validated. Graphical representations of TAS values' errors at 140 model and 32 test data can be seen in Figure. 4-5 respectively.

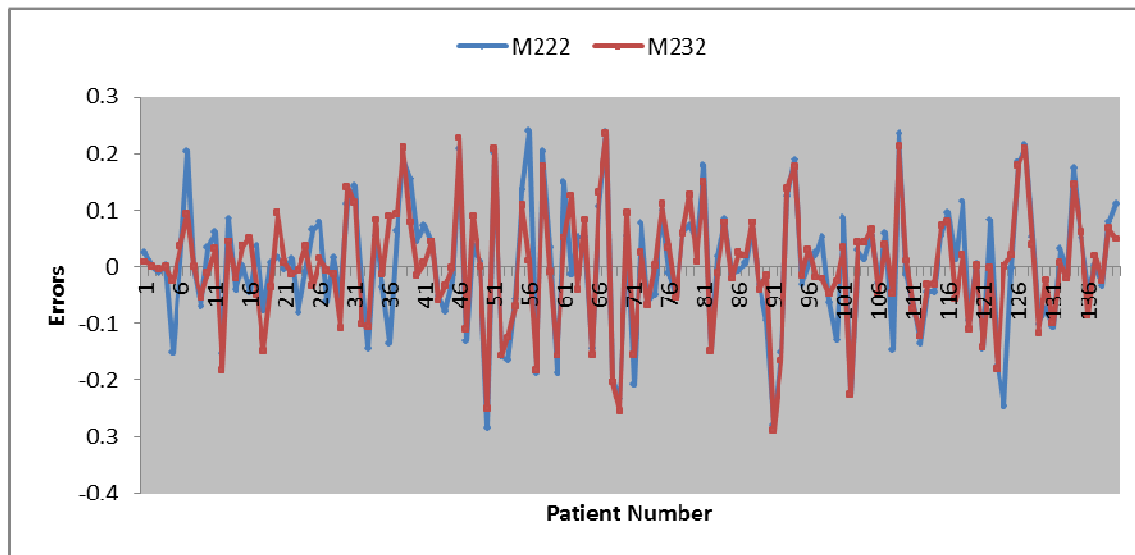


Figure 4: Errors between measured and calculated TAS values at 140 model data.

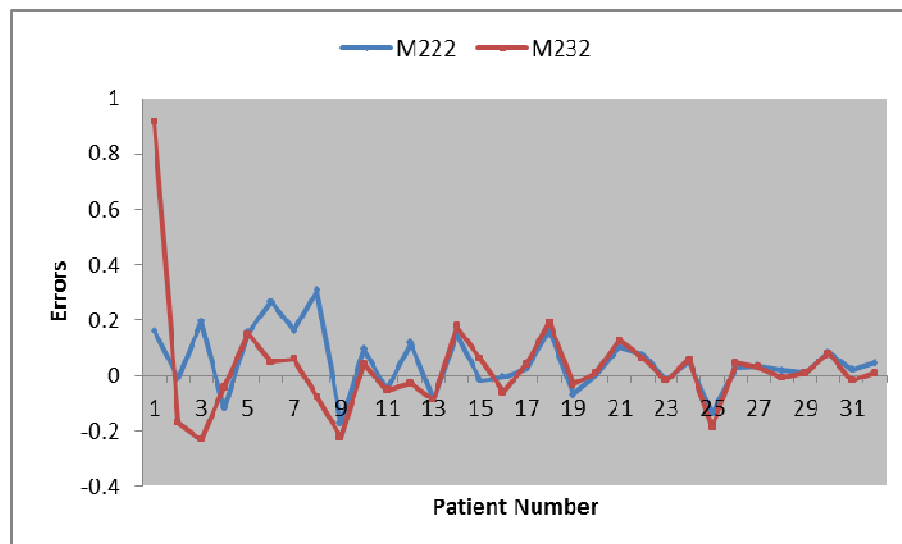


Figure 5: Errors between measured and calculated TAS values at 32 test data.

As we look at results from the model data, nearly 13 patient values are suspicious since patient values are calculated using all 8 fuzzy models and each model give worse results at these patient values. These patient values can be incorrect. If we had more data, it is better to eliminate these 13 patient values and this leads to get best results. Same thing can be said for 5 test patient values.

CONCLUSION

Oxidative stress is a cell and tissue damage in a living organism because of reactivity properties of free oxygen radicals. Oxidative stress can play vital role in many diseases process such as ALS, Parkinson's disease, Alzheimer's disease, Huntington's disease, and Multiple sclerosis. Oxidative stress is thought to be one of the underlying pathophysiological processes of epileptogenesis leading to epilepsy. During different use of antiepileptic drugs is known to increase oxidative stress. In this study we investigated that the effects of three different antiepileptic agents on oxidative stress. Levels of total antioxidant serum (TAS) reflect the total effect all antioxidants found in plasma and body fluids.

In this study, we tried to calculate a patient's TAS value using formed fuzzy model which is constructed by patients' diastolic (DBP) and systolic (SBP) blood pressures and, age values. Results showed that fuzzy model can be used to (predict) patient @TAS values. If we got more patients data, we can estimate TAS value of patients more accurately.

It is very important to predict TAS value of patients because their treatment process. Furthermore, if we get sufficient number of accurate data, fuzzy model can be provide better results and this can save one more life which is priceless.

REFERENCES

1. Akyılmaz, O, Ayan, T, Özlüdemir, T, 2003. Geoid surface approximation by using Adaptive Network Based Fuzzy Inference Systems, AVN p. 308 – 315.
2. Aguiar CC, Almeida AB, Araujo PV, de Abreu RN, Chaves EM, do Vale OC, Macedo DS, Woods DJ, Fonteles MM, Vasconcelos SM. Oxidative stress and epilepsy: literature review. *Oxid Med Cell Longev* 2012;79:52-59.
3. Balanica, V, Dumitrache, I, Caramihai, M, Rae, W, and Herbst C. Evaluation of breast cancer risk using fuzzy logic. *U.P.B.Science Bulletin Series*, Vol:73, Issue:1, p:53-64, 2011.
4. Chang SJ, Yu BC. Mitochondrial matters of the brain: mitochondrial dysfunction and oxidative status in epilepsy. *Journal of Bioenergetics and Biomembranes*, Vol:42, Issue:6, p: 457-459, December 2010.
5. Duodu, Q, Panford, JK and Hafron-Acquas, JB. Designing algorithm for malaria diagnosis using fuzzy logic for treatment (AMDFLT) in Ghana. *International Journal of Computer Applications* Vol: 91, Issue:17, p:22-27, April 2014.
6. Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. *Clinical Biochemistry*, Vol:37, Issue:2, , p:112–119, February 2004.
7. Halliwell B. Oxidative stress and cancer: have we moved forward? *Biochem J*. 1;401(1):p:1-11, January 2007.
8. Hines, JW. MATLAB supplement to Fuzzy and neural approaches in engineering, John Wiley & Sons Inc, New York, 1997.

9. James SJ, Cutler P, Melnyk S, Jernigan S, Janak L, Gaylor DW, Neubrandner JA. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. *The American Journal of Clinical Nutrition*. Vol:80, Issue:6, p:1611-1617, December 2004.
10. Jyh- Shing, R J,. ANFIS: adaptive – network based fuzzy inference system, *IEEE Transactions on systems, man, and Cybernetics*, **23**, No:3, p:665-685, 1993.
11. Jyh- Shing, R J. Neuro – fuzzy modelling and control, *Proceedings of the IEEE*, **83**, No:3, p:378-406, 1995.
12. Kennedy G, Spence VA, McLaren M, Hill A, Underwood C, Belch JJ. Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. *Free Radical Biology and Medicine*. Vol:39 Issue:5, p:584-589, September 2005.
13. Kumar, S. and Kaur, G. Detection of heart diseases using fuzzy logic. *International Journal of Engineering Trends and Technology* Vol:3, Issue :6 p:2694-2699, June 2013.
14. Li H, Horke S, Förstermann U. Vascular oxidative stress, nitric oxide and atherosclerosis. *Atherosclerosis*, Vol:237, Issue:1, p:208–219, November 2014,
15. Malathi, A, and Santra, AK. Diagnosis of lung cancer disease using neuro-fuzzy logic. *CARE journal of Applied research*, Vol:1, Issue:1, p:6-9, May 2013.
16. Miller NJ, Rice-Evans C, Davies MJ, Gopinathan V, Milner A. A novel method for measuring antioksidant capasity and its application to monitoring the antioxidant status in premature neonates. *Clinical Science*, Vol:84, Issue:4, p:407-412, 1993.
17. Patel, A, Choubey, J, Gupta, Sk, Verma, MK, Prasad, R, Rahman, Q. Decision support system for the diagnosis of asthma severity using fuzzy logic. *Proceedings of the International Multiconference of Engineers and Computer Scientist*, Vol:1, Hong Kong, March 2012.
18. Poongodi, M, Manjula, L, pradeepkumar, S, and umadevi, M. Cancer prediction technique using fuzzy logic. *International Journal of Current Research*, Vol:3, Issue :11 p:333-336, December 2011.
19. Sies, H. Oxidative stress: Oxidants and antioxidants. *Experimental Physiology*, Vol:82, Issue:2, p:291–295, March 1997.
20. Sikchi, SS, Sikchi, S and Ali, MS. Design of fuzzy expert system for diagnosis of cardiac diseases. *International Journal of Medical Science and Public Health* , Vol:2, Issue:1, p:56-61, 2012.
21. Takagi, T, Sugeno M, 1983. Derivation of fuzzy control rules from human operator's control actions. *Proc. Of the IFAC Symp. on Fuzzy Information, Knowledge Representation and Decision Analysis*, 55-60.
22. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *International Journal of Biochemistry & Cell Biology*, Vol:39, p:44-84, 2007.

23. Pohanka M. Alzheimer's disease and oxidative stress: a review. Current Medicinal Chemistry. Vol:21, Issue:3, p:356-364, 2013.
24. Varoglu AO, Yildirim A, Aygul R, Gundogdu OL, Sahin YN. Effects of valproate, carbamazepine, and levetiracetam on the antioxidant and oxidant systems in epileptic patients and their clinical importance. Clinical Neuropharmacology.;Vol:33, Issue:3, p:155-7, May 2010.
25. Yilmaz, A, and Ayan, K. Cancer risk analysis by fuzzy logic approach and performance status of the model Turkish Journal of electrical Engineering & Computer Science Vol:21, p:897-912, May 2013.
26. Yilmaz M and Arslan E. Effect of the type of membership function on geoid height modelling with fuzzy logic, Survey Review, Vol:40, p:379-391, 2008.