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Evaluation of Effective Electrospinning Parameters Controlling Gelatin Nanofibers Diameter via Modelling Artificial Neural Networks

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Abstract: The aim of this work was to evaluate the effective parameters for prediction of the electrospun gelatin nanofibers diameter using artificial neural network (ANN) technique. The various sets of electrospinning process including temperature, applied voltage and polymer and solvent concentrations were designed to produce pure gelatin nanofibers. The obtained results by analyzing Scanning Electron Microscopy (SEM) images indicated that the produced nanofibers diameter was in the range of 85 to 750 nm. Due to the volume of the data, *k* fold cross-validation method was used for data setting. Data were divided into the five categories and trained and tested using ANN technique. The results indicated that the network including 4 input variables, 3 hidden layers with 10, 18 and 9 nodes in each layers, respectively, and one output layer had the best performance in the testing sets. The mean squared error (MSE) and linear regression (R) between observed and predicted nanofibers diameter were 0.1531 and 0.9424, respectively. The obtained results demonstrated that the selected neural network model had acceptable performance for evaluating involved parameters and prediction of nanofibers diameter.

Keywords: Gelatin, Nanofibers, Electrospinning, Modeling, ANN

Introduction

Nanofibers can be used in the various fields, such as tissue engineering, filtration and drug delivery systems, because of their several unique properties such as high porosity and high specific surface area [1-3]. The different methods e.g. phase separation, melt blowing, self-assembly and electrospinning are used for preparation of nanofibers in vitro, but electrospinning is more popular than the others [4]. Electrospinning is a process with high level of complexity and producing electrospun nanofibers with desired diameter would be a costly and time-consuming process [5,6].

The defined diameters of nanofibers are required for specific goals such as cell scaffolds or air and water filters [7]. Therefore, the efforts have been done to find scientific models for prediction of patterns in different process and areas for many years [8-10]. The results indicated that data mining; a way to discover new meaning in data, is the effective technique. It is based on using sophisticated data search capabilities and statistical algorithms to find out patterns and correlations in preexisting databases and then create the automatically relationships between data sectors. There are the various methods to predict and analyze patterns including one at the time, and modeling optimization techniques such as response surface methodology (RSM) techniques. Artificial neural network (ANN) is one of the useful methods of data mining in recent years. This method is designed based on the artificial intelligence to mimic the human neural network. Designed networks with data mining and giving the desired weights to the variables, predict the relationship between the values. In comparison with standard optimization methods such as response surface methods it would be more efficient [11,12]. Regarding accuracy of these methods, using them is being developed on predicting nanofibers diameter produced by electrospinning technique [13,14]. For example, Sarkar and colleagues used ANN and k-fold cross-validation method to predict electrospun polyethylene oxide (PEO) nanofibers diameter with an acceptable errors [15]. Four independent parameters include conductivity, applied voltage; solution concentration and flow rate were used as the input variable for ANN models. The results indicated viability of ANN control technique for regulation of nanofibers diameter in an electrospinning process.

ANN viability also was estimated by other researchers, and the results confirm ANN efficiency in prediction of nanofibers diameter [6,16]. Similarly, Faridi and colleagues recently studied on the network using artificial neural network to predict the nylon 6 nanofibers diameter. The variables consisted of the polymer concentration, flow rate, spacing between nozzle and collector, and the applied voltage. The results indicated that nanofibers diameter has directly correlation with the polymer concentration and inversely relationship with the flow rate [6].

Estimation and efficiency evaluations of predictive networks using ANN models were reviewed within the same studies [17,18]. Mengshan and colleagues used artificial neural networks in combination with the other algorithms to predict the solubility of gases in polymer networks which provided

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appropriate predictive results [17]. Recently, Esmaeilzadeh and colleagues studied chitosan nanoparticles obtained from ultrasonication process. The ANN model for predicting chitosan nanoparticles size indicated appreciate outcomes using independent variables including polymer concentration, solution acidity, amplitude and the time of the ultrasonication [18].

There are a few works to predict kinds of polymer nanofibers diameter using neural networks, but to our knowledge, prediction of electrospun gelatine nanofibers diameter via modelling ANN has not been studied. In this paper, various sets of electrospinning were used to prepare gelatin nanofibers. Moreover, the validity of ANN models in prediction of gelatin nanofibers diameter is evaluated.

Gelatin is a natural, biocompatible and biodegradable polymer with a variety of applications in different fields of science [19]. It can be extracted from animal skin and bones by the thermal denaturation of collagen, with very dilute acid. Since gelatin chemical composition is very similar to collagen, it may be a good candidate to mimic the chemical composition of natural collagen in tissue engineering. Therefore, as a biopolymer, its unique properties may potentially offer growth opportunities in field of tissue engineering.

Materials and Methods

In this study, the following materials were used: gelatin (approximately bloom=110 (130-90). (Merck, Germany), Glacial acetic acid as solvent (Merck, Germany) and the electrospinning process performed using Electroris (FNM Ltd., Iran, www.fnm.ir).

Methods

Nanofibers Production

According to the database of Table 1, four independent variables include gelatin and acetic acid concentration, applied voltage and temperature with different values were used for electrospinning of gelatin. Distance between metallic needles of plastic syringe, containing gelatin solution, and conductive collector (drum) and drum rpm fixed were 10 cm and 200 rpm, respectively. Images were taken from corresponding samples by scanning electron microscopy (SEM), after sputtering with gold. Then, the mean diameter of random 50 fibers was calculated and considered as the diameter of the fibers for each sample (Figure 1).

Table 1. List of input variable for electrospinning

Independent input variable	Description
X_1	Gelatine concentration (w/v)
X_2	ACOH concentration (v/v)
X_3	Applied voltage (kV)
X_4	Temperature (^oC)

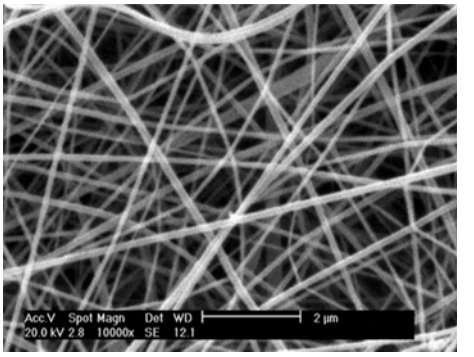


Figure 1. SEM images of electrospun gelatin nanofibers.

Using Artificial Neural Network

The predictive networks with various hidden layers and nodes were designed, and validation of ANN models in prediction of the nanofibers diameter using MATLAB software was evaluated. According to the database, *k* fold cross-validation method was used to achieve better results.

Network Models Designed for Prediction

The research was carried out to predict the electrospun fibers diameter. Several parameters affect on electrospun nanofibers morphology include internal and external factors. The main external factors include the kind of the applied polymer and solvent, flow rate of solution, electric field, and the distance between the syringe and the collector plate. The main internal factors include the nature of solvents, and surface tension, viscosity, conductivity and concentration of the solution [20]. Based on the references, several factors affect to stretch and uniform generation of fibers such as the solution viscosity, electric field and the molecular weight of the polymers [21]. But, due to the difficulties in measuring some parameters like solvents surface tension and viscosity, it is reasonable to measure and control variables such as concentration [15].

Various settings of four effective variables on electrospun nanofibers diameter include gelatin concentration (X1) (w/v), acetic acid solvent concentration (X2) (v/v), the applied voltage (X3) (kV) and temperature (X4) (^oC) are used (Table 1).

Data are partitioned into the two training and testing categories. Training data are used to adjust the network weights and the testing dataset are also applied to evaluate network performance.

Studies have shown that using simple dataset for prediction via ANN is not effective when the database is small [15]. On the other hand, with a large database, efficiency of ANN models may be ineligible or invalid to estimate future samples if a simple training-test dataset dividing procedure is used.

One of the approaches to achieve this result is using *k* fold cross validation. Using *k* fold cross validation method leads to less bias than the simple training-test dataset dividing

process [22].

In this method, database randomly partitioned into the *k* equal subsets (Table 2) including testing and training set, and function of approximation repeated k times to fit function using training dataset. At each step, *k*-1 subsets are put together to form a training set and one remaining of the *k* subsets is also used as the test set. Then the mean squared error (MSE) across all *k* trials is computed, and finally is referred to evaluate the network validity.

Table 2. Training-testing partition pairs using 5 fold cross-validation method

Partition pairs	Training set	Testing set
1	Partition {1,2,3,4}	Partition {5}
2	Partition {1,2,3,5}	Partition {4}
3	Partition {1,2,4,5}	Partition {3}
4	Partition {1,3,4,5}	Partition {2}
5	Partition {2,3,4,5}	Partition {1}

Network Training Using *k* Fold Cross Validation Procedure

30 samples of electrospun nanofibers were prepared by electrospinning and used as ANN models training- testing dataset (Table 3). The results of the Table 3 indicate no forming of fibers in 5 samples (1, 2, 3, 6, 25). These samples composed of only beads without fibers. Thus, practically only 25 of the 30 samples were used in practice to train and test the ANN models.

Table 3. Training data set for ANNs modeling

Sample no	Gelatin concentration (wt%)	AcOH concentration (% v/v)	Applied voltage (kV)	Temprature (^{o}C)	Comment	Obsereved diameter (nm)	Predicted diameter (nm)
1	11	55	9	28.1	Only beads	-	
2	12	90	14	28.3	Only beads	-	
3	14	9	10.3	31.3	Only beads	-	
4	14	35	15	27		159	102
5	14	35	7	40		97.5	129
6	15	100	10	28	Only beads	-	
7	15	50	15	35	Beads+nanofibers	94	77
8	15	20	11	39		103	60
9	16	100	7.5	27.5		214	179
10	16	5	14	43		99	93
11	17	50	13.3	30.7	Beads+nanofibers	88	71
12	17	50	7.7	40.5		125	125
13	18	80	13	40	Beads+nanofibers	131	83
14	20	10	10	25		197	153
15	20	50	6.5	43		234	297.5
16	20	5	13.3	42.5		133.5	135
17	21	60	14.3	29.4		129	108
18	21	45	11.7	29.2		109	93
19	22	40	7	38		245	217
20	22	40	16	29		123	209
21	23	70	14.5	28.3		136	142
22	23	70	8	35.5		157	165
23	24	75	16.5	27.4		136	101
24	25	10	8	45		232	191
25	28	90	13	33	Only Beads	-	
26	29	55	12	30.5		220	171
27	29	7	14	37.8		754	663
28	29	90	6	33.5		300	278.5
29	29	10	8.8	40		263	201.5
30	30	20	10	27		197	156

Table 4. ANN training parameters

Algorithm = trainlm
(Levenberg-Marquardt backpropagation)
Transfer function in hidden layers=log-sigmoid and purelin
Number of epochs between showing the progress = 50
Learning rate = 0.09
Momentum constant = 0.9
Maximum number of epochs to train = 300;
Performance goal= 1e-5;

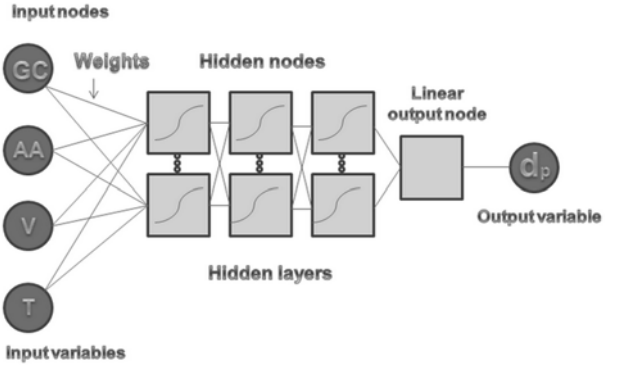


Figure 2. The designed ANN model using prediction of nanofibers diameter.

Before Using ANN Technique, Data Normalization was Performed

The data normalization is given by equation (1):

$$y_{\text{norm}} = (y_{\max} - y_{\min})(x - x_{\min})/(x_{\max} - x_{\min}) + y_{\min} \quad (1)$$

where $y_{\min}$ and $y_{\max}$ are equal to −1 and 1 respectively. The parameter of x is the data that should be normalized. $x_{\max}$ and $x_{\min}$ are the maximum and minimum values of x. the training parameters set for ANN models was shown in Table 4.

ANN Models Training

After designing 7 neural networks with various structures include four input units, one output unit and various hidden layers with different nodes (Figure 2), the network was trained using training dataset and was tested using testing data.

Results and Discussion

The mean square error and correlation coefficient (R) of test dataset obtained from ANN models is shown in Table 5. (Hidden layers=3) (Numbers of node in hidden layers=10, 18, 9 respectively).

Mean square prediction error (MSPE) is given by equation (2):

$$MSPEn = \frac{100}{Nte\,\sigma_{dn}^2} \sum_{i=1}^{Nte} (d_n(i) - d_{pn}(i))^2,\ n = 1, \ldots, 5 \quad (2)$$

Where d_n and d_{pn} are observed and predicted size of nanofibers in n network respectively. Variables of *Nte* are the numbers of samples used for network testing and σ_{dn}^2 is the variance of d_n.

To understand the observed and predicted average fibers diameter and standard deviation, Spss 17 software was used (are shown in Table 5).

The correlation between the observed and predicted diameter of the fibers, a linear regression was calculated (shown in Figure 3). According to the results, the differences between observed and predicted mean gelatin nanofibers diameters in 25 samples was about 17 nm (as shown in Table 6).

The Pearson correlation coefficient between observed and predicted fiber diameter was achieved equal to 0.956 that is significant beyond the 0.01 % level (as shown in Table 7). Considering the very high degrees of complexity in relations

Table 5. Results of MSE and linear regression in tests data

Data set	TEST MSPE	TEST R
1	0.1823	0.98405
2	0.2419	0.9503
3	0.1926	0.9015
4	0.0476	0.9629
5	0.1013	0.9132
Mean	0.1531	0.9424

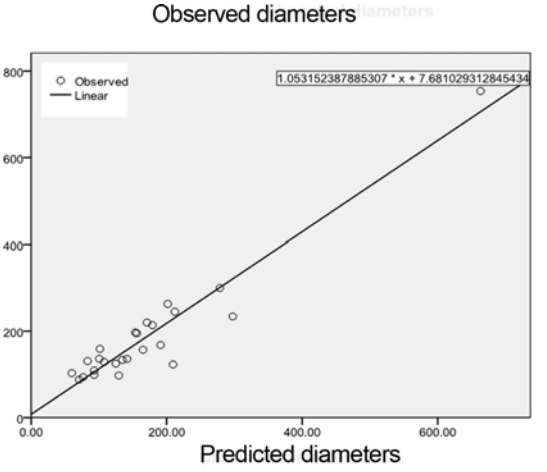


Figure 3. Regression plot between observed diameters and predicted diameters.

Table 6. Descriptive statistics of mean size of observed and predicted nanofibers

Nanofibers	Mean (nm)	Std (nm)	N
Observed	184.40	±132.179	25
Predicted	167.8000	±120.01860	25

Table 7. Pearson correlations between observed and predicted diameters

	Observed	Predicted
Observed		
Pearson correlation	1	.956**
Sig. (2-tailed)		.000
N	25	25
Predicted		
Pearson correlation	.956**	1
Sig. (2-tailed)	.000	
N	25	25

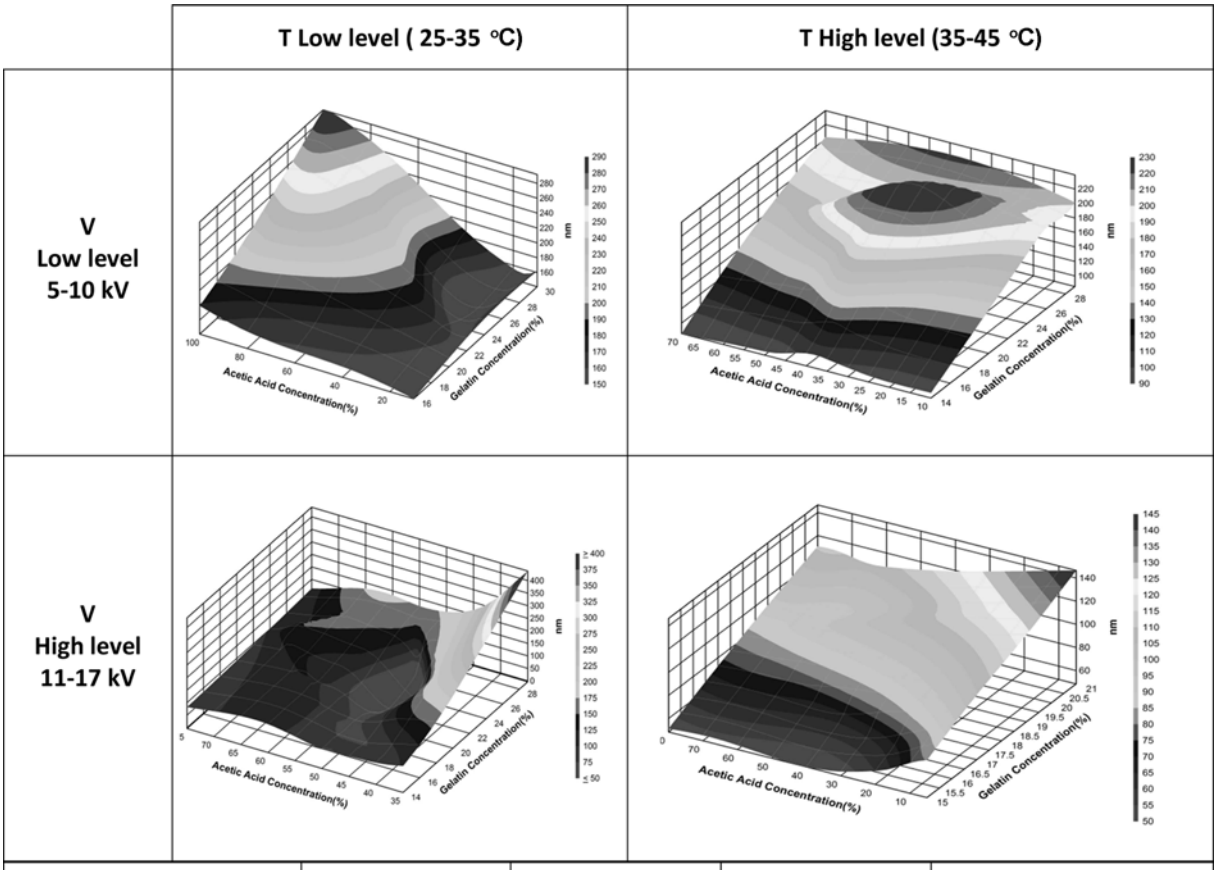
**Correlation is significant at the 0.01 level (2-tailed).

between the processing conditions and the diameter of the electrospun nanofibers, these values indicate a satisfactory trained model [23]. Similarly, the R-squared of 0.83 for test validation obtained in ANN model designed for predicting PEO nanofibers diameter [16].

The Pearson correlation coefficients (r) between the observed (d_n) and predicted (d_{pn}) nanofibers diameter is given by equation (3):

$$r = \frac{n(\Sigma d_n d_{pn}) - (\Sigma d_n)(\Sigma d_{pn})}{\sqrt{[n(\Sigma d_n^2) - (\Sigma d_n)^2][n(\Sigma d_{pn}^2) - (\Sigma d_{pn})^2]}} \quad (3)$$

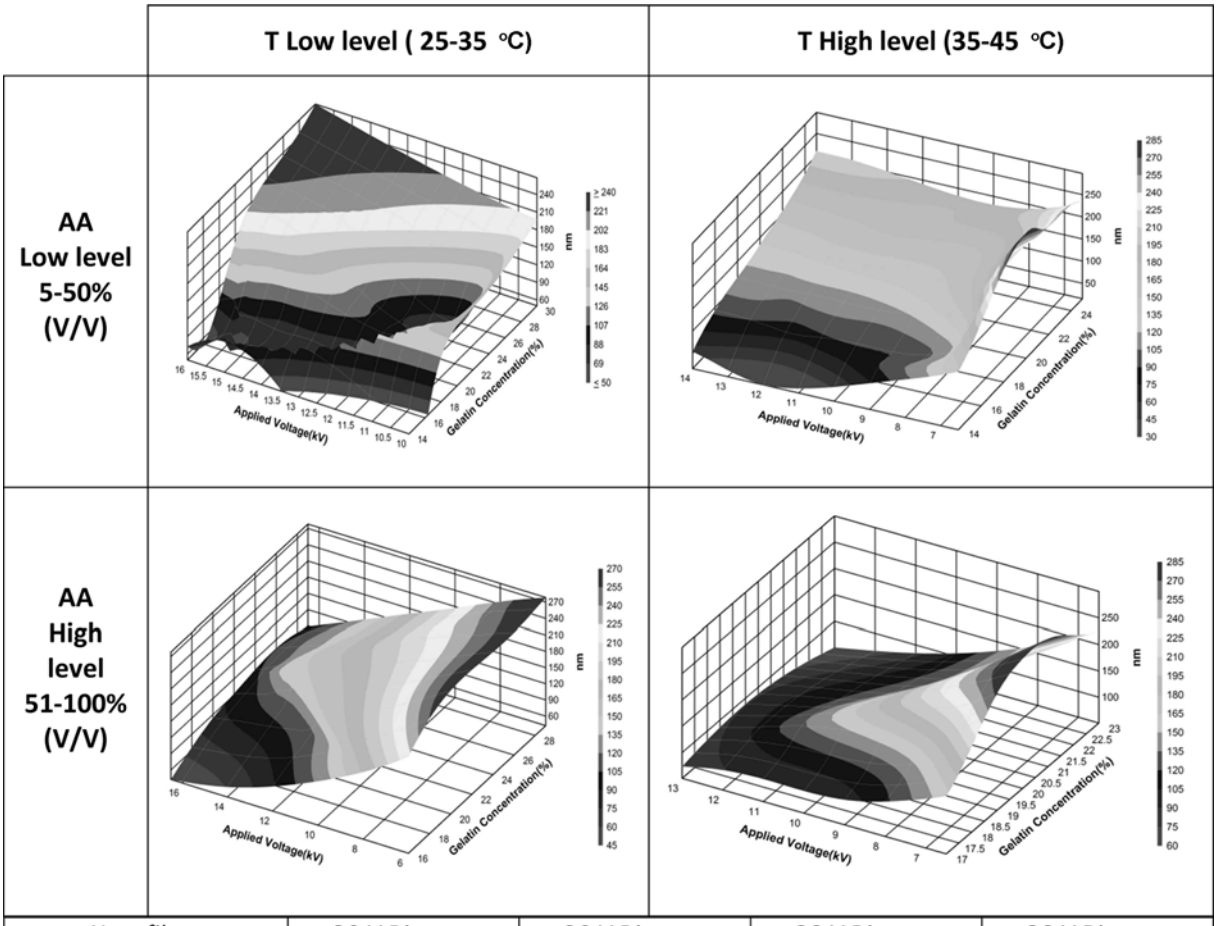
In this equation, n is the number of data.



Nanofibers(Z) Data	GC-AA Diagram Low V-Low T	GC-AA Diagram Low V-High T	GC-AA Diagram High V- Low T	GC-AA Diagram High V- High T
Minimum Z	153 nm at X = 20, Y = 10	102 nm at X = 14, Y = 35	71 nm at X = 17, Y = 50	60 nm at X = 15, Y = 20
Maximum Z	278.5 nm at X = 29, Y = 90	217 nm at X = 22, Y = 40	209 nm at X = 22, Y = 40	135 nm at X = 20, Y = 5
Mean	191.625 nm	166.9167 nm	119.3333 nm	95.8 nm
Standard deviation	59.0697	45.29726	45.83939	28.0125

AA=Acetic Acid Concentration (%), GC= Gelatin Concentration (%), T= Temperature (*C), V= Applied Voltage (kV), X= GC, Y=AA

Figure 4. 3D plots and table of nanofibers diameter data predicted by ANN fixed in identified levels (GC-AA Diagrams).



Nanofibers Diameter(Z) Data	GC-V Diagram Low AA-Low T	GC-V Diagram Low AA-High T	GC-V Diagram High AA- Low T	GC-V Diagram High AA- High T
Minimum Z	71 nm at X = 17, Y = 13.3	60 nm at X = 15, Y = 11	101 nm at X = 24, Y = 16.5	83 nm at X = 18, Y = 13
Maximum Z	209 nm at X = 22, Y = 16	297.5 nm at X = 20, Y = 6.5	278.5 nm at X = 29, Y = 6	297.5 nm at X = 20, Y = 6.5
Mean	128.8571 nm	161.0556 nm	163.25 nm	167.625 nm
Standard deviation	57.28999	72.54113	64.76091	92.83083

AA=Acetic Acid Concentration (%), GC= Gelatin Concentration (%), T= Temperature (*C), V= Applied Voltage (Kv), X= AA, Y=T

Figure 5. 3D plots and table of nanofibers diameter data predicted by ANN fixed in identified levels (GC-V Diagrams).

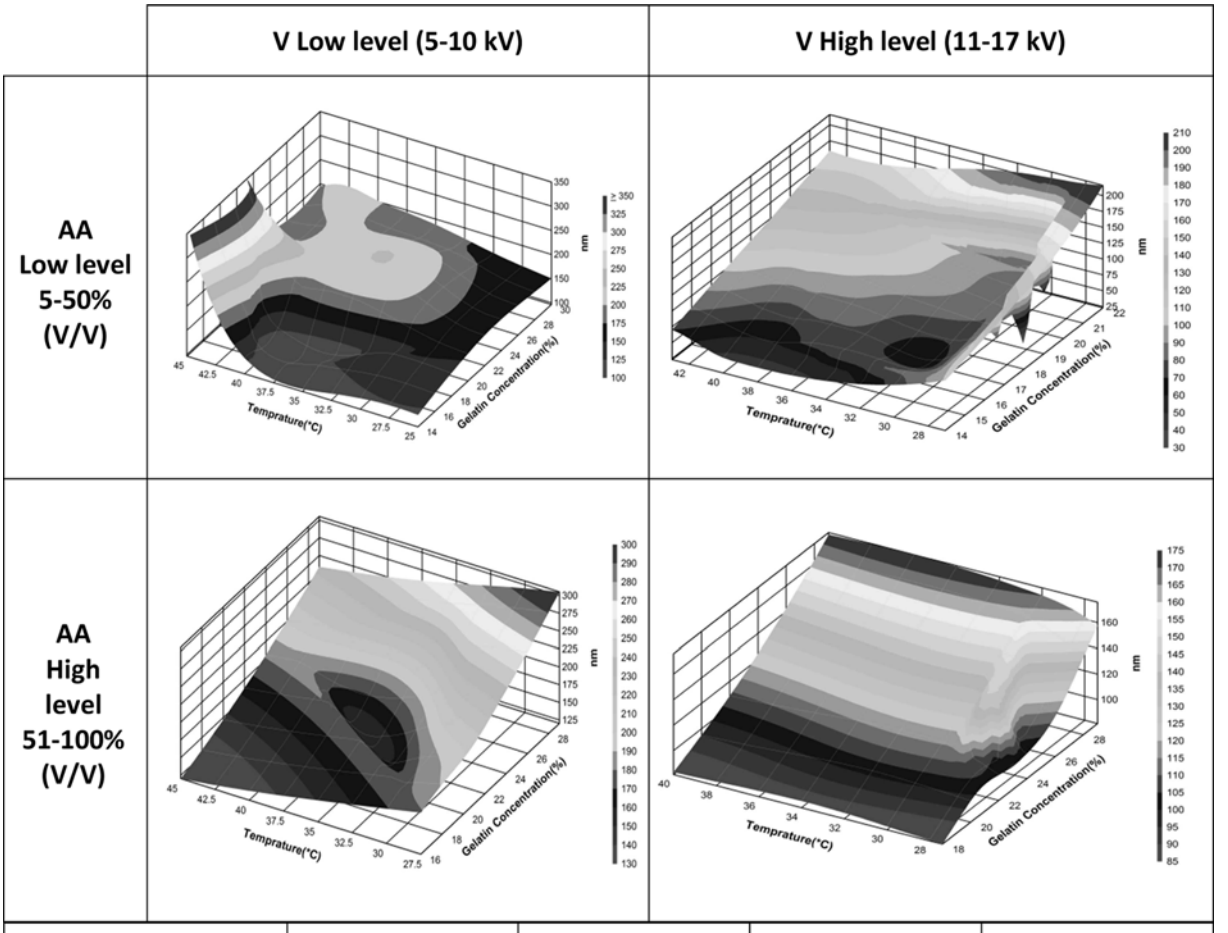
3D Plots of Gelatin Nanofibers Diameters Predicted Patterns

In order to understand the effects of various selected parameters (Gelatin and ACOH concentration, applied voltage and temperature) on gelatin nanofibers diameter (Figures 4 to 9), 3D Plots are indicated at defined levels.

The results show that the minimum size of the fibers is about 96 nm in high applied voltage- high temperature level (High V-High T) (Figure 4). On the other hand, the maximum size of the fibers is approximately 191 nm within the low applied voltage- low temperature level (Low V-Low T).

The results show that there is an inverse relationship between the diameter of the fibers and the applied voltage (V) and the operating temperature (T). It means that increasing V and T leads to decreasing the fibers size. In contrast, by reduction of temperature and applied voltage, nanofibers diameter will increase. It may be because of the better and easier stretch of fibers due to the greater potential difference between the collector and the liquid polymer.

The 3D plots (Figure 4) show that increasing and decreasing the gelatin concentration leads to increasing and decreasing the fibers diameter respectively. This is visible in almost all graphs, except within the Low V-Low T graph, in which simultaneously increasing both concentration of acetic acid and gelatin directly affect on fibers diameter.



Nanofibers Diameter (Z) Data	GC-T Diagram Low AA-Low V	GC-T Diagram Low AA-High V	GC-T Diagram High AA- Low V	GC-T Diagram High AA- High V
Minimum Z	125 nm at X = 17, Y = 40.5	60 nm at X = 15, Y = 39	165 nm at X = 23, Y = 35.5	83 nm at X = 18, Y = 40
Maximum Z	297.5 nm at X = 20, Y = 43	209 nm at X = 22, Y = 29	278.5 nm at X = 29, Y = 33.5	171 nm at X = 29, Y = 30.5
Mean	183.75 nm	105 nm	204.5 nm	121 nm
Standard deviation	56.7916	47.77626	44.41002	35.19233

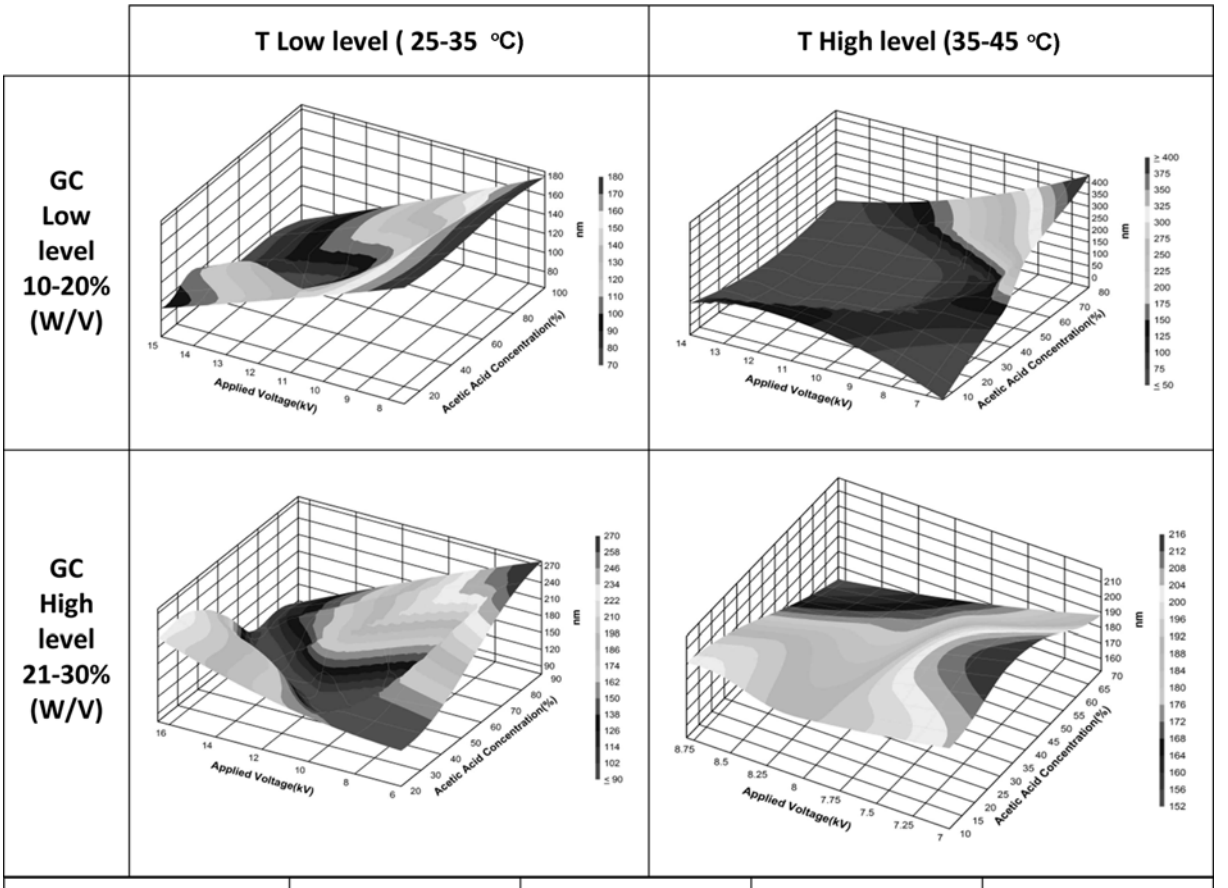
AA=Acetic Acid Concentration (%), GC= Gelatin Concentration (%), T= Temperature (*C), V= Applied Voltage (kV), X= GC, Y=T

Figure 6. 3D plots and table of nanofibers diameter data predicted by ANN fixed in identified levels (GC-T Diagrams).

The results show that in the Low AA-Low T level, the fibers diameter was minimal, about 129 nm. In contrast, the size of the nanofibers increased as temperature and concentration of acetic acid (as the gelatin solvent) enhanced. In this situation, the average size of nanofibers was about 167 nm (Figure 5).

Also, 3D graphs show that there is the inverse relationship between gelatin concentration and nanofibers diameter. In other words, nanofibers size increase or decrease as the concentration of gelatin increase or decrease. An inverse relationship was also seen between the applied voltage and fibers diameter, as ascending peak in nanofibers diameter occurred with decreasing the applied voltage and increasing gelatin concentration. Only in the Low AA-Low T area, the peak of nanofibers diameter was observed in the range of high-voltage and high polymer concentration.

Based on the results of the graph minimum mean fibers diameter in the range of low acetic acid concentrations and high applied voltage was equal to 105 nm (Figure 6). The maximum size of the fibers is seen in the Low V-High AA area (about 205 nm). The plot is consistent with previous plots, so that the diameters of the nanofibers are inversely



Nanofibers(Z) Data	AA-V Diagram Low GC-Low T	AA-V Diagram Low GC-High T	AA-V Diagram High GC- Low T	AA-V Diagram High GC- High T
Minimum Z	71 nm at X = 50, Y = 13.3	60 nm at X = 20, Y = 11	93 nm at X = 45, Y = 11.7	165 nm at X = 70, Y = 8
Maximum Z	179 nm at X = 100, Y = 7.5	297.5 nm at X = 50, Y = 6.5	278.5 nm at X = 90, Y = 6	217 nm at X = 40, Y = 7
Mean	113.83 nm	131.86 nm	157.31 nm	193.625 nm
Standard deviation	43.07397 nm	78.06019	62.70164	21.86845

AA=Acetic Acid Concentration (%), GC= Gelatin Concentration (%), T= Temperature (*C), V= Applied Voltage (kV), X= AA, Y=V

Figure 7. 3D plots and table of nanofibers diameter data predicted by ANN fixed in identified levels (AA-V Diagrams).

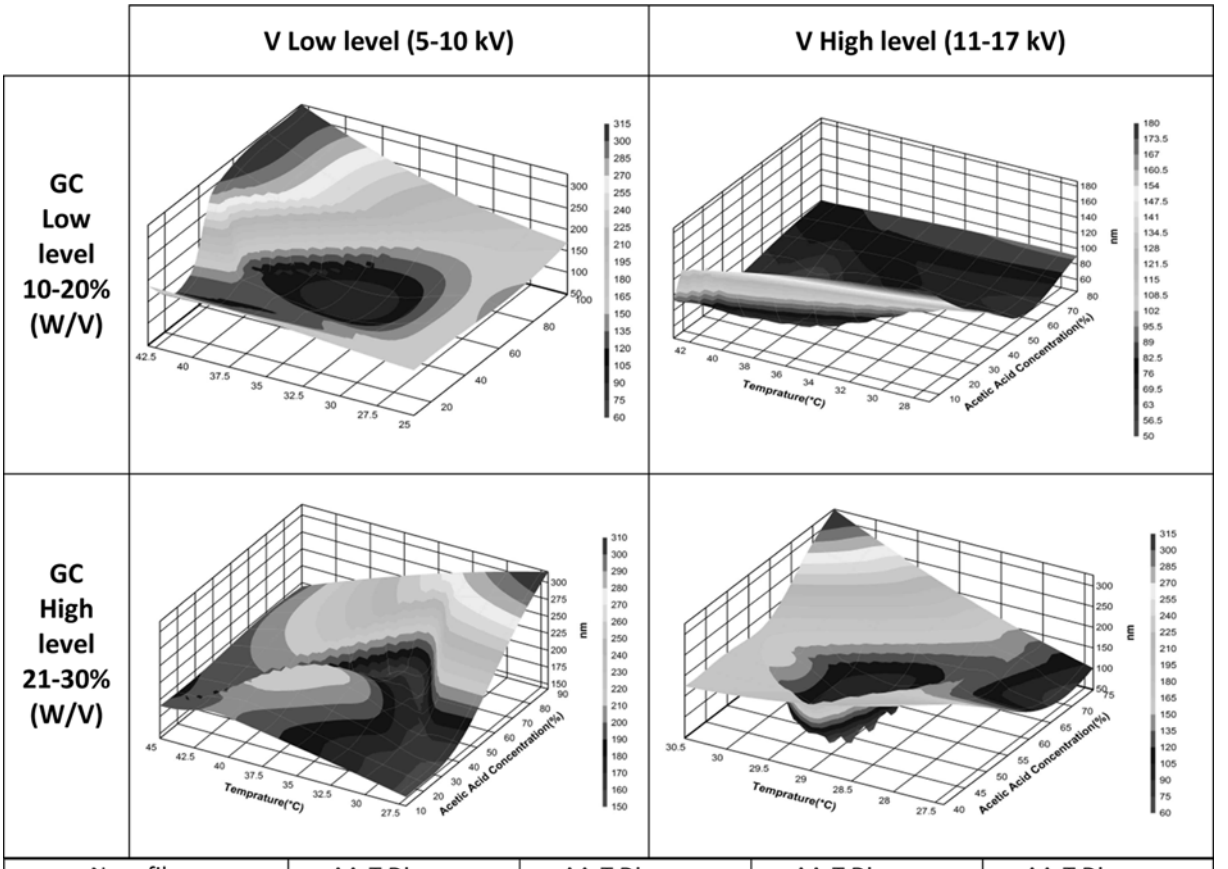
correlated with acetic acid concentrations and directly correlated with applied voltage.

The plot shows that the fibers diameter is increased primarily by enhancing the concentration of gelatine. Previous plots indicated inverse correlation between temperature and nanofibers diameter, but in this 3D graph in Low AA-Low V area, the nanofibers diameter show direct correlation with temperature.

The minimum diameter of gelatin fibers (about 114 nm) was seen in the Low GC-Low T area (Figure 7). In contrast, the maximum size of nanofibers (about 193 nm) was reported in the High GC-High T area. Ascending peak of fibers diameter can be obtained with increasing the acetic acid concentration and decreasing the applied voltage, as fibers size pass through a maximum at the highest concentration of acetic acid and the lowest value of the applied voltage.

The obtained result also consistent with the previous results, and show that the size of the fibers is directly associated with the concentration of gelatin and acetic acid, and inversely associated with the applied voltage.

The results show that the minimum size of fiber (about 89 nm) is obtained in Low GC- High V area (Figure 8). The maximum diameter of the fibers is about 201 nm which is related to High GC-Low V area. The results again demonstrate



Nanofibers Diameter(Z) Data	AA-T Diagram Low GC-Low V	AA-T Diagram Low GC-High V	AA-T Diagram High GC- Low V	AA-T Diagram High GC- High V
Minimum Z	125 nm at X = 50, Y = 40.5	= 60 nm at X = 20, Y = 39	156 nm at X = 20, Y = 27	93 nm at X = 45, Y = 29.2
Maximum Z	297.5 nm at X = 50, Y = 43	135 nm at X = 5 , Y = 42.5	278.5 nm at X = 90, Y = 33.5	209 nm at X = 40, Y = 29
Mean	176.7 nm	88.71 nm	201.5 nm	137.33 nm
Standard deviation	70.90099	24.64896	44.00455	45.6888

AA=Acetic Acid Concentration (%), GC= Gelatin Concentration (%), T= Temperature (*C), V= Applied Voltage (kV), X= AA, Y=T

Figure 8. 3D plots and table of nanofibers diameter data predicted by ANN fixed in identified levels (AA-T Diagrams).

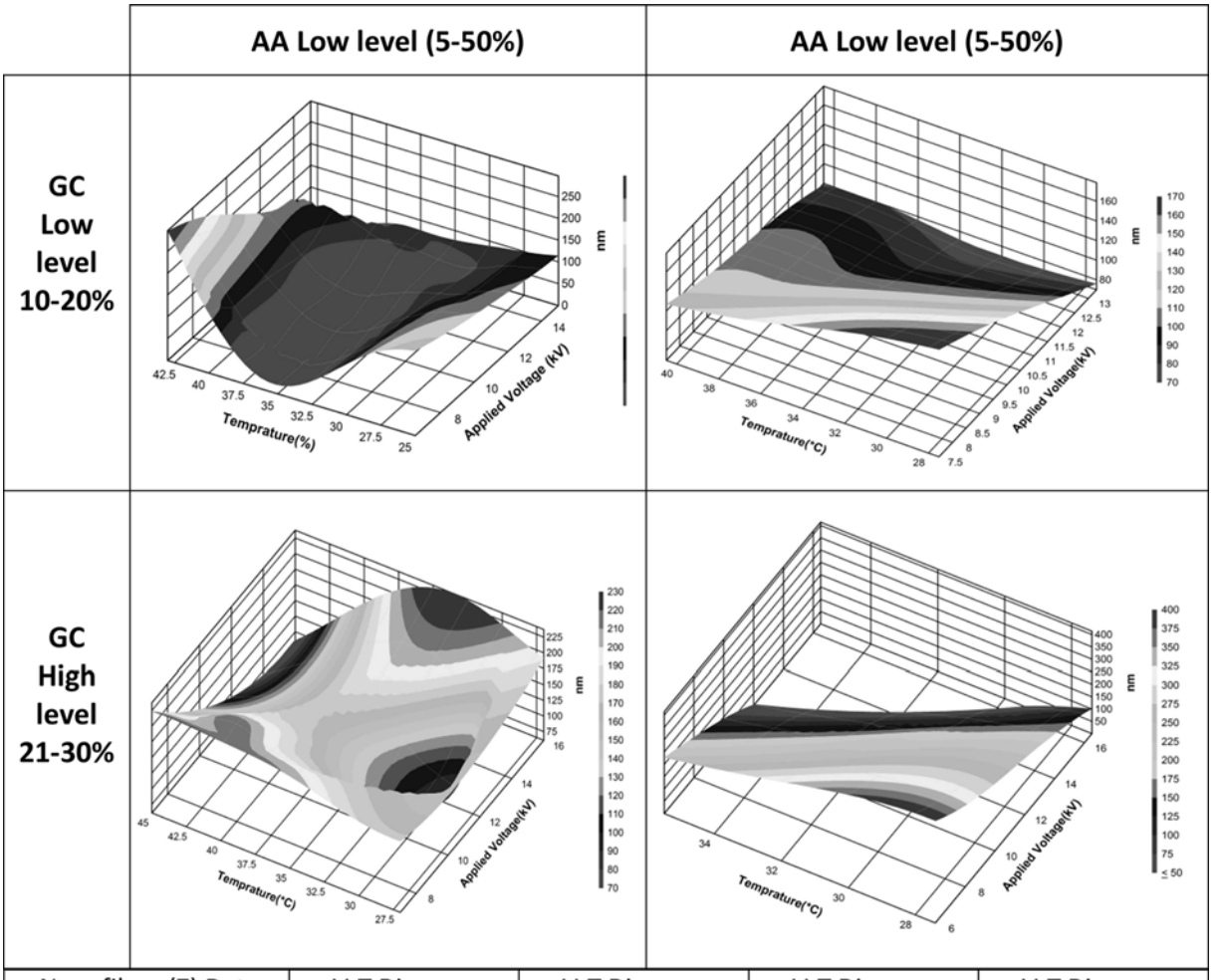
directly correlation between gelatin concentrations and fiber diameter and inversely relationship between the applied voltage and fibers size. All 3D plots show that in the two areas of High GC-High V and Low GC-Low V, fibers size will ascending when temperature and concentration of acetic acid increase. In the High GC-Low V stage with decreasing temperature and increasing acetic acid concentration, diameter ascending peak is observed.

Results of table show that the minimum size of the fibers (114.5 nm) is related to the Low GC-High AA area (Figure 9). The maximum size of the fibers (about 178 nm) obtained in the High GC-Low AA stage. Our expectation was the less size of fibers in the less concentration of gelatin and acetic acid, but the diameter of the fibers in this region is close to the low concentration of gelatin and high acetic acid (about 124 nm) that may be due to the interactions between the applied voltage and temperature. 3D plots of the High GC-High AA and Low GC-Low AA regions clearly shows that fibers size decrease with increasing the applied voltage and temperature.

Conclusion

In this study, 30 different models were designed to produce electrospun gelatin nanofibers.

The parameters including polymer and solvent concentration, applied voltage and temperature were used as variables.According to the obtained images from SEM, we



Nanofibers(Z) Data	V-T Diagram Low GC- Low AA	V-T Diagram Low GC- High AA	V-T Diagram High GC- Low AA	V-T Diagram High GC- High AA
Minimum Z	60 nm at X = 11, Y = 39	71 at X = 13.3, Y = 30.7	93 nm at X = 11.7, Y = 29.2	101 nm at X = 16.5, Y = 27.4
Maximum Z	297.5 nm at X = 6.5, Y = 43	179 at X = 7.5, Y = 27.5	217 nm at X = 7, Y = 38	278.5 nm at X = 6, Y = 33.5
Mean	124.25 nm	114.5 nm	177.9167 nm	160.9167 nm
Standard deviation	68.02665	48.83646	46.71661	64.33072

AA=Acetic Acid Concentration (%), GC= Gelatin Concentration (%), T= Temperature (*C), V= Applied Voltage (kV), X= V, Y=T.

Figure 9. 3D plots and table of nanofibers diameter data predicted by ANN fixed in identified levels (V-T Diagrams).

successfully produced electrospun nanofibers of gelatin. The designed ANN predicted diameter of nanofibers with acceptable MSE and regression coefficient, so that the correlation between observed and predicted fibers diameter was significant and artificial neural network model worked well. Therefore, the designed ANN to predict the nanofibers diameter can be used to produce gelatin nanofibers with defined diameter in trials and studies. Besides, the study demonstrated that ANN is an accurate method to predict gelatin nanofibers diameter using the four input variables. Nonetheless, applying other kinds of solutions and polymers and investigating other involved variables can provide a better insight to predict electrospun nanofibers diameter via ANN technique.

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