SAKARYA ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ DERGİSİ

Sakarya University Journal of Science
SAUJS

e-ISSN 2147-835X Period Bimonthly Founded 1997 Publisher Sakarya University
http://www.saujs.sakarya.edu.tr/

Title: Metabolism Determination by Soft Computing Methods From Breath Molecules

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Recieved: 2021-04-12 00:00:00

Accepted: 2022-04-08 00:00:00

Article Type: Research Article

Volume: 26
Issue: 2
Month: April
Year: 2022
Pages: 429-437

How to cite
Sedat METLEK, Hatice AKMAN, Ismail BAYRAKLI; (2022), Metabolism Determination by Soft Computing Methods From Breath Molecules. Sakarya University Journal of Science, 26(2), 429-437, DOI: 10.16984/saufenbilder.911990
Access link
https://dergipark.org.tr/tr/journal/1115/issue/69580/911990

Sakarya University Journal of Science 26(2), 429-437, 2022

Metabolism Determination by Soft Computing Methods From Breath Molecules

Sedat METLEK[1], Hatice AKMAN*[2], Ismail BAYRAKLI[3]

Abstract

The breath analysis is a non-invasive risk-free and painless method used to diagnose specific diseases. Since the breath analysis method is a new study field than the other methods, there are many unsettled standards and unknown parameters. Numerous complex metabolisms are constantly working in the human body. Therefore, there are numerous unknown molecular relationships. ANN can produce solutions in these unexplained situations.

In our pilot study, breath of 19 healthy people has been analyzed. The TD / GC-MS method, which is an analytical method of breath analysis, has been used to detect molecules in the breaths. Using soft computing methods to the results of the 19 breath samples, the relation between fermentation and carbon hydrate metabolism has been associated with breath analysis technique. The results indicated that, there can be a relationship between these metabolisms. There must be done more studies for the exact results.

Keywords: Breath Analysis, Artificial Neural Network, acetone, hexanal, butanol.

1. INTRODUCTION

Breath analysis method gains importance day by day in the diagnosis of diseases and in monitoring the health status of the patient. Breath molecules are exhault by the different and unknown metabolisms. The present study has been done to understand the relationship between molecules from lipid metabolism and lipid peroxidation metabolism. Acetone and butanol molecules are the products of lipid metabolism and hexanal is known as the product of the lipid peroxidation metabolism.

Acetone is an organic compound that is one of three ketone bodies together with acetoacetate and 3-β-hydroxybutyrate. These bodies are produced in the liver (Figure 1). Acetone is produced in two ways: by acetoacetate decarboxylation and by isopropanol dehydration. Acetone is produced by the spontaneous decarboxylation of acetoacetate

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[1]. Acetone cannot be converted into acetyl-CoA [2] again and is therefore excreted with urine and breath. In the literature, acetone sources and formation ways are summarised in detail [3] The brain usually uses glucose necessarily as an energy source. However, when carbohydrates are limited with starvation, the brain cannot use glucose anymore. With the change of metabolism, the brain obtains ketone bodies from fats instead of carbohydrates, which are the main energy source. The fats taken generally dissolve into acetyl-CoA molecules by β-oxidation in the liver, then, produce energy through adenosine triphosphate (ATP) production by entering the cycle of the tricarboxylic acid (TCA). Acetyl-CoA, which is required for the biosynthesis of ketone bodies, is an important intermediate product in the energy metabolism. In the case of fasting, the tissues increase the fatty acid oxidation to meet the energy requirement, and as a result of this, a part of the excess acetyl-CoA is incorporated into the ketone body biosynthesis. The liver lacks the necessary enzymes to degrade ketone bodies. β-hydroxybutyrate and acetoacetate participate in the circulation through tissues such as the brain and muscle. Thus, the brain is able to utilise ketones, which are the main oxidative substrates for cerebral metabolism, through fasting or high fat/low carbohydrate uptake. Due to fasting, the ketones pass through the blood-brain barrier with an easy diffusion with the monocarboxylate transporter. With fasting, the brain monocarboxylate transporter levels get better. Neurons and glial cells separate β-hydroxybutyrate and acetoacetate into the acetyl-CoA fragment. (β-hydroxybutyrate dehydrogenase and 3 oxoacid CoA-transferase) Acetyl-CoA molecules can be considered to enter the Krebs Cycle and produce energy [4, 5]. In the brain, ketone bodies are an essential source of energy during fasting or strenuous exercise. In the brain, ketone bodies are an essential source of energy during fasting or strenuous exercise. The studies indicated that breath acetone can be used for the ketogenic state during fasting [6-9].

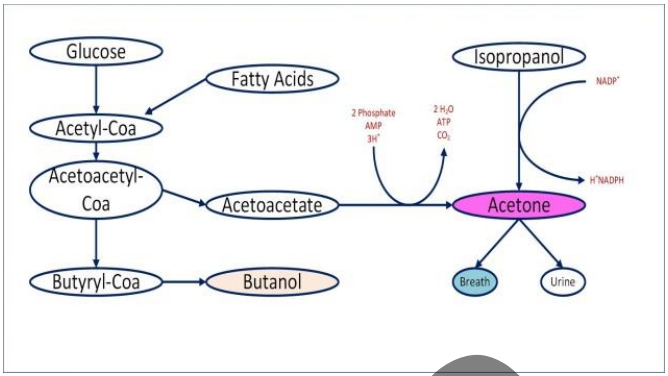

Figure 1 Biochemical pathways of acetone and butanol [10, 11]

Butanol can be produced from the microbial fermentation of carbohydrates such as glucose, for example, clostridium acetobutylicum [10]. This process has been metabolised to produce acetone and butanol from carbohydrates for various applications by means of acetone-butanol fermentation. Butyryl-CoA produced from acetoacetyl-CoA is converted to butanol in this process. Butanol was detected in human breath samples [12]. Filipiak et al. [13], analysed VOCs released by streptococcus pneumonia and haemophilus influenza cultures using the GC-MS method and found butanol at slightly high concentrations in both bacterial cultures. Kushch et al. [14], compared the breaths of smokers with those of non-smokers and found that the butanol molecule was not a significant biomarker for smokers. However, the butanol molecule was found at a significantly higher concentration in the breaths of lung cancer patients compared to the healthy control group.

There is not enough information about how the butanol molecule is formed and its effects on the cellular system. Some studies have shown the effects of acetone and butanol as anti-inflammatory agents [15, 16].

During lipid peroxidation, along with the increase in the formation of reactive oxygen species (ROS) that cause the increase in oxidative stress and neurotoxicity in the brain, an increase in lipid peroxidation markers as hexanal [17]. Lipid peroxidation metabolism is shown in Figure 2. Hexanal lipid peroxidation during lipid peroxidation is the molecule that occurs in the breath as a biomarker [18-22].

At the first stage of lipid peroxidation, lipid radical is formed by removing an H atom containing an electron from conjugated double bonds in fatty acids. The lipid radical forms the lipid peroxide radical (LOOH) by reacting with oxygen. LOOH degradation occurs with the ion catalysis of the transition metals. The cell membrane and organelle lipid peroxidation can be stimulated by free radicals and increases in the presence of transition metals. The formation of the hydroxyl radical ($OH^{\cdot}$) from hydrogen peroxide (H_2O_2) can initiate a chain reaction. As a result of these reactions, aldehydes (e.g. hexanal) emerge as end products [23]. The lipid peroxidation metabolism progressing without enzymes is a very harmful chain reaction. In these reactions, the membrane structure is directly damaged and the produced reactive aldehydes indirectly damage other cell components. This can cause many diseases [24], [25].

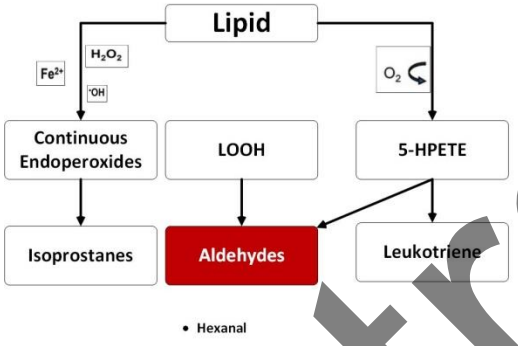

Figure 2 Lipid peroxidation metabolism [26]

2. MATERIAL METHOD

2.1. Breath Collection

Breath of 19 healty people has been collected via tubes from markes and translated to TENAX-TA 200 cartridge stored at the $4C^0$ to preserve VOCs (Figure 3). The information of the people breath collected from are shown at the Table 1.

Figure 3 Breath collection tube and cartage

Table 1 Breath Samples Collected Group

Gender (male/female)	10/9
Age (years)	Between 21 and 43 years Average: 28,8 years Standard Deviation (SD): 7,3
BMI (kg m^{-2})	Between 21 and 25,2 Average :23,2 SD: 1,5

2.2. GC-MS/TD Method

In conjunction with MS, GC is commonly used for breath analysis. In this study, TD - GCMS was used for analysis of breath acetone hexanal and butanol levels (Agilent Technologies 7890A 5975C). VOCs are thermally decomposed by thermal decomposers injected into GC / MS. Conditions for thermal decomposer are shown in Table 2.

The undifferentiated (non-split) mode has been applied to the TD system. GC / MS injector temperature was set to 250 ° C and the flow rate was set to 20 psi. The column oven temperature was raised to 180 ° C by keeping it at 60 ° C for 4 minutes and then increasing it by 20 ° C per minute. After holding at 180 ° C for 15 minutes, the temperature was raised again to 215 ° C at a rate of 4 ° C / min. It was held at this temperature for 20 minutes. In addition, the column oven was heated up to 240 ° C at 4 ° C per minute. It was held at this temperature for 35 minutes. Analytes were then injected into a DB-5 non-polar capillary column of 30 m length and 0.25 mm inner diameter. Selective ion tracking / imaging (SIM) mode was used to obtain lower detection limits. SIM mode allows us to get much more effective results in full scan mode. Helium gas (99.999%)

was used as a carrier in the analytical column with a flow of about 20 psi. Ionization of individual compounds was accomplished by electron impact ionization at 70 eV.

Table 2 Thermal desorption unit settings

Pre-desorption settings	
Split on in standby	
Flow path temperature	200°C
Minimum transporter pressure	5 psi
Pre-purification time	1 min
Tube / sample desorption settings	
Tube desorption time	5 min
Tube desorption temperature	250°C
Trap Settings	
Pre-trap fire purge	Minimum 1 min of trap flow
Trap low	−10°C
Trap heating rate	Maximum
Trap fixation / minute	3 min
Split	Open
Trap maximum	300°C

2.3. ANN

Artificial neural networks (ANN) are computer programs that are developed on the basis of the human brain, which are mainly connected to each other and which perform parallel and distributed information processing, each of which performs its own processing [27]

Examples related to the operations to be made to artificial neural networks are given. Thus, ANN can collect relevant information, make generalizations, and then decide on those samples using information learned in comparison with samples that have never been seen. Due to these learning and generalization features, artificial neural networks now find wide application in many scientific fields and demonstrate their ability to solve complex problems successfully [28].

ANN can be applied to many fields such as control and system identification, image and voice recognition, prediction and estimation, failure analysis, medicine, communication, traffic, production management [29].

There are also many different types of ANN developed for linear and non-linear systems such as perceptron neural networks, multi-layered artificial neural networks (MLF-ANN), and ADALINE / MADALINE. Since the nonlinear data are used in the study, the MLF-ANN structure of ANN is preferred.

2.3.1. Multi-layered Artificial Neural

Networks (MLF-ANN)

It is a structure developed for systems without linear solution. The MLF-ANN is a model in which the inputs are entered during the training phase and outputs are expected to be generated for these inputs.

Generated output based on network input [30]. The Multilayer Network structure is shown in Figure 4. The layer that the incoming information is transmitted to the hidden layer is the input layer. The hidden can be one or more. Here, the information received at the input layer is processed. On the output layer, the output values are calculated for each input against the information received from the hidden layer.

2.3.2. Feedback

Feedback in Artificial Neural Networks is done when the output of at least one neuron enters itself or other neurons and obtain error is usually made.

The feedback can be between neurons in a layer as well as between neurons in a layer. With this structure, feedback-driven ANN shows a non-linear dynamic behavior. Therefore, the feedbacks with different structures and behavior can be obtained according to the shape of the artificial neural networks.

Figure 4. below shows an ANN structure with three layers and feedback to the input layer.

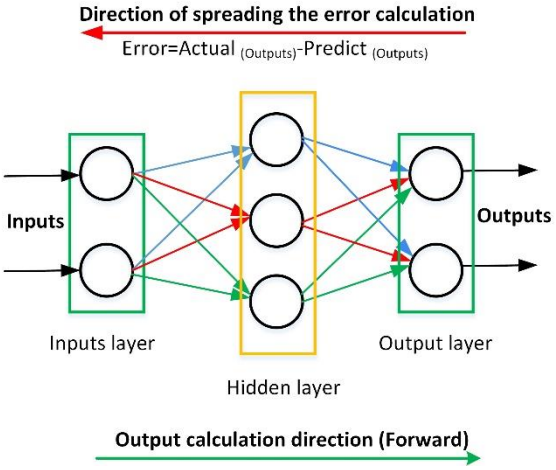

Figure 4 Feedback Neural Network

2.3.3. Back Propagation Algorithms

The backpropagation algorithm finds the error signal between the inputs and outputs, and the weights are updated with this error signal. The error e(t) is the difference between the actual output t(t) and the output of the neural network y(t) [31].

$$e(t) = t(t) - y(t); \quad t = 1,..,m \tag{1}$$

The backpropagation algorithm spreads the effects of the e(t) function on all weights on the network. Thus, the total error value is the lowest.

$$TH = \frac{1}{2}\sum_m E^2 \tag{2}$$

In Equation 2, TH represents the Total Error value. m is the output layer m. it is the element. Equation 2 shows that if the TH value is reduced in any experiment, the system error will decrease.

Methods that re-update the weight values on the network based on the decrease in system error and to support this decrease are used. The training process is based entirely on this update process.

With this algorithm xi. For input, the wji (t) change in weights between the i and j times processing elements is calculated. This expression is given in Equation 3.

$$\Delta w_{ji}(t) = \eta\delta_j x_i + \alpha\Delta w_{ji}(t-1) \tag{3}$$

In Equation 3, η is the learning coefficient, α is the momentum coefficient, and δj is a factor of any j-neuron at the intermediate or output level. For the output stage, this factor is given as follows.

$$\delta_j = \frac{\partial f}{\partial net_j}(y_j^{(t)} - y_j) \tag{4}$$

Where $y_j^{(t)}$ is the target output of the j processor element. For the Process Elements (PE) in the hidden layers (Process Elements - Neurons), this factor is expressed as in Equation 5.

$$\delta_j = \left(\frac{\partial f}{\partial net_j}\right)\sum w_{qi}\delta_q \tag{5}$$

Since there is no target output for neurons in hidden layers, Equation 5 is used instead of Equation 4. Depending on this situation, starting at the output layer, δj factor is calculated for neurons in all layers. The weights are then updated for all links based on the form in Equation 3. The activation function to be used in the backpropagation algorithm should have several important properties.

The activation function must be a continuous, derivative-derived function that does not degrade in a uniform manner. The reason for this preference is that the derivation of this function is easy. In general, the function is expected to lie between the minimum and maximum asymptotes [32].

In our study, the breathing of 19 healthy persons was examined. The TD / GC-MS method, which is an analytical method of breath analysis, has been used to detect molecules in the breaths. Breath samples taken from 19 individuals are shown in Table 3 and structure of prepared MLF-ANN Model is created.

Table 3 Inputs and outputs used in Feedback Multilayer Artificial Neural Network

	Inputs		**Outputs**
	Hexanal (ppb)	Acetone (ppb)	Butanol
1	0,62	92	0,18
2	2,02	97	0,57
3	1,13	97	0,25

4	2,23	114	0,63
5	8,22	119	0,67
6	5,55	148	1,26
7	1,11	148	1,12
8	5,69	199	0,25
9	0,98	210	0,89
10	2,56	216	0,36
11	6,56	219	0,36
12	0,85	243	1,25
13	1,62	267	0,44
14	0,82	305	0,3
15	2,5	305	0,56
16	1,99	307	1,51
17	1,25	309	0,75
18	1,92	317	0,56
19	5,05	772	0,28

MATLAB 2017a version was used to process the data. The structure of the prepared model is shown in Figure 5. In this structure Hexanal and Aceton were taken as input and Butanol was taken as output. Thirteen of the data in the Table 1 are used for training (70%), 3 data (15%) for testing, and 3 data (15%) for validation.

Levenberg-Marquart, Bayesian Regularization and Scaled Conjugate Gradient functions were tested for training. The results obtained are shown in Table 4. Mean squared error values are used to evaluate the performance of the system.

When Table 4 and Figures 5,6,7 examined, it is seen that the Bayesian Regularization method gives better results in training and test results in two-input, 10 hidden-layer and one output system than the other two methods.

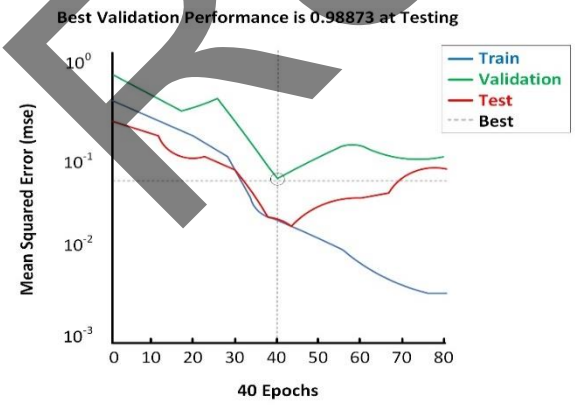

Figure 5 Levenberg-Marquart

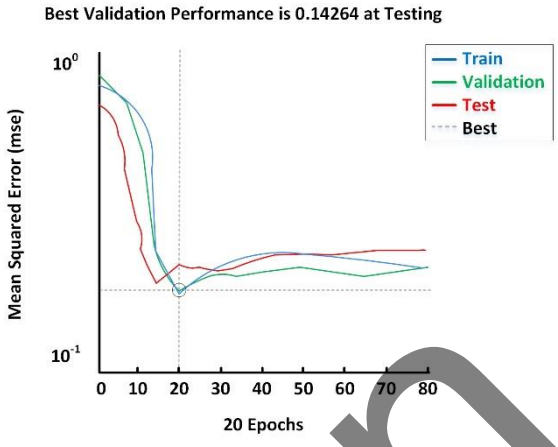

Figure 6 Bayesian Regularization

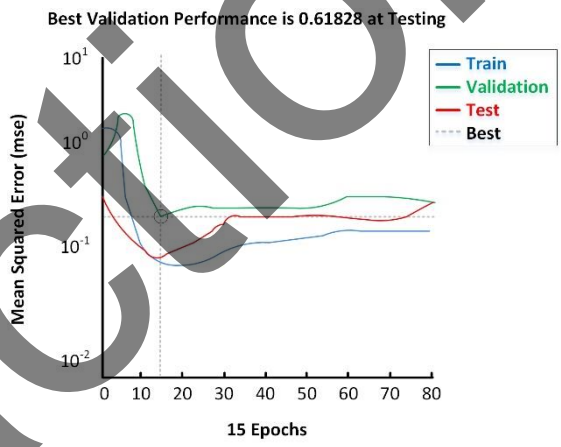

Figure 7 Scaled Conjugate Gradient

Table 4 Results Obtained from Feedback Model Neural Network Model

		Samples	Number of neurons in hidden layer	Iterations	Mean Squared Error (MSE)
Levenberg-Marquart	Training	13	10	40	0,80314
	Validation	3	10	40	0,64211
	Testing	3	10	40	0,98873
Bayesian Regularization	Training	13	10	20	0,12345
	Validation	3	10	20	0,13708
	Testing	3	10	20	0,14294
Scaled Conjugate Gradient	Training	13	10	15	0,73701
	Validation	3	10	15	0,70095
	Testing	3	10	15	0,61828

Despite the small number of data used in the study, high accuracy was obtained in the training and testing processes as the data completely covered the research subject.

3. CONCLUSIONS

Hexanal and acetone is the end product of the carbon hydrate metabolism and can be detected from breath. Butanol is the end product of the carbon hydrate fermentation. Many complex metabolisms occur in the body and there are lots of undefined metabolisms. This pilot study is done to understand the indeterminate metabolisms' products. This is a preliminary study to discover metabolism, and can be a method to diagnose diseases but more data is needed. Hexanal and Acetone are defined as input and Butanol as a output at the model which is prepared by using feedback artificial neural network method which is a flexible calculation method. The prepared ANN model is also an example of human metabolism. According to this pilot study there can be a relationship between fermentation and carbon hydrate metabolism.

An association is established between these non-linear data. It is a preliminary study of what chemicals will enter the human metabolism in the future and which components will result in a reaction. If there are more and more data from human metabolism, they can be explained more clearly in relation to each other. As a result, the personalized ANN model can be obtained. Thus, according to certain chemical results to be taken from the person, the anomalies of the person's body can be determined much more quickly and accurately.

The Declaration of Research and Publication Ethics

In the writing process of this study, international scientific, ethical and citation rules were followed, and no falsification was made on the collected data. Sakarya University Journal of Science and its editorial board have no responsibility for all ethical violations. All responsibility belongs to the responsible author and this study has not been evaluated in any academic publication environment other than Sakarya University Journal of Science.

The Declaration of Ethics Committee Approval

The authors declare that this document does not require an ethics committee approval or any special permission. B

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by the authors.

Authors' Contribution

Sedat Metlek: Artificial Neural Network Design, Writing

Hatice Akman: Breath Analysis, Writing

İsmail Bayraklı: Breath Analysis

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