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Application of the Adaptive Neuro-Fuzzy Inference System (ANFIS) and Sobol Approaches for Modeling and Sensitivity Analysis of the Biosorption of Triglyceride from the Blood Serum

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ABSTRACT

An adaptive neuro-fuzzy inference system (ANFIS) was applied to simulate the batch adsorption of triglyceride (TG) from the human blood serum using the cinnamon powder, which has appeared as a potential biosorbent for serum purification, in our previous work. The obtained experimental results were used to train and evaluate the ANFIS model. Temperature (°C), the adsorption time (h), the stirring rate (rpm), the dose of adsorbent (g) and the adsorbent milling time (min) (or the particle sizes of the powder) were considered as the model inputs and TG removal (%) was chosen as the model response. The ANFIS model was trained with 75 % of the available data while 25 % of the remaining data was used to verify the validity of the obtained model. Sobol sensitivity analysis results indicated that the cinnamon dose with 71 % and the adsorbent milling time (or the particle size of the powder) with 15 % impact share were the most influential variables on the TG removal. Furthermore, the specific surface area and the number of reactive adsorption sites were found to be the most important characteristics of the adsorbent. Generally, the results of this study confirmed the advantages of applying the ANFIS and Sobol approaches for the data-based modeling of the bioprocesses.

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1. Introduction

Despite the advancement of healthcare, the number of people experiencing hyperlipidemia is increasing worldwide and cardiovascular disease is an important reason for mortality [1]. Therefore, in addition to medical treatments, changes in diet and lifestyle are also necessary to cure hyperlipidemia [2]. Triglyceride, an ester including one glycerol and three fatty acid precursor units (e.g., oleic acid, linoleic

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acid), is accumulated in fat cells and regarded as an energy source [3]. TG is necessary for human health but excessive TG can cause arteries to tighten, blood pressure to increase, apoplexy, heart attack and some other related diseases [4-6]. Herbal medicines are promising therapies for health issues due to some advantages such as less side effects, acceptable effectiveness and relatively low price [7, 8]. A popular type of herbs used worldwide is the skin of various types of cinnamon which can be found in the bark of several tree species [9]. Cinnamon is a spice routinely used for cookery, but it has some novel therapeutic applications [10-12]. Four general types of cinnamon including Mexican cinnamon, Indonesian cinnamon, Vietnamese cinnamon and Chinese cinnamon have been identified so far [13]. The ingredients of cinnamon are moisture (10 %), carbohydrate (23 %), protein (5 %), fibrin (20 %), total ash (3.5 %), calcium (1.5 %), phosphorus (0.05 %), iron (0.04 %), sodium (0.01 %), potassium (0.4 %) and small amounts of vitamin B_1, vitamin B_2, vitamin C and niacin [14]. It should be noted that the cinnamon aroma is mainly determined by the amount of the cinnamaldehyde content as well as the oxygen uptake rate [15]. Based on the literatures, cinnamon has the potential to reduce the lipid level in the rats' blood [16, 17]. Khan et al. [18] indicated that using controlled doses of cinnamon per day can reduce the levels of glucose, triglycerides and cholesterol in the blood serum. In recent years, researchers have shown increasing interest in studying the influences of cinnamon on various diseases [19-22]. Adsorption, a conventional separation process with a rich background, is highly popular among researchers, especially for the separation in biological media like the blood environment mainly due to its bio-adaptability, effectiveness and controllability [23, 24].

Current authors have employed different types of the Thymus Vulgaris powder for the in-vitro adsorption of cholesterol molecules from the human blood serum [25]. The results of our study uncovered that Thymus Vulgaris could reduce the content of cholesterol in the blood by about 85 %. The batch adsorption of the TG of the blood serum using the cinnamon powder as an effective biosorbent has been investigated by Salehi et al. [26]. Results disclosed the conspicuous impact of cinnamon on lowering the TG level in the blood serum. Besides the superior capacity for the adsorption of blood lipids, cinnamon displayed a higher rate of removal when compared with thymus under similar conditions [27].

Finding the best operating conditions for the adsorption process is vital for the scale-up and efficient use of the adsorbents [28, 29]. There are few works done on modeling the biological systems like biosorption. In recent years, data-based optimization and modeling methods have been employed to assess very challenging multivariate systems [30]. Artificial neural networks (ANNs) can successfully anticipate and transfer the hidden knowledge of the experimental data to their processing network [31, 32]. ANNs require no presumption regarding the distribution and quality of the data, so these methods are superior to the conventional statistical methods [33]. On the other hand, ANNs utilize nonlinear approaches for modeling the data and provide more accurate estimations of a nonlinear database [34]. The better trainability of ANNs, especially when combined with Fuzzy systems, makes them very successful in modeling complex systems [35]. The combination of ANNs/Fuzzy systems can compensate for the insufficiency of the individual methods and bring about a powerful class of databased systems, the adaptive neuro-fuzzy inference system [36]. An adaptive neuro-fuzzy inference system (ANFIS) employs training approaches of the ANN system to find fuzzy parameters including membership functions and appropriate fuzzy rules [37]. ANFIS is an ANN-Fuzzy system with a united training algorithm. This method focuses on modeling different complicated engineering systems [38-40]. ANNs cannot provide a model in an optimal time frame. On the other hand, the fuzzy modeling needs training in experimental data for predicting the output of the model. This successful combination provides an ANN-Fuzzy system to prognosticate the outputs of the model, especially where the ANN-Fuzzy approach is integrated with the sensitivity analysis methods [41].

Recently, researchers have shown increasing interest in using ANFIS for the optimization of and modeling the adsorption systems. Ronda et al. [42] employed full factorial design combined with the ANFIS in order to absorb lead from olive stone and the experimental data were in good agreement ($R^2 > 95$ %) with a second-order predictive equation. Bingol et al. compared the ANFIS and MLR (multiple linear regression) models in the process of modeling batch adsorption including copper ions as the adsorbate and date seeds as the new adsorbent in an aqueous medium [43].

In the current study, for the first time, an ANFIS was employed for modeling the batch adsorption of TG from the human blood plasma. The process variables include the dose of the adsorbent, particle size, adsorption time, temperature and stirring rate. The expert model was trained using the experimental data. After evaluating the performance of the developed model, the Sobol sensitivity analysis was applied to quantify the impact share of the input variables on the TG removal. The aim of the current study is to propose an ANFIS model for predicting the experimental data as well as carrying out the sensitivity analysis of the objective function (TG removal) variation to variations in the input variables.

2. Materials and methods

2.1. Experimental data and the adsorption procedure

The required data have been obtained from our previous study [26]. The effects of the adsorption time (h), dose of the adsorbent (g), adsorbent milling time (min) (representing the particle sizes of the powder), temperature (°C) and stirring rate (rpm) were studied on the TG removal (%). Table 1 represents the ranges of all important and effective parameters considered in this study to calculate their impacts on and interactions with the TG removal as the system response. For batch adsorption experiments, it is required to define an appropriate range for the key variables to model the process and also determine the best biosorption performance [44]. Therefore, the range of each variable was calculated based on the pretest experiments and validated by similar literatures.

10 ml of the blood serum with a predetermined level of TG was equilibrated with 0.1 g of the cinnamon powder for 2 h at a constant temperature. Afterwards, the powder was separated from the solution using a proper cellulosic filter. The equilibrium concentration of TG in the supernatant serum was determined using a serologic auto-analyzer. The removal percentage (as the response parameter) was calculated by the following equation:

$$\mathrm{R}\ (\%) = \frac{C_0 - C_f}{C_0} \times 100 \tag{1}$$

where, C_f and C_0 are the concentrations of TG before and after the reaction respectively.

Table 1

Range of effective independent parameters in the biosorption process.

Parameter	Unit	Range
Adsorption time	h	0.5 - 3
Adsorbent dose	g	0.01 - 1
Stirring rate	rpm	50 - 300
Temperature	°C	20 - 30
Adsorbent milling time	min	0.5 - 9.5

2.2. Sensitivity analysis

From a process control viewpoint, in modeling the adsorption process, it is useful to quantify the sensitivity of the target function to any changes in the amounts of input variables [45]. The sensitivity analysis is a promising technique for obtaining the effectiveness share of the input variables involved in systems/processes. It is also possible to investigate the effects of the interactions of two or more variables on the model response [46]. In terms of their functions, sensitivity analysis methods are categorized into deterministic and probabilistic [47]. These methods can be also classified into graphical, mathematical and statistical methods [48]. The Sobol analysis is a statistical method independent of the model functionality. In comparison with other graphical methods, in which one parameter is changed and other parameters kept constant, in the Sobol method all of the parameters are allowed to change simultaneously [49]. This approach is mainly based on the variance decomposition and can be employed for non-linear and non-uniform functions.

For a Y=f (X) model where Y is the response function and X $(x_1, x_2, \dots, x_n)$ is an input vector, output variance V can be introduced by Equation (2):

$$V(Y) = \sum_{i=1}^{n} V_i + \sum_{i \leq j \leq n}^{n} V_{ij} + \cdots + V_{1,\dots,n} \tag{2}$$

where V_i is the first order effect for each input variable, $x_i (V_i = V[E(Y|x_i)])$ and V_{ij}) $V_{ij} = V[E(Y|x_i, x_j)] - V_i - V_j$) to $V_{1,\dots,n}$ are the interactions between the n factors.

Sensitivity indices are defined as the ratio of the variance of a certain order to the total variance. For example, $S_i = \frac{V_i}{V}$ is the first order sensitivity index and $S_{ij} = \frac{V_{ij}}{V}$ is the second order sensitivity index. The total sensitivity indice which determine the overall effectiveness of each parameter in the response is defined as the summation of all sensitivity indices of all orders. More details of the Sobol sensitivity analysis can be found elsewhere [50, 51].

2.3. Adsorption modeling by ANFIS

The ANFIS system, a combination of the computational capacity of the neural network and the logic of the Fuzzy method, is a promising tool to model complex systems [52]. Similarly to other Fuzzy systems, the ANFIS structure contains antecedent and consequent parts connecting to each other through a set of rules. There are commonly five layers in an ANFIS structure. A common type is the Sugeno Fuzzy system with two inputs and one output, as presented in Figure 1. There are five distinct processing steps in utilizing the Sugeno fuzzy system and their connections and interactions are presented in this schematic [53, 54]. Variables x and y are inputs and f is the output, related together according to the following relations:

if $x=A_1$ and $y=B_1$ then $f_1 = p_1x + q_1y$

if $x=A_2$ and $y=B_2$ then $f_2 = p_2x + q_2y$

where A_i and B_i are fuzzy components, f_i is the system output and p_i and q_i are design parameters that are obtainable during the system training. If O_i^j presents the i^th node output of the j^th layer of the ANFIS system, then functions ascribed to each of the ANFIS system layers can be described as [52, 55]:

Layer 1: In this layer, each node is a fuzzy component and its output equals the membership degree of the input variable. Parameters of each node introduce the membership function in the fuzzy components. Gaussian membership functions are usually employed and so, Equation (3) is exercised:

$$\mu_{Ai}(x) = e^{-\frac{1}{2}\left(\frac{x-c_i}{\sigma_i}\right)^2} \tag{3}$$

where x is the input value of each node while c_i and σ_i are the center and width of the Gaussian membership function respectively.

Layer 2: In this layer, the input signal values of each node are multiplied to compute the firing strength of the rule, as presented in Equation (4):

$$O_i^2 = \omega_i = \mu_{Ai}(x)\mu_{Bi}(y) \quad i = 1,2 \tag{4}$$

where μ_{Ai} is the membership degree of x in the fuzzy component A_i and μ_{Bi} is the membership degree of y in the fuzzy component B_i.

Layer 3: Nodes in this layer calculate the relative weight of the laws where ω_i^n is the normalized weight of the rules of the i^th width which can be presented by Equation (5):

$$O_i^3 = \omega_i^n = \frac{\omega_i}{\omega_1 + \omega_2} \quad i = 1,2 \tag{5}$$

Layer 4: This layer is a rule layer and is computed using the multiplication of normalized firing strength (computed in the previous layer), and output of the Sugeno fuzzy system as presented in Equation (6).

$$O_i^4 = \omega_i^n f_i = \omega_i^n(p_i x + q_i y + r_i) \quad i = 1,2 \tag{6}$$

Layer 5: This layer is the last layer of the system where all inputs to the layer are merged as defined by Equation (7):

$$O_i^5 = \sum_{i=1}^{2} \omega_i^n f = \frac{\omega_1 f_1 + \omega_2 f_2}{\omega_1 + \omega_2} \quad i = 1,2 \tag{7}$$

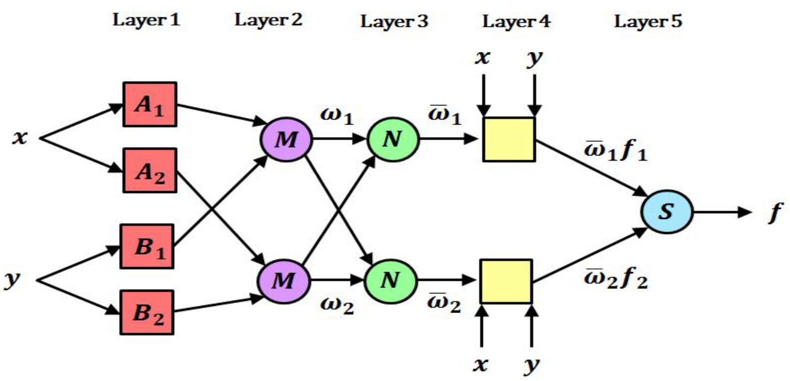


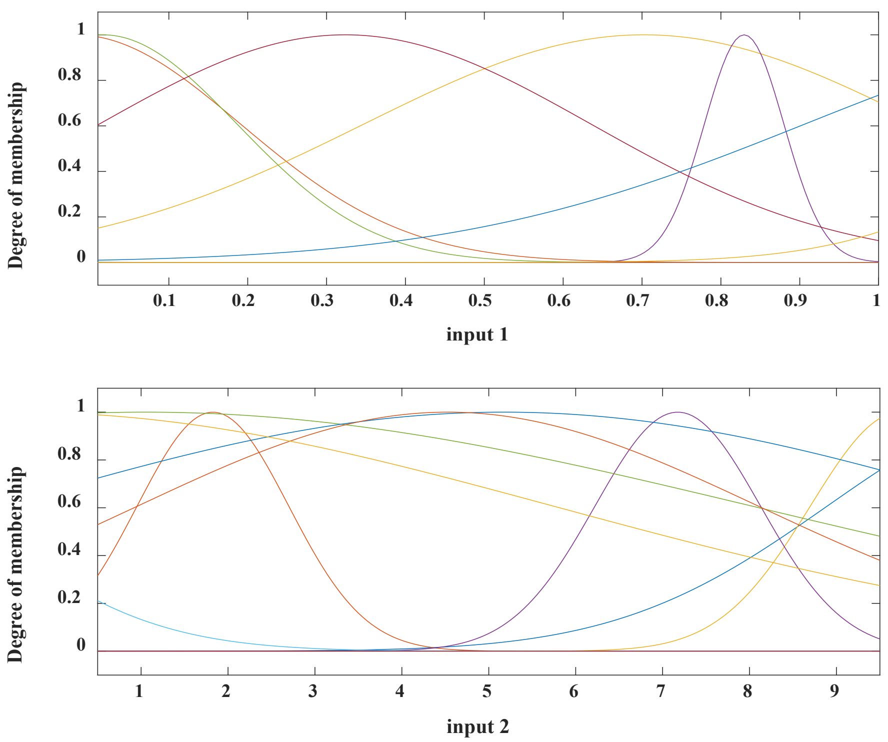
Figure 1. Sugeno fuzzy system structure, a common type of ANFIS systems.

In brief, the function of the first layer in the ANFIS structure is the formation of a fuzzy system while the second layer's role is defining the principle of if-then fuzzy logic laws. The third layer normalizes member functions and the fourth layer includes the secondary fuzzy logic laws. Finally, the last layer predicts the output of the expert system. Thus, the first and last layers in ANFIS are compatible layers. It should be mentioned that c_i and σ_i in the first layer are input member function parameters and r_i, q_i and p_i are compatible parameters known as the resultant parameters.

3. Results and discussion

1000 epoch were employed to train the network. Totally, there are 47 sets of data available with known amounts of the TG removal. The ANFIS system was made by five input variables and each data set was divided into a 75 % portion for training the system and a 25 % portion for the system validation. Fuzzy laws are defined by an expert model while in the ANFIS system if-then laws are generated spontaneously. The member functions of the input variables are presented in Figure 2 and some graphical methods were used to evaluate the performance of the proposed model. It is worth mentioning it in here that the attained ANFIS structure is not an optimal structure, however, it has succeeded to show high accuracy in approximating the output variable. Here, is the “anfis” command used in the MATLAB software to obtain the tuned ANFIS model. The “Anfis” command generates a single-output Sugeno fuzzy inference system (FIS) and tunes the system parameters using the specified input/output training data. The FIS structure is automatically generated using grid partitioning. The training algorithm uses a combination of the least-squares and backpropagation gradient descent methods to model the training data set.

The removal rate in terms of the degree of membership is shown depending upon effective factors, such as the adsorption time, dose of the adsorbent, stirring rate, temperature and adsorbent milling time.



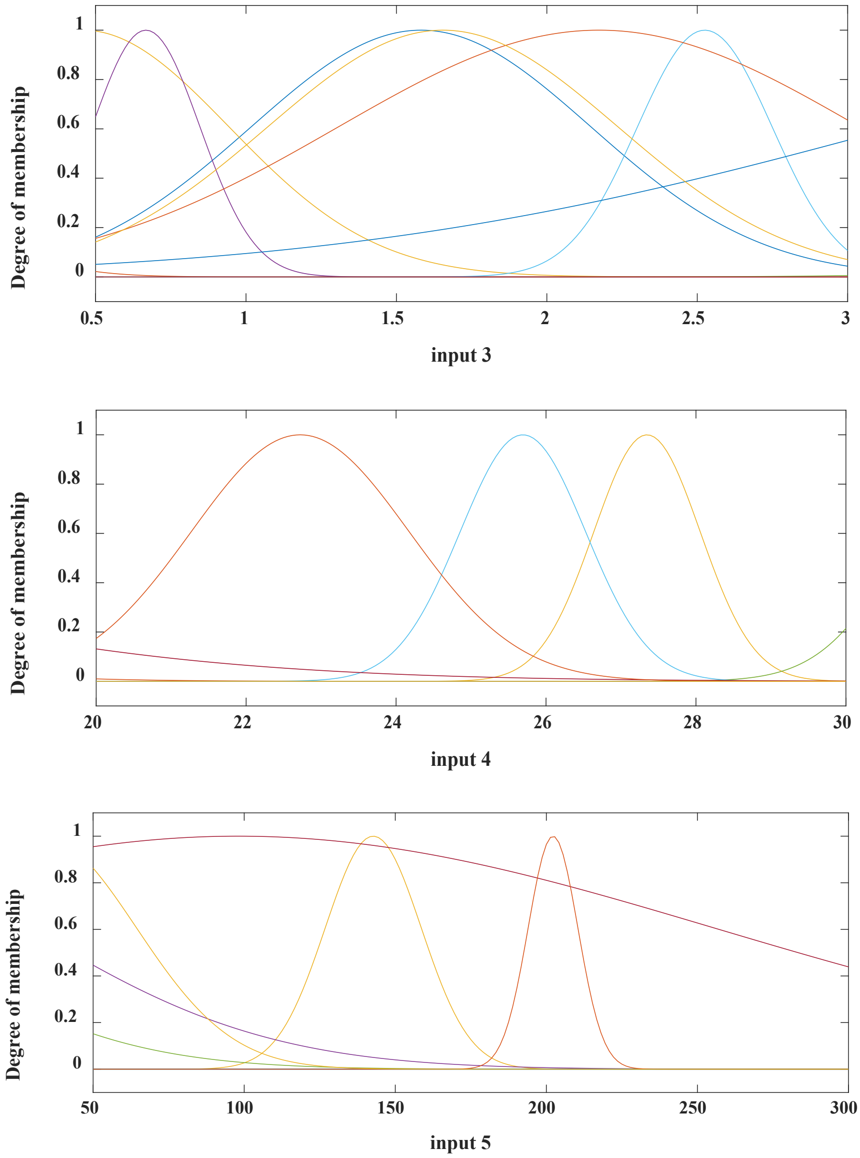


Figure 2. ANFIS member functions for predicting the system's response.

Most of variations are happening for the dose of the adsorbent and adsorbent milling time as observed in this figure and that may result in these two factors being the main deciding parameters in the biosorption process. However, to accurately and quantitatively determine the effectiveness of process parameters, it is necessary to use sensitivity analysis methods.

Figure 3 shows the scatter plot of actual data and ANFIS predictions. In this figure, blue circles illustrate the data used for training the system and red squares represent those used for the system validation (ANFIS outputs). As it can be observed, the ANFIS system could well correlate with the training data points and also well predict the output values related to the testing data.

It can be inferred that the developed model is capable of predicting the data related to the network test set with excellent accuracy, as the square symbols are very close to the midline. The slight discrepancy observed, may be due to the unavoidable measurement errors in the experiments.

Finally, to evaluate the statistical accuracy of the developed model, root mean square error (RMSE) and correlation factor (R) functions were employed as presented in Equations (8) and (9) respectively:

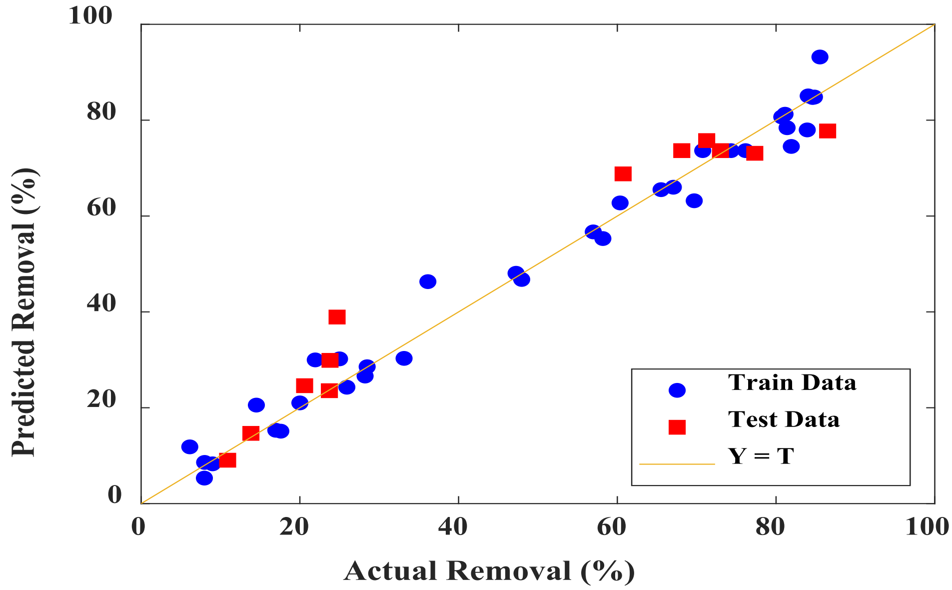


Figure 3. Scatter plot of the experimental values vs predicted ones of the removal rate from ANFIS.

$$\mathrm{RMSE} = \sqrt{\frac{1}{n} \times \sum_{i=1}^{n} (O_A - O_p)^2} \tag{8}$$

$$R = \frac{\sum_{i=1}^{n}[(O_A - \bar{O}_A)(O_p - \bar{O}_p)]}{\sqrt{[\sum_{i=1}^{n}(O_A - \bar{O}_A)^2][\sum_{i=1}^{n}(O_p - \bar{O}_p)^2]}} \tag{9}$$

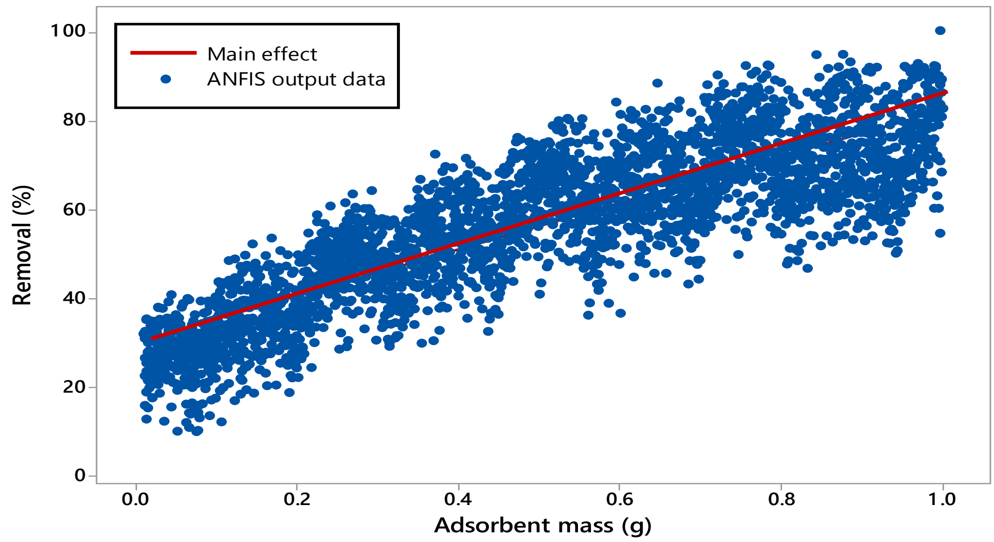
where O_A is the real output for the i^{th} sample, O_p is the ANFIS- predicted value for the i^{th} sample, $\bar{O}_A$ is the average measured data and $\bar{O}_p$ is the average predicted data.

The statistical data associated with the proposed ANFIS model were gathered to validate the accuracy of the model. The RMSE of 3.88 and 6.26 and R^2 of 0.99 and 0.97 for training and testing data points respectively were obtained. The presented values clearly confirmed that the developed ANFIS network is highly successful in predicting the TG removal results.

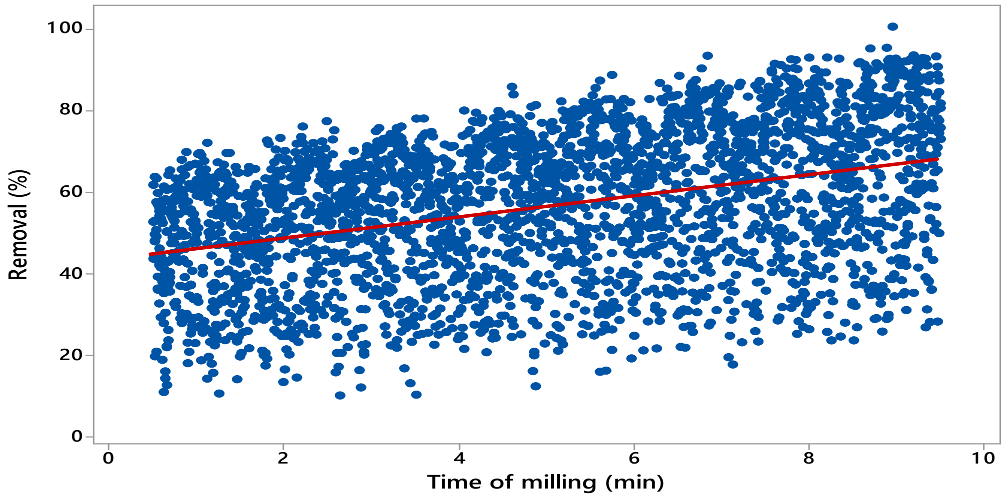
3.1. Sensitivity analysis

It was attempted to quantitatively evaluate the effectiveness of the input variables and their interactions in the objective function, the percentage of the TG removal. Figure 4 shows the distribution of the removal percentage data for input parameters changing simultaneously. In such graphic diagrams, the slope of the curve shows the effectiveness intensity of the parameter in a way that the higher the slope, the higher the effectiveness of the corresponding parameter.

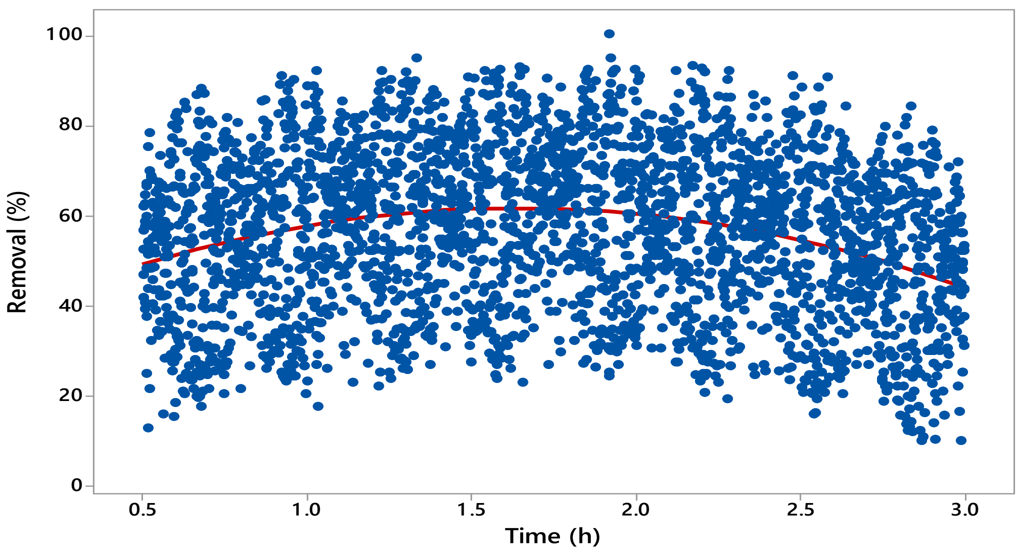
Within the defined ranges of the input parameters, the importance of the impacts of the variable on the response follows this order: the dose of the adsorbent > the adsorbent milling time (powder size) > the adsorption time > temperature > the stirring rate.


Main effect
ANFIS output data
Removal (%)
Adsorbent mass (g)
0
20
40
60
80
100
0.0
0.2
0.4
0.6
0.8
1.0

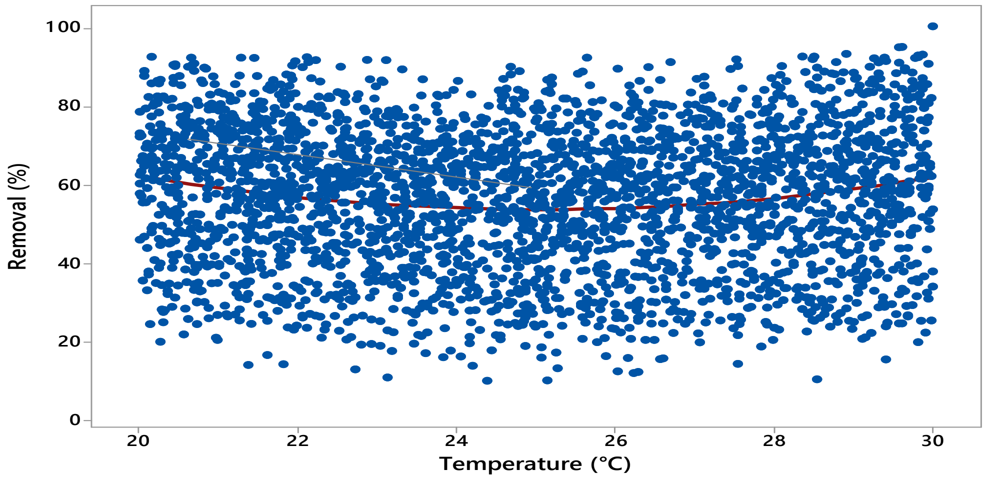
(a)


Removal (%)
Time of milling (min)
0
20
40
60
80
100
0
2
4
6
8
10

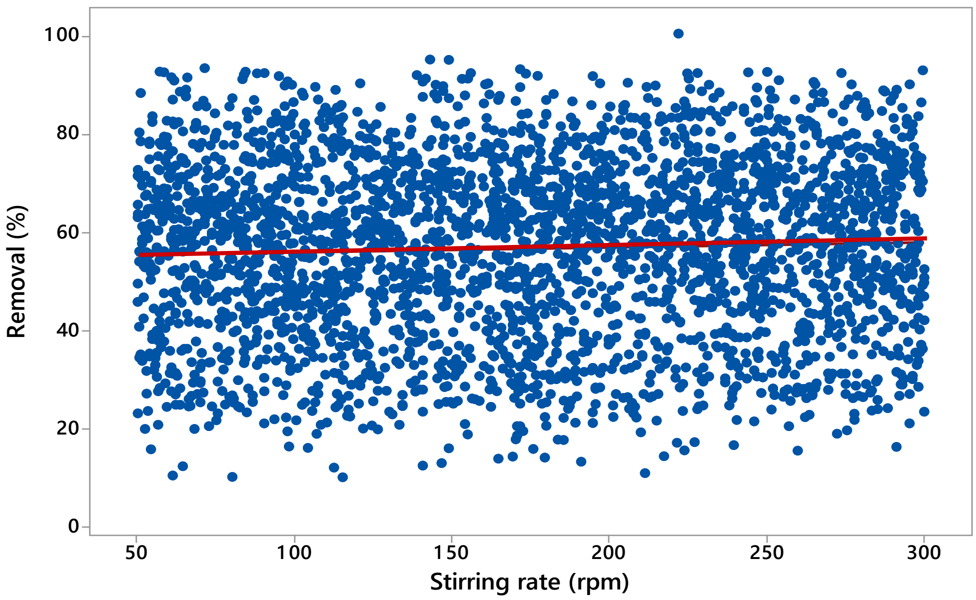
(b)


Removal (%)
Time (h)
0
20
40
60
80
100
0.5
1.0
1.5
2.0
2.5
3.0

(c)



(d)



(e)

Figure 4. Removal rate distributions with the simultaneous variations in effective parameters,

a) The effect of the dose of the adsorbent on the removal rate
b) The effect of the adsorbent milling time on the removal rate
c) The effect of the absorption time on the removal rate
d) The effect of temperature on the removal rate
e) The effect of the stirring rate on the removal rate.

Figure 5 shows the results of the Sobol sensitivity analysis which approves the aforementioned results. Accordingly, the Sobol sensitivity analysis shows that the dose of the adsorbent with 71 % share, adsorbent milling time (powder particles size) with 15 % share, adsorption time with 6 % share, temperature with 4 % share and stirring rate with 4 % share are the most influential input variables. This result was obtained by performing the Sobol analysis using the Sim Lab software. The dose of the adsorbent is in tune with the total number of the reactive adsorption sites which play the most important role in the adsorption of TG. So, the dose of the adsorption is the most important parameter effecting the TG removal. The size of the adsorbent particles (the adsorbent milling time) is tabulated in the second position. The adsorbents with smaller particle sizes suggest larger specific surface area for the adsorption. Greater surface areas can cause higher adsorption capacities accordingly. This fact clarifies the impact of the particle size of the adsorbent on the TG removal. It can be concluded from the sensitivity analysis results that the specific surface area of adsorbents and the number of reactive sites play the most crucial roles in the adsorptive removal of TG from the blood serum.

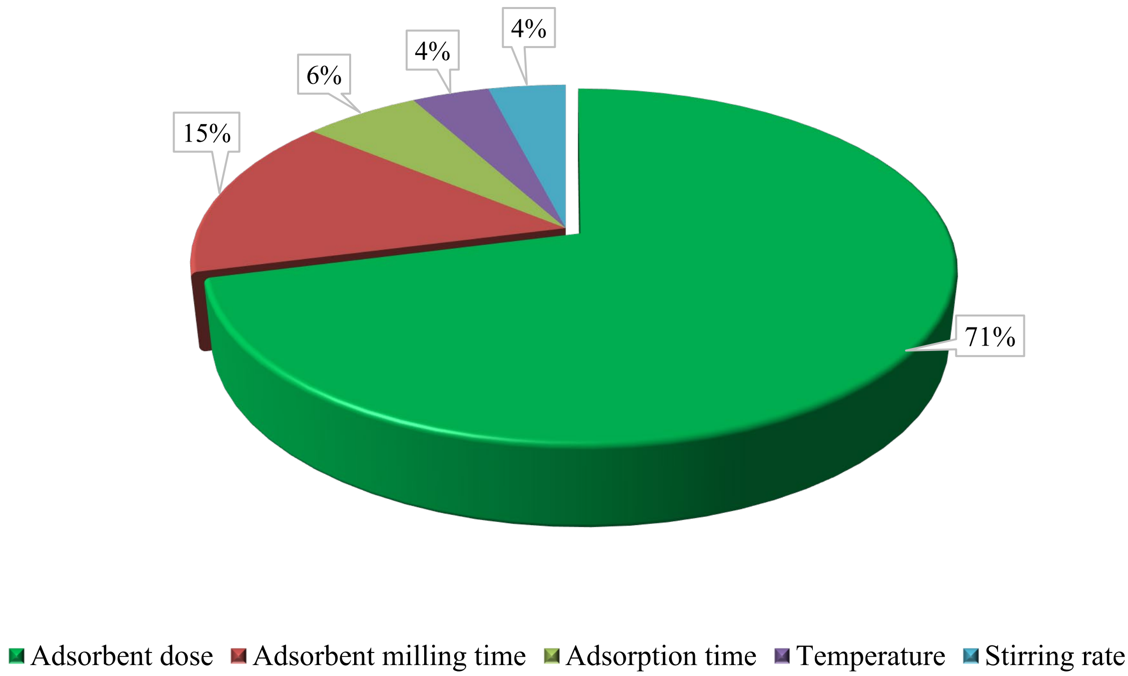


Figure 5. Effect of the rotational speed on the segregation index, the Sobol sensitivity analysis for the determination of the most effective input variables.

4. Conclusions

An expert ANFIS network was proposed for the batch adsorption of TG from the human blood serum by cinnamon powder as a good adsorbent. The adsorption time (h), stirring rate (rpm), Temperature (°C), dose of the adsorbent (g) and adsorbent milling time (min) (or the particles size of the powder) were the input variables and the TG removal was considered as the model output. The ANFIS model was trained with 75 % of the data whereas the remaining 25 % of the data were applied to confirm the validity of the proposed model. The ANFIS model showed a good accommodation with the experimental data and the obtained results approved the capability of ANFIS to model the adsorption process. The Sobol method was used for performing the model sensitivity analysis. Results showed the dominating effect of the dose of the adsorbent (71 %) on the adsorption of TG. In addition, the adsorbent milling time, adsorption time, temperature and stirring rate tabulated as the the next ranks with 15 %, 6 %, 4 % and 4 % shares of effectiveness respectively. It could be stated that the number of reactive adsorption sites and surface areas are the most effective properties of the adsorbent.

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