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

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ABSTRACT

Oxidative stress reflects an imbalance between the manifestation of systemic detoxification of reactive oxygen species and reactive intermediates or easily a biological system's ability to repair the damage caused. Normal redox peroxides and disorders of cells, proteins, lipids and deoxyribonucleic acid (DNA) of the cell including the free radical damage to all components may lead to toxic effects. Additionally, Some reactive oxidative species act as cellular redox signaling messengers. Thus, oxidative stress, may cause disruption in normal cellular signaling mechanisms. Oxidative stress is thought to lead major in neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, and Multiple sclerosis. Indirect proof by monitoring biomarkers like reactive oxygen species, and reactive nitrogen species production, antioxidant defense indicates oxidative damage might be concerned to 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 the 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 prevents the oxidation of other molecules. Transferring electrons or hydrogen from a substance to an oxidizing agent is called oxidation. Oxidation reactions can create free radicals and in turn, these radicals can begin chain reactions. When a chain reaction happens in a cell, it may result damage or death to the cell. Removing free radical intermediates by antioxidants abort these chain reactions and inhibit other oxidation reactions. Antioxidants do this by being oxidized themselves, therefore antioxidants are often reducing agents such as

thiols, ascorbic acid, or polyphenols (Sies 1997, Baillie et al. 2009, Bjelakovic et al. 2007, Abner et al. 2011 and Bjelakovic et al. 2013)

Although oxidation reactions are very important for life, oxidation reactions may also be harmful; 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. Inadequate levels of antioxidants or prevention of the antioxidant enzymes result stress and might harm or kill cells. Oxidative stress is harm to structure and function of cell by overly reactive oxygen-containing molecules and chronic excessive inflammation. Oxidative stress sounds playing a substantial role in many human diseases, including cancers. The use of antioxidants in pharmacology is thoroughly studied, particularly as treatments for stroke and neurodegenerative diseases. Therefore, oxidative stress can be considered to be both the reason and the result of some diseases (Pais and Dumitraşcu 2013, Vinceti et al. 2014).

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 humans such as cancer (Hallwell 2007), Parkinson's (Wood-Kaczmar et al. 2006) and Alzheimer's disease (Butterfly et al. 2001), (Valko et al. 2007, Pohanka 2013 Christen Y 2000, Nunomura et al. 2006), atherosclerotic disease (Li et al. 2014), autism (James et al. 2004), chronic fatigue syndrome (Kennedy et al. 2005). In many of these events, it is uncertain if oxidants initiate the disease, or if they are caused as a secondary consequence of the disease and from general tissue damage; one event in which this link is particularly well-understood is the role of oxidative stress in cardiovascular disease. Here, low density lipoprotein (LDL) oxidation seems to lead the process of atherogenesis, which results in atherosclerosis, and finally cardiovascular disease (Van Gaal L et al. 2006, Aviram 2000). Sezen et al. 2010 and Skarbek et al. 2014 also showed the relationship between Oxidative stress and coronary artery ectasia in their studies. 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 that 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).

TAS was determined by a new automated measurement method, invented by Erel 2004. By this method, hydroxyl radical, the most potent biological radical, is produced. Therefore, TAS value could not be estimated using by any methods so far. This is the first study estimating TAS value with DBP, SBP and age.

The interaction between doctors and engineers from different field led the exceptional occasions almost in every subject. This has just possible because of the emergence multidisciplinary technologies during past few years. The progresses in computer technology are playing a major role in development of medical diagnostic systems with demand for development of more intelligent and knowledge based systems. Computerized technologies to assist in diagnosis and access the related information are also used by the medical practitioners. They contradict in diagnosis and opinions s medical diagnosis is full of uncertainty. Decision support and expert systems with powerful reasoning capabilities in the form of approximate reasoning are ensured by fuzzy techniques. Powerful framework for combination of evidences and deduction of consequences based on knowledge stored in are also provided by fuzzy logic. Fuzzy logic can supply 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 calculating of total antioxidant capacity by employing the fuzzy logic.

Why do we prefer to use fuzzy logic?

The fuzzy logic method was preferred to current mathematical models because of its ability in modeling the obscurity in the related problem, working with lower cost and easy application, level of higher mechanical intelligence, solving 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.

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

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

Adaptive Network based Fuzzy Inference Systems (ANFIS)

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

All types of fuzzy inference systems (type 1, type 2 and type 3) shown in Figure 1 can be subjected to such a procedure. However, the complexity of the problem depends on the type of reasoning in the consequent part even if the results of all three types would not change significantly for the same data set. Therefore, in this section, Type-3 ANFIS is explained which is least complex and hence used for the prediction of the geoid heights. For simplicity, assume that the fuzzy inference system under consideration has two inputs x and y and one output f. Additionally, suppose that the rule base contains two fuzzy *if-then* rules of Takagi and Sugeno's type (Takagi and Sugeno 1983) as

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

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

Where x and y are input parameters and A_1 and A_2 are the values of input x and B_1 and B_2 are the values of B. f_1 and f_2 are the polynomial equations which gives the results of these rules. Related ANFIS architecture is shown in Figure 1.

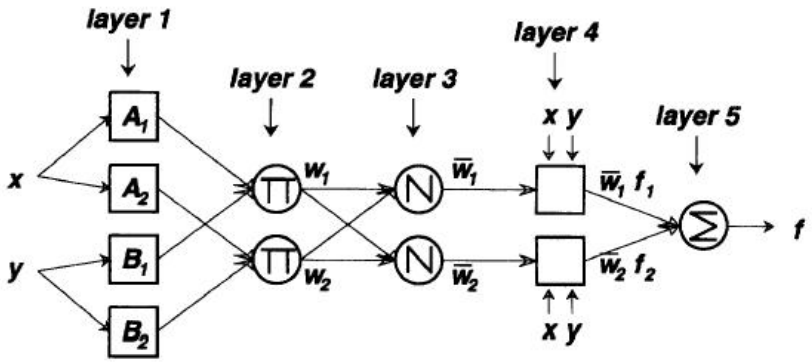

Figure 1: A simple two inputs and a single output of ANFIS structure

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: Each node *i* in this layer is a square node with a node function

$$O_{1,i} = «_{Ai}(x) \qquad i=1,2$$
$$O_{1,i} = «_{Bi-2}(y) \qquad i=3,4 \qquad (1)$$

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 defines the degree to which the given *x* satisfies the quantifier A_i. Usually, the membership function $«_{Ai}(x)$ is chosen to be bell-shaped (it is preferred in many reference books)with the maximum value equal to 1 and the minimum value equal to 0 such as, e.g., the generalized bell function (Figure. 2)

$$«_{Ai}(x) = \frac{1}{1+\left[\left(\frac{x-c_i}{a_i}\right)^2\right]^{b_i}} \qquad i=1,2 \qquad (2)$$

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 different membership functions on linguistic label Ai are characterized. In fact, any continuous and piecewise differentiable functions, such as mostly used trapezoidal or triangular-shaped membership functions can also be taken into account as qualified candidates for node functions in this layer. Parameters in this layer are defined as "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,

$$O_{2,i} = w_i = «_{Ai}(x).«_{Bi}(y) \qquad i=1,2 \qquad (3)$$

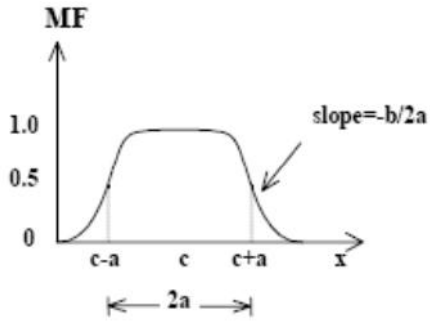

Figure 2: Meanings of the parameters in the generalized bell membership function

The equation on the left 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 every node output symbolizes the firing strength of a rule.

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

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

Outputs of layer 3 can be called normalized firing strengths.

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

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

Where $\overline{w}_i$ 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 calculates the overall output by using the weighted average defuzzification method as

$$O_{5,i} = f = \sum_i \overline{w}_i f_i = \frac{\sum_i w_i f_i}{\sum_i w_i} \qquad (6)$$

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.

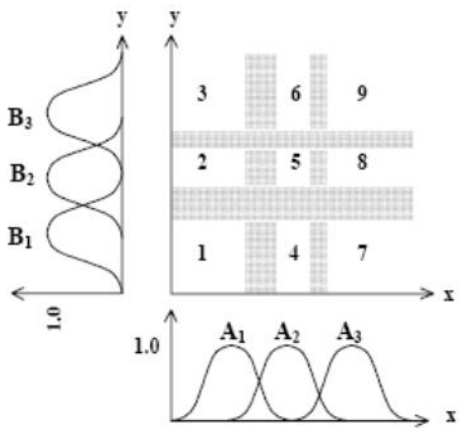

Figure 3: Corresponding fuzzy subspaces for a two-input Type-3 ANFIS with 9 rules

5. USED DATA and RESULTS

Data in this study were taken a previously conducted study at Harran University School of Medicine by Associate Prof. Yusuf Sezen and his friends between 2008 and 2009. Prior to initiating subject recruitment, their study was approved by the local ethics committee of the university, in accordance with the ethical principles for human investigations, as outlined in the second Declaration of Helsinki. All subjects provided written informed consent prior to participating.

A total of 172 patients' Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) age and TAS values were used to form fuzzy models. Of them 140 patients' values were selected as model data to construct fuzzy models and 32 of them were 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.

I tried to choose patients who have different DBP, SBP and Age to investigate the effect of these on TAS. Therefore, I didn't select just one age, DBP or SBP. I tried to distribute both

model and test patient group who has different age, DBP and SBP so that it reflects whole patient groups.

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

	Model Data				Test Data			
	SBP (mmHg)	DBP (mmHg)	Age (years)	TAS (Mmol Trolox equiv./L).	SBP (mmHg)	DBP (mmHg)	Age (years)	TAS (Mmol Trolox equiv./L).
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 and R^2 of fuzzy models on both model and test data.

	Model Data				**Test Data**			
Fuzzy Model	Max. Error (Mmol Trolox equiv./L).	Min. Error (Mmol Trolox equiv./L).	RMSE (Mmol Trolox equiv./L).	R^2	Max. Error (Mmol Trolox equiv./L).	Min. Error (Mmol Trolox equiv./L).	RMSE (Mmol Trolox equiv./L).	R^2
M222	-0.285	0.240	0.113	0.674	-0.173	0.308	0.122	0.372
M232	-0.290	0.235	0.102	0.669	-0.232	0.915	0.194	0.294

M223	-0.310	0.247	0.104	0.654	-0.289	1.321	0.267	0.276
M233	-0.273	0.248	0.093	0.734	-2.704	0.277	0.526	0.261
M322	-0.282	0.248	0.104	0.652	-0.180	1.381	0.329	0.191
M323	-0.272	0.267	0.091	0.748	-1.744	0.751	0.482	0.205
M332	-0.219	0.318	0.089	0.763	-0.186	2.889	0.628	0.168
M333	-0.230	0.274	0.073	0.846	-3.677	5.331	1.294	0.128

Table 3: Coefficients of fuzzy model M222 (f1= A_1*p+B_1*q+C_1*r+s, where A, B and C show SBP, DBP and Age respectively)

Rules	**p**	**q**	**r**	**s**
f_1	0.00739174191050109	-0.00332248527711028	-0.0433754126126195	1.8438283755026
f_2	-0.0061099993490957	-0.00747027455005307	-0.00508067680517975	2.16324736819968
f_3	0.0467085696406769	0.382362643310387	-0.411676814021122	-22.080297844991
f_4	-0.0848432067834117	-0.879024674462964	-0.0367832191170355	93.5268884036649
f_5	-0.0160608137797678	0.0274715195413936	-0.00355422234420872	1.24579713594714
f_6	-0.00122019201361275	-0.0202429417031759	0.000543931657092774	2.530889247295
f_7	-0.00189214396863684	0.0600489426919757	0.0347751433703262	-6.49963087880703
f_8	-0.00585724570537077	0.000979353052516373	0.00484522001208006	1.44592330304714

If we look at Table 2, the best fuzzy model is M222 because RMSE values (which is calculated with $\sqrt{\sum vv/n}$, 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. Same thing can be said for R^2 values at model and test data. Although the best R^2 values were obtained M333, M332 and M323 at model data, but the best R^2 values were got at M222, M232 and M223 respectively. If R^2 values at both model and test data close enough to each other, the fuzzy model was verified. Therefore, fuzzy model M222 is the best model of all again. Graphical representations of TAS values' errors and error percentage at 140 model and 32 test data can be seen in Figure. 4, 5, 6 and 7 respectively.

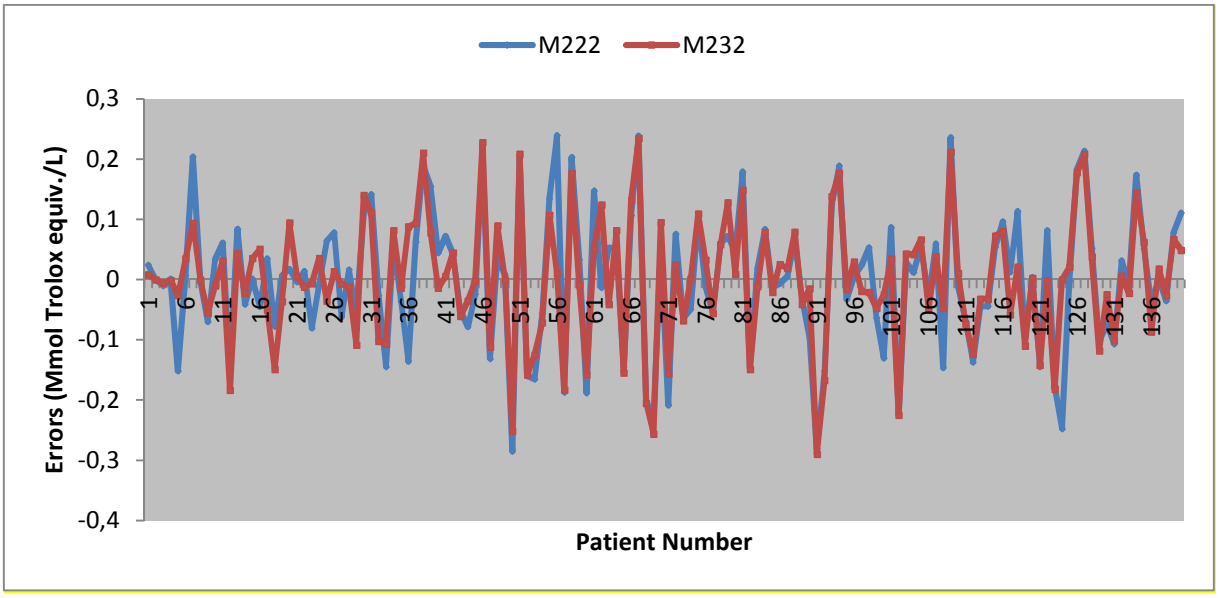

Figure 4: Errors between measured and calculated TAS values at 140 model data.

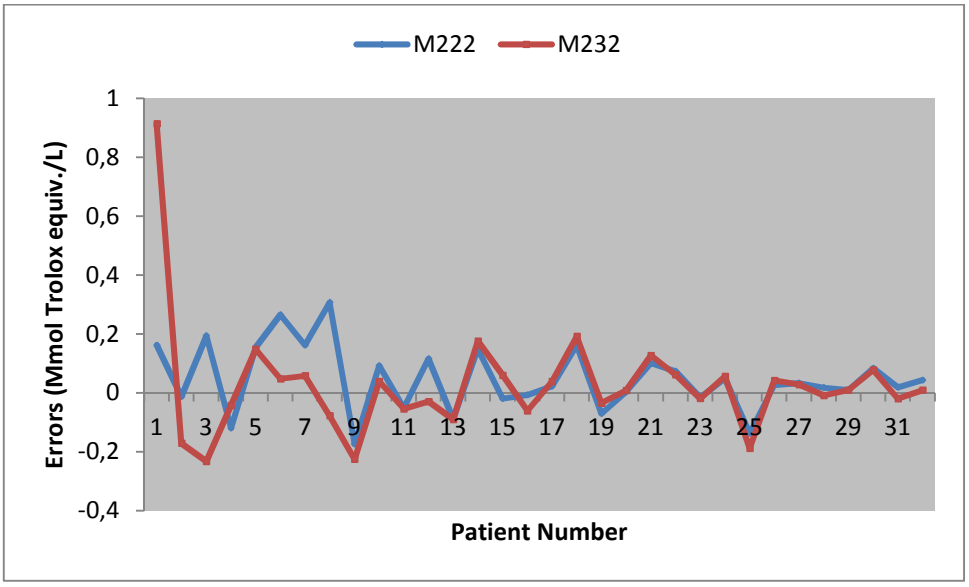

Figure 5: Errors between measured and calculated TAS values at 32 test data.

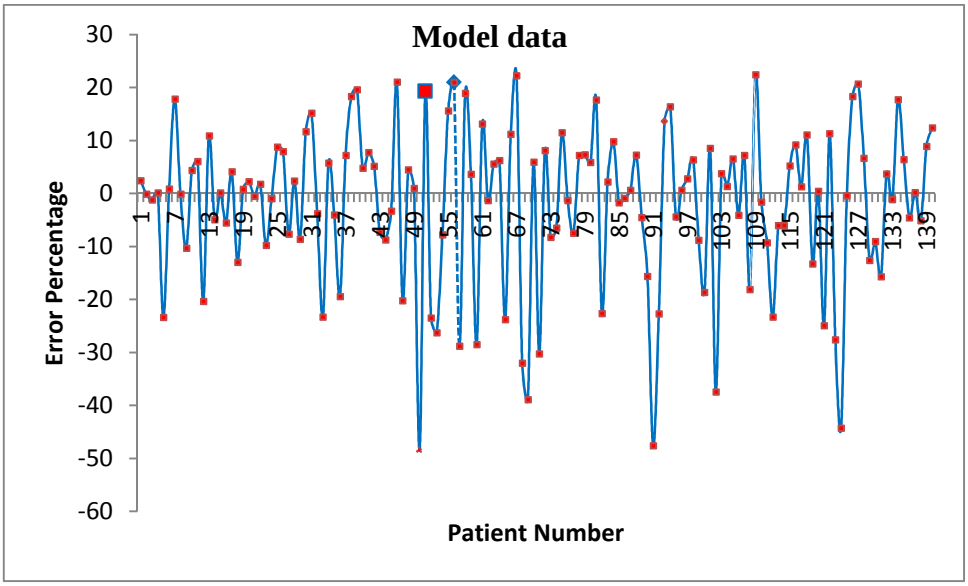

Figure 6: Error percentage {(error/measured)*100} of TAS values at 140 model data.

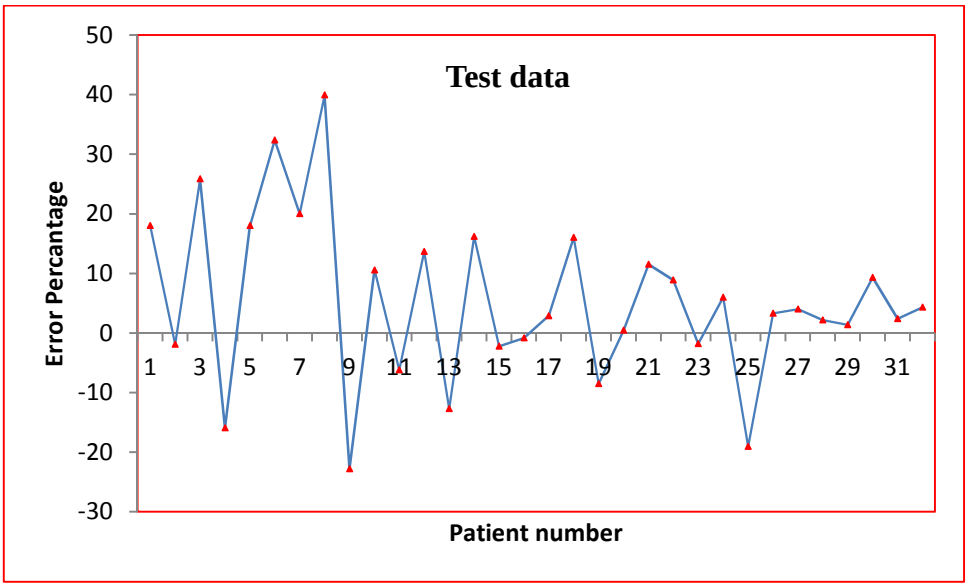

Figure 7: Error percentage {(error/measured)*100} of TAS values at 32 test data.

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 gave worse results with 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. The 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 pathophysilogical processes of epileptogenesis leading to epilepsy. During different use of antiepileptic drugs is known to increase oxidative stress.

When antioxidant defenses are weakened, body cells and tissues become more prone to developing dysfunctions and/or disease. Then, the maintenance of adequate antioxidant levels, but not overdosage, is essential to prevent or even manage a great number of disease conditions.

Recently published studies have revealed oxidative stress to be independently related to coronary artery disease CAD. However, it unclear whether oxidative stress is a natural cause of CAD or the result of several metabolic pathways. However, irrespective of how it occurs, it has been concluded that oxidative stress has some causative role in atherosclerosis formation. Levels of total antioxidant serum (TAS) reflect the total effect all antioxidants found in plasma and body fluids.

TAS value is measured at the laboratory so far. This is the first study that estimates TAS values using fuzzy logic using DBP, SBP and age values instead of measuring.

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. Therefore, we formed 8 different fuzzy models to estimate TAS value of patients. We formed fuzzy models as DBP, SBP and age values as inputs and TAS values as output in the fuzzy models. 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 values of patients to determine their treatment process. Furthermore, if we get sufficient numbers of accurate data, fuzzy model can provide better results and this can save one more life which is priceless.

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