Modeling and optimization of the core-shell nanofibrous composite mat as a scaffold via hybrid models

Fatemeh Haghdoost¹, Milad Razbin¹, Hajir Bahrami², Jalal Barzin³ and Azadeh Ghaee⁴

Abstract
It has been a challenging subject for researchers to manipulate the electrospinning key factors to achieve a composite nanofiber with proper properties. In this study, an experiment according to central composite design to investigate the effect of parameters including polyvinylpyrrolidone concentration, zeolite concentration, voltage, core flow rate and shell flow rate on diameter, maximum strength and porosity of polyethersulfone/polyvinylpyrrolidone/zeolite core-shell composite nanofiber has been designed. Later on, two sets of models consisting of response surface methodology and artificial neural network are trained. Then, their performance was evaluated based on the definition of a novel goodness function. In the next step, the genetic algorithm is used to find the optimal design for scaffold applications. The results demonstrated that the average goodness value of models based on an artificial neural network (≈1.999) is higher than response surface methodology ones (≈1.780). Additionally, the genetic algorithm was able to find an optimal design with lower cost value (0.006) than the optimum sample (0.113) among the produced ones. Finally, the scanning electron microscopy micrographs highlighted that there is a strong and good cell proliferation on the selected design of nanofiber composite mat as the optimum scaffold.

¹Department of Textile Engineering, Amirkabir University of Technology, Tehran, Iran
²Amirkabir University of Technology, Tehran, Iran
³Biomedical, Iran Polymer Research Center, Tehran, Iran
⁴Tissue engineering, Iran University of Medical Sciences, Tehran, Iran

Corresponding author:
Hajir Bahrami, Amirkabir University of Technology, 424, Hafez Ave, Tehran 15875-4413, Iran.
Email: hajirb@aut.ac.ir

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Keywords
Nanoﬁbrous composite mat, scaffold, response surface methodology, artiﬁcial neural network, vgenetic algorithm

Introduction
Tissue engineering primarily aims at presenting a substitute for prevalent transplants via developing biomimetic scaffolds.1 In the following, the tissue engineers have presented strategies undergoing a ﬂourishing period in the last years through developments in nanobiomaterials and nanotechnology. Thus, a scaffold with a 3D porous arrangement has been accepted as an alternative providing a suitable substrate for cell growth and migration.2–5

The tissue fate and cells are highly inﬂuenced by nanopatterned and nanoporous structures due to protein adsorption and large surface area, resulting in enhanced cell attachment and topology guiding the cellular activities toward certain objectives. Also, the nanoporous structure is claimed to inﬂuence cellular function through making a change in the conformation of speciﬁc cellular attachment proteins or through surface energy alteration.2,6–9 Due to the property of the crystallinity, zeolite is a multi-aspect material possessing a nano- and micro-structure. Zeolite-based platforms are a special group of multidisciplinary nanomaterials employed in tissue engineering attracting considerable interest.2 Besides, it is less expensive and considered to be non-toxic to humans. As a result, many studies have attempted to assess its signiﬁcance in biomedical applications such as antidiarrheal agents, hemorrhage control, detoxicates, antibacterial agents and biomedical application scaffolds.6–9 Nevertheless, an additional process is required for zeolite in powder form, like the honeycomb monolith form the fabrication so that they can be available commercially. Despite studies with regard to the process of coating zeolite on the surface and composites of the ﬂexible material, there are still some difﬁculties in the fabrication of ﬂexible zeolite, such a complex process for degradation and development of properties.10–13 The electrospinning technique, which is an easy-to- implement, economical, and simple method, can be used for increasing efﬁciency in this respect and ﬂexible zeolite ﬁbers are created using biocompatible polymers.10,14–16

In order to fabricate a bio-scaffold, bioengineers should carefully select biocompatible polymers with relative degradability for remodeling the tissue.1 Polyvinylpyrrolidone (PVP) is regarded as a key amorphous polymer, which has good spinnability, high biocompatibility, low chemical toxicity, and great solubility in most organic solvents. This polymer is regarded as a good material that can be potentially applied in medical tools and shielding, as well as biological engineering materials.17 Hence, it can be properly blended with zeolites as an adhesive for binding zeolite nanoparticles. Also, it is assumed that the mechanical characteristics of nanofiber mats are critical parameters in their ultimate applications. However, the strength of PVP nanofibers is not adequate for usage in tissue engineering. Thus, researchers have utilized polyethersulfone (PES) polymers as reinforcement in the core-shell electrospinning process. In fact, PES has drawn high attraction during the past decade in the biomaterial area. Furthermore, it is a semicrystalline
hydrophobic polymer with a long-term degradation that has a relatively cheap cost of production, easy manipulation, flexible surface modification, approval of food and drug administration (FDA), and tailor-made and appropriate physicochemical properties. Due to these special properties, PES and its blends are suitable for usage in drug delivery, tissue engineering, fixation tools, and wound dressing.\textsuperscript{18}

Currently, researchers are highly interested in the systematic examination of the effect of electrospinning variables effect on the diameter and morphology of the electrospun fibers. Thus, it is required to fabricate fibers with uniform and small-sized fibers that the electrospinning process can be applied on a large scale in industries.\textsuperscript{19–20} The dimensions and morphological structure of electrospun fibers can be affected by various parameters consisting of solution factors, electrospinning factors and environmental factors. So, a systematic investigation of the parameter impacts on experimental output is essential.\textsuperscript{21,22} Among the many statistical methods, response surface methodology (RSM) is a useful method for designing and optimizing an experiment. Through this method, an empirical model to express the relationship between the variables and responses is established. More and still, with regard to designing an experiment, RSM reduces the number of required experimental runs for providing statistically significant information. This method has been implemented in recent studies for optimizing variables that affect the nanofiber fabrication process.\textsuperscript{23–29} The RSM was employed by Gholipour et al. for modeling and optimizing the electrospinning parameters to spin blend chitosan/polyvinylalcohol for controlling fiber diameter at various spinning parameters. There was a correlation between fiber diameter and fabrication variables by using a second-order polynomial function. The estimated fiber diameters showed an acceptable consistency with the empirical results.\textsuperscript{30} The quantitative relationship between the average diameter of PVP nanofibers and electrospinning process variables was evaluated by Nasouri et al. using the RSM method.\textsuperscript{20} Besides, Yazdanpanah et al. investigated the effect of applied voltage, polymer concentration, flow rate, interaction, and distance on the poly (vinyl alcohol) (PVA) nanofibers’ diameter by the use of the method. Hence, CCD seems to be an efficient approach for designing, analyzing, modeling, and optimizing the electrospinning process, and it is a technique with several influential variables.\textsuperscript{21} Also, the RSM was used by Pirsa et al. for optimizing the carboxymethyl cellulose/gelatin/TiO\textsubscript{2}–Ag nanocomposite antioxidant/antimicrobial film.\textsuperscript{31}

The application of artificial intelligence approaches in mechanical engineering has been gradually increasing in the last two decades. It is chiefly due to the effectiveness of artificial intelligence modeling systems in the improvement of the engineering area. Since artificial neural networks (ANNs) employ various parameters (biases and weights), they have the capability of estimating the target data of systems in engineering usages with high accuracy.\textsuperscript{32} Additionally, ANNs are used for modeling the electrospinning process, primarily aiming to predict the diameter of electrospun polycaprolactone/gelatin/polycaprolactone nanofiber,\textsuperscript{33} and polyurethane nanofibers.\textsuperscript{34} ANNs are modeling tools to overcome issues regarding nonlinear multivariate regression-based models. Due to the massive interconnected structure, ANN is a great approach that learns via experimental data, with the capability of modeling incomplete data, which is not influenced by data noise. Moreover, it has been proven that these approaches have higher efficiency
compared to standard modeling approaches, like the RSM. The electrospinning process could be influenced by different parameters, like the solution properties and processing conditions, as well as other environmental parameters with unknown or known interactions. Therefore, electrospinning is a complicated process, highlighting the requirement for employing an ANN model rather than classical statistical procedures. The ANN model contains some technical parameters directly affecting the predicted results, which need to be optimized. However, no order is presented for completely determining the value of these parameters. Thus, the trial-and-error approach has been used by previous studies for finding the optimal option among these parameters. For this reason, the values obtained are not essentially the best options. That is, only one global optimum exists, one or more local optimum options might be present in the search space. Following optimization, it is possible to find the best option for these parameters. Thereupon, it is a challenging task to solve such multi-objective problems and select the best option. Additionally, coupling the ANN-GA techniques has been extensively applied for predicting and finding the optimal parameters in scientific surveys and engineering design. Besides, such method has been employed for optimizing the structural features of the biological scaffolds for meeting the needed mechanical features of native tissues. Using the same approach, the structural features of the silk tendon scaffold were optimized by Naghashzargar et al. Moreover, researchers have used this technique for optimizing the structural features of bone nanofibrous scaffolds so that the growth of osteoblast cells can be maximized. In the following, the mechanical features of a bi-layered knitted/nanofibrous esophageal prosthesis were optimized by Yekrang et al. by the use of the same procedure.

To wrap it up, by using hybrid models including RSM-GA and ANN-GA, a practical approach can be used to produce such an optimum scaffold. In the present study, we undertake an optimization problem using the mentioned hybrid models to find the optimal design of PES/PVP/zeolite socony mobil-5 (ZSM-5) nanofibrous composite mat (NFCM) for scaffold applications. In the following, an experiment according to central composite design (CCD) is designed and then the data are used to develop three second-order polynomial regression models with various coefficients and also three feed-forward back-propagation neural networks with the same architecture but different weights and biases. The proposed models are to generalize the relationship between variables and responses of electrospun fibers. Next, the performance of the models is evaluated based on a novel goodness function and hereafter the best-performed ones are chosen as objective functions for the optimizing step. Finally, the effect of population size on precision of optimization is investigated and the cell proliferation of the optimum sample is carried out.
Experimental data

Materials

Polyethersulfone (PES) E6020P (Mw = 58 kDa) was obtained from BASF (Germany). Polyvinylpyrroldione (PVP) (Mw = 1300 kDa) was purchased from Rahavard Tamin Pharmaceutical Co., Ltd. (Iran). Acetone (purity: 99.5% w/w), N,N-Dimethylformamide (DMF, purity: 99.9% w/w) was purchased from Merck (Germany), zeolite socony mobil-5 (ZSM-5) was obtained from Iran zeolite Co. Ultrapure water was also used. All the chemicals used were of reagent grade unless otherwise.

Experimental design

To carry out a tentative investigation, an experiment with regard to the CCD to analyze the effect of key factors including PVP and zeolite concentration, voltage, core and shell flow rate on diameter, maximum strength and porosity of the NCFM is designed. Table 1 depicts the codes, units and levels of corresponding factors.

In order to determine the number of experiments, equation (1) has been used.

\[ n = k^2 + k + cp \]  

(1)

where \( k \) and \( cp \) are number of factors (5) and the center of the design (20) to estimate the relationships between variables and responses. It is worth mentioning that the Design-Expert 13 software was implemented to design the experiment.

Production of samples

PES/PVP/ZSM NFCM samples were produced according to the previously reported method as presented in Figure 1. In the following, core spinning of PES flakes in a DMF solvent (25% (v/v)) at room temperature for 3 h until a clear solution was undertaken. In order to produce the shell, firstly, PVP solution was prepared by dissolving PVP powder in DMF: acetone with the ratio of 1:1 for 12 h until a clear solution was obtained. Then, ZSM-5 zeolite was added directly to the PVP solution and stirred at room temperature for 24 h to achieve homogeneous solutions. Next, these dispersions were sonicated (Universal Ultrasonic Cleaner; 100 W Power and 60 kHz) for at least 1 h before using the composite PVP/Zeolite electrospinning solutions. In addition, each electrospun solution

Table 1. Independent variables for the central composite design.

| Variable           | Code | Unit | Levels  |
|--------------------|------|------|---------|
| PVP concentration  | A    | wt.% | 0.00 5.00 12.50 20.00 30.34 |
| Zeolite concentration | B    | wt.% | 0.00 10.00 20.00 30.00 43.78 |
| Voltage            | C    | kV   | 3.04 12.00 18.50 25.00 33.96 |
| Core flow rate     | D    | mL/h | 0.00 0.40 1.20 2.00 3.10  |
| Shell flow rate    | E    | mL/h | 0.00 0.40 1.20 2.00 3.10  |
was loaded into a 5 mL polyethylene syringe capped with inner and outer needle gauges of 22 G and 16 G, respectively. The needle-to-collector length was set at 15 cm (Humidity 65% Temperature 25°C).

**Characterization of samples**

Scanning electron microscopy (SEM) was used to examine the morphologies of nanofibers (SEM, XL30-SFEG and FEI Philips, Japan). The average fiber diameter was estimated using Digimizer software to analyze SEM images, and the fiber diameters were measured based on 100 repetitions.

The maximum strength of NFCMs was studied using an (Instron 5566) testing device. To do so, samples with 5 × 30 mm² dimensions were prepared. During the measurement, the crosshead speed of the moving jaw was 5 mm/min and five repetitions have been considered.

In order to determine the porosity percentage (\(\varnothing(\%)\)) of the electrospun nanofiber composite mat, the SEM image of samples is processed through a program written based on the MATLAB software according to equation (2).

\[
\varnothing(\%) = \frac{B}{W + B} \times 100
\]  

where \(W\) and \(B\) are white pixels indicating the nanofibers composite mat (NFCM) and black pixels indicating the open area, respectively. It should be pointed out that the images firstly were imported into Photoshop to determine the suitable threshold at boundaries. During the image processing, after recalling the files in the MATLAB program for cropping the SEM information, a gray threshold with the level of 0.5 has been applied. In the next step, the image has been binarized before applying a square morphological closing function to remove any noises.
Morphological analyses of fibroblast cells on developed nanofibers were carried out 24 h of cell growth, using SEM images prepared from their surfaces. Then, the nanofibers were washed twice using PBS before being fixed for 2 h in 2.5% glutaraldehyde. Next, scaffolds were then cleaned with deionized water and dehydrated in a graded ethanol series. Following a final wash with 100% ethanol, the samples were immersed in hexamethyldisilane (HMDS). By maintaining the samples in a fume hood, the HMDS was air-dried. Finally, the samples were sputter-coated with gold and examined under an SEM (S-4160, Hitachi) to reveal cell morphology.

**Developing the objective functions**

To find optimal design the existence of an objective function to express the relationship between variables and responses of the system is required. In the following, RSM and ANN models will be developed with the same data set (training/testing) to generalize the effect of variables on responses.

**RSM models**

Generally, the resulting prediction $\hat{y}$ for the quantitative response of observations including diameter, maximum strength and porosity of nanocomposite mat with different variables consisting of $A.B.C.D.E$ can be written as equation (3).

$$\hat{y} = \hat{f}(A.B.C.D.E) \pm \varepsilon$$

where $\hat{f}$ and $\varepsilon$ are some fixed but unknown estimated functions that indicate the systematic information that variables provided for $\hat{y}$ and variables independent random error term, respectively.40 One of the most famous functions to estimate the relationships between variables and the response of a system is a second-order RSM. In fact, it is a second-ordered polynomial regression equation with statistically acceptable results as equation (4).

$$\hat{f} = a_0 + \sum_{i=1}^{5} a_i x_i + \sum_{i=1}^{5} \sum_{j=1}^{5} a_{ij} x_i x_j + \sum_{i=1}^{5} a_{ii} x_i^2$$

where $a_0$, $a_i$, $a_{ij}$ and $a_{ii}$ are offset, linear effect of $x_i$, quadratic effect of $x_i$ and linear-linear interactions between $x_i$ and $x_j$, respectively.41,42 In this work, in order to determine the coefficients of regression analyses, a novel criterion namely called total goodness function ($TGF$) as equation (5) is formulated.

$$TGF = \chi_{train} GF_{train} + \chi_{test} GF_{test}$$

In which

$$\chi = \frac{n}{N}$$
where $n$ and $N$ are numbers of training or testing data and the total number of data, respectively. To calculate the goodness value ($GF$), equation (7) will be used as reported in previous study,$^{43}$ respectively.

$$GF = R^2 + 1/e^{MSE}$$

In equation (7), $R^2$ and $MSE$ are the coefficient of determination and mean squared error, respectively. In order to calculate them, Equations (8) and (9) will be used, respectively.

$$MSE = \frac{1}{n} \sum_{i=1}^{n} [t_i - O_i]^2$$

$$R^2 = 1 - \frac{\sum_{i=1}^{n} (t_i - O_i)^2}{\sum_{i=1}^{n} (t_i - \bar{t})^2}$$

where $t_i$, $O_i$, and $\bar{t}$ and $n$ are the target, output, mean values of target and amount of data during the testing or training step of the network, respectively. When the $MSE$ is minimized and $R^2$ is maximized, the goodness value converges to value 2. Similarly, when the goodness values of training and testing steps are maximized, the total goodness value converges to value 2. To perform the above-mentioned regression analyses, the generalized reduced gradient (GRG) nonlinear toolbox of Excel software has been utilized.$^{41,42}$

**ANN models**

Over the past several decades, ANN-based models are wieldy used to find complex relationships in various kinds of scientific areas which are not possible to obtain with conventional analytical models. An ANN-based model consists of nodes as processing elements and connections between them as weights to empower the output of the nodes. Such models are also called connectionist models due to the connections found between the nodes.$^{44}$ Among the various types of ANN, the feed forward-back propagation learning algorithm attracted the attention of many researchers as tool to predict the response of systems. In this algorithm, the total squared error of network output is minimized during the training step by back-propagation of the associated error.$^{45}$ In the following, three parallel feed forward-back propagation networks will be considered to predict the diameter, maximum strength and porosity of NFCM. According to the experimental design, the input variables are PVP concentration and Zeolite concentration, voltage, core flow rate and shell flow rate which indicates five nodes in the input layer. Using a trial-and-error approach, the activation function of hidden and output layers is set tan-sigmoid and pure linear functions as Equations (10) and (11), respectively.
\[
\text{tansig}(n) = \frac{2}{(1 + e^{-2n})} - 1 \quad (10)
\]

\[
\text{purelin}(n) = n \quad (11)
\]

The learning rate and momentum value have been set as 0.9 and 0.9, respectively. The Levenberg-Marquardt algorithm has been used as a training function to enhance the training process. 1000 epochs have been considered for the training cycles. The parameter settings of the ANN models are summarized in Table 2. It has to mention that the same settings have been considered for all the networks.

To define the number of nodes in the hidden layer, the criterion used for regression analyses (total goodness value) has been used to evaluate the performance of different networks. To develop the above-mentioned networks, the ANN toolbox of MATLAB software has been utilized.

**Optimization problem**

A GA is an evolutionary algorithm that mimics the process of evolution in nature. This method results in each solution as a vector of inputs namely called chromosome or individual. During the processing, each chromosome is ranked based on the cost function using the objective function or functions.\(^46\) In this work, three responses indicating three objective functions will be chosen by comparing the results of the RSM and the ANN models. Then, a genetic algorithm will be implemented using the MATLAB toolbox set as summarized in Table 3.

The parameters settings of GA are selected that how to provide a search space with suitable diversity to avoid early convergence. In order to evaluate the cost function, a single objective optimization problem based on the Euclidean distance between the target and individual has been defined as equation (12).

| Table 2. Parameter settings of the ANN models. |
|-----------------------------------------------|
| Parameter                                     | Value            |
| Number of units in input layer                | 5                |
| Number of units in output layer               | 1                |
| Number of units in hidden layer               | 10               |
| Activation function of hidden layer           | Tan-sigmoid      |
| Activation function of output layer           | Pure linear      |
| Learning rate                                | 0.900            |
| Momentum value                               | 0.900            |
| Learning function                            | Levenberg-marquardt |
| Number of training cycles (epochs)            | 1000             |
\[ \text{minimize: } f(\vec{x}) = \sqrt{\left(d(\vec{x}) - 0.4999\right)^2 + \left(\sigma(\vec{x}) - 0.7186\right)^2 + \left(\phi(\vec{x}) - 0.4995\right)^2} \]

\[ (12) \]

\[ \vec{x}_i = \{A_i, B_i, C_i, D_i, E_i\} \quad \& \quad i = 1, \ldots, n \]

\[ (13) \]

which, the lower and upper boundaries can be expressed as below.

\[ 0 \leq A \leq 30.34 \quad (14) \]

\[ 0 \leq B \leq 43.78 \quad (15) \]

\[ 3.04 \leq C \leq 33.96 \quad (16) \]

\[ 0 \leq D \leq 3.10 \quad (17) \]

\[ 0 \leq E \leq 3.10 \quad (18) \]

where \( \vec{x} \) is a vector that stores input variables for the problem and \( d, \sigma \) and \( \phi \) are objective functions that return normalized value of diameter, maximum strength and porosity of NFCM, respectively. Based on equation (12), an individual with a minimum cost value will be chosen as the best individual. Based on our previous studies, the optimal design considered for NFCM used as a scaffold is a diameter of 765 nm (normalized to 0.4999), the maximum strength of 3.1 MPa (normalized to 0.7186) and porosity of 51.6% (normalized to 0.4995).\(^{47-49}\) Furthermore, the precision of optimization with different population sizes is investigated. The flowchart of mentioned optimization problem is depicted in Figure 2.

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**Table 3. Parameter settings of GA.**

| Parameter                          | Value                                 |
|------------------------------------|---------------------------------------|
| Population type                    | Double vector                         |
| Creation function                  | Uniform                               |
| Scaling function                   | Rank                                  |
| Selection function                 | Stochastic uniform                    |
| Elite count                        | 1                                     |
| Mutation function                  | Uniform                               |
| Mutation fraction                  | 0.100                                 |
| Crossover function                 | Scattered                             |
| Crossover fraction                 | 0.900                                 |
| Migration direction/interval       | Forward/10% of population size        |
| Migration fraction                 | 0.900                                 |
| Nonlinear constraints algorithm    | Penalty                               |
| Generation number                  | 100                                   |
| Cost limit                         | 1e-6                                  |

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Results and discussion

Statistical analysis

Table 4 presents a CCD design of five different variables including PVP concentration (A), zeolite concentrating (B), voltage (C), core flow rate (D), shell flow rate (E) which are affecting response variables consisting of average diameter, strength and porosity of fibers that were empirically obtained from running 50 samples. All estimations of diameter, strength and porosity are based on 30, 5 and 8 (only sample 43) repetitions, respectively. In addition, all reported data are estimated with a 95% confidence level.

Additionally, equation (19) will be used to normalize data between 0.1 and 0.9 to avoid any quantitative effect in further analysis then it will be utilized to denormalize data in the last step.

\[ N = (0.9 - 0.1) \left( \frac{A - \min(A)}{\max(A) - \min(A)} \right) + 0.1 \]  

where \( A \) and \( N \) are the actual and normalized values of responses, respectively. Besides, the data are split into training/testing data sets with a ratio of 39:4 for the modeling step as mentioned in Table 4 using the minus and plus indexes.
| Sample | A     | B     | C     | D     | E     | Diameter (nm) | Strength (MPa) | Porosity (%) | Train | Test |
|--------|-------|-------|-------|-------|-------|---------------|----------------|--------------|-------|------|
| 1      | 5.00  | 10.00 | 12.00 | 0.40  | 0.40  | 240.352 ± 16.042 | 1.301 ± 0.0402 | 52.460 ± 7.662 | +     | -    |
| 2      | 20.00 | 10.00 | 12.00 | 0.40  | 0.40  | 221.021 ± 18.010 | 1.231 ± 0.021  | 55.933 ± 4.062 | -     | +    |
| 3      | 5.00  | 30.00 | 12.00 | 0.40  | 0.40  | 257.202 ± 21.093 | 1.263 ± 0.044  | 66.842 ± 1.601 | +     | -    |
| 4      | 20.00 | 30.00 | 12.00 | 0.40  | 0.40  | 545.404 ± 29.844 | 2.011 ± 0.064  | 38.381 ± 9.130 | +     | -    |
| 5      | 5.00  | 10.00 | 25.00 | 0.40  | 0.40  | 226.521 ± 12.154 | 1.401 ± 0.054  | 54.423 ± 7.600 | +     | -    |
| 6      | 20.00 | 10.00 | 25.00 | 0.40  | 0.40  | 296.520 ± 25.142 | 1.680 ± 0.114  | 34.370 ± 8.161 | +     | -    |
| 7      | 5.00  | 30.00 | 25.00 | 0.40  | 0.40  | 207.071 ± 10.590 | 1.401 ± 0.033  | 59.284 ± 5.864 | +     | -    |
| 8      | 20.00 | 30.00 | 25.00 | 0.40  | 0.40  | 424.402 ± 40.260 | 1.983 ± 0.073  | 57.142 ± 3.112 | +     | -    |
| 9      | 5.00  | 10.00 | 12.00 | 2.00  | 0.40  | 274.292 ± 27.222 | 1.452 ± 0.034  | 62.891 ± 9.542 | +     | -    |
| 10     | 20.00 | 10.00 | 12.00 | 2.00  | 0.40  | 767.891 ± 52.651 | 3.201 ± 0.162  | 65.692 ± 7.061 | +     | -    |
| 11     | 5.00  | 30.00 | 12.00 | 2.00  | 0.40  | 198.442 ± 11.943 | 0.703 ± 0.021  | 70.412 ± 4.162 | +     | -    |
| 12     | 20.00 | 30.00 | 12.00 | 2.00  | 0.40  | 347.064 ± 20.562 | 1.504 ± 0.030  | 49.074 ± 8.540 | +     | -    |
| 13     | 5.00  | 10.00 | 25.00 | 2.00  | 0.40  | 200.371 ± 11.451 | 1.081 ± 0.041  | 74.301 ± 1.642 | +     | -    |
| 14     | 20.00 | 10.00 | 25.00 | 2.00  | 0.40  | 856.783 ± 66.133 | 3.203 ± 0.093  | 71.352 ± 7.102 | +     | -    |
| 15     | 5.00  | 30.00 | 25.00 | 2.00  | 0.40  | 185.501 ± 13.692 | 0.901 ± 0.022  | 82.202 ± 7.563 | +     | -    |
| 16     | 20.00 | 30.00 | 25.00 | 2.00  | 0.40  | 323.16 ± 17.702   | 1.200 ± 0.011  | 59.031 ± 4.101 | +     | -    |
| 17     | 5.00  | 10.00 | 12.00 | 0.40  | 2.00  | 534.172 ± 32.594 | 2.301 ± 0.064  | 63.983 ± 7.662 | +     | -    |
| 18     | 20.00 | 10.00 | 12.00 | 0.40  | 2.00  | 1280.00 ± 130.314| 3.402 ± 0.123  | 70.734 ± 8.602 | +     | -    |
| 19     | 5.00  | 30.00 | 12.00 | 0.40  | 2.00  | 173.661 ± 7.662  | 0.501 ± 0.044  | 78.543 ± 9.634 | +     | -    |
| 20     | 20.00 | 30.00 | 12.00 | 0.40  | 2.00  | 627.964 ± 55.202 | 3.081 ± 0.032  | 60.871 ± 9.232 | +     | -    |
| 21     | 5.00  | 10.00 | 25.00 | 0.40  | 2.00  | 259.791 ± 13.861 | 1.724 ± 0.041  | 65.221 ± 7.140 | +     | -    |
| 22     | 20.00 | 10.00 | 25.00 | 0.40  | 2.00  | 929.600 ± 112.290| 3.301 ± 0.163  | 67.242 ± 6.241 | +     | -    |
| 23     | 5.00  | 30.00 | 25.00 | 0.40  | 2.00  | 152.251 ± 8.030  | 0.561 ± 0.031  | 83.710 ± 9.432 | +     | -    |
| 24     | 20.00 | 30.00 | 25.00 | 0.40  | 2.00  | 949.653 ± 63.211 | 3.274 ± 0.054  | 75.052 ± 6.661 | +     | -    |
(continued)
Table 4. (continued)

| Sample | A   | B   | C   | D   | E   | Diameter (nm) | Strength (MPa) | Porosity (%) | Train | Test |
|--------|-----|-----|-----|-----|-----|---------------|---------------|-------------|-------|------|
| 25     | 5.00| 10.00| 12.00| 2.00| 2.00| 168.693 ± 8.752 | 0.822 ± 0.033 | 86.312 ± 4.654 | +     | -    |
| 26     | 20.00| 10.00| 12.00| 2.00| 2.00| 1218.35 ± 122.730 | 3.571 ± 0.063 | 68.013 ± 7.701 | +     | -    |
| 27     | 5.00| 30.00| 12.00| 2.00| 2.00| 174.271 ± 9.130 | 0.804 ± 0.012 | 74.131 ± 9.654 | +     | -    |
| 28     | 20.00| 30.00| 12.00| 2.00| 2.00| 1296.201 ± 116.101 | 3.813 ± 0.132 | 62.070 ± 6.982 | +     | -    |
| 29     | 5.00| 10.00| 25.00| 2.00| 2.00| 170.303 ± 7.740 | 0.752 ± 0.071 | 60.114 ± 8.680 | -     | +    |
| 30     | 20.00| 10.00| 25.00| 2.00| 2.00| 882.302 ± 76.941 | 3.001 ± 0.124 | 62.143 ± 4.451 | +     | -    |
| 31     | 5.00| 30.00| 25.00| 2.00| 2.00| 164.601 ± 6.823 | 0.684 ± 0.023 | 47.891 ± 9.230 | +     | -    |
| 32     | 20.00| 30.00| 25.00| 2.00| 2.00| 488.002 ± 41.004 | 1.871 ± 0.032 | 57.341 ± 7.341 | +     | -    |
| 33     | 0.00| 20.00| 18.50| 1.20| 1.20| 237.001 ± 15.444 | 1.502 ± 0.082 | 75.203 ± 6.892 | +     | -    |
| 34     | 30.34| 20.00| 18.50| 1.20| 1.20| 1446.002 ± 122.453 | 3.981 ± 0.171 | 7.334 ± 5.056 | +     | -    |
| 35     | 12.50| 0.00| 18.50| 1.20| 1.20| 439.621 ± 26.443 | 0.204 ± 0.020 | 95.972 ± 8.904 | +     | -    |
| 36     | 12.50| 43.78| 18.50| 1.20| 1.20| 84.312 ± 4.252 | 0.102 ± 0.011 | 67.131 ± 9.602 | +     | -    |
| 37     | 12.50| 20.00| 3.04| 1.20| 1.20| 566.001 ± 33.593 | 2.101 ± 0.034 | 46.564 ± 1.130 | -     | +    |
| 38     | 12.50| 20.00| 33.96| 1.20| 1.20| 672.742 ± 30.531 | 2.911 ± 0.073 | 39.251 ± 3.130 | +     | -    |
| 39     | 12.50| 20.00| 18.50| 0.00| 1.20| 640.001 ± 37.151 | 2.674 ± 0.152 | 70.623 ± 8.130 | +     | -    |
| 40     | 12.50| 20.00| 18.50| 3.10| 1.20| 772.253 ± 38.601 | 3.631 ± 0.111 | 48.104 ± 5.441 | +     | -    |
| 41     | 12.50| 20.00| 18.50| 1.20| 0.00| 139.391 ± 9.782 | 0.893 ± 0.092 | 77.302 ± 0.053 | +     | -    |
| 42     | 12.50| 20.00| 18.50| 1.20| 3.10| 707.401 ± 27.463 | 3.502 ± 0.121 | 67.501 ± 0.053 | +     | -    |
| 43     | 12.50| 20.00| 18.50| 1.20| 1.20| 570.452 ± 34.414 | 3.051 ± 0.053 | 61.612 ± 6.121 | +     | -    |
| 44     | 12.50| 20.00| 18.50| 1.20| 1.20| — | — | — | — |
| 45     | 12.50| 20.00| 18.50| 1.20| 1.20| — | — | — | — |
| 46     | 12.50| 20.00| 18.50| 1.20| 1.20| — | — | — | — |
| 47     | 12.50| 20.00| 18.50| 1.20| 1.20| — | — | — | — |
| 48     | 12.50| 20.00| 18.50| 1.20| 1.20| — | — | — | — |
| 49     | 12.50| 20.00| 18.50| 1.20| 1.20| — | — | — | — |
| 50     | 12.50| 20.00| 18.50| 1.20| 1.20| — | — | — | — |
**Determining the objective functions**

In order to evaluate the performance of the RSM models, the normalized experimental data against the predicted values are demonstrated in Figure 3.

According to Figure 3, the settlement regions have existed in both steps which results in a lack of prediction capability. This indicates the unreliability of the RSM models and the existence of a complex non-linear relationship between the variables and responses. Table 5 numerically displays the performance of the RSM models.

It is obvious that the performance of the RSM models during the testing is better than training steps. Thus, it can be said that the RSM models were able to generalize the relationship more than overfitting. The coefficients and offset values of the RSM models are summarized in Table 6.

By using the same coefficients and offset values given in Table 6, the same RSM-based model to predict the diameter, maximum strength and porosity of samples could be...
constructed. Besides, Figure 4 demonstrates the architecture of the developed network for the prediction of diameter, maximum strength and porosity of NFCM.

As it can be seen that nodes in the previous layer are fully connected to all nodes in the further layer and nodes in all the layers but the input layer, have been connected to corresponding the bias nodes. In order to evaluate the performance of the ANN models, the normalized experimental data against the predicted values are illustrated in Figure 5.

As shown in Figure 5, it can be said that the ANN models demonstrate a better performance than the RSM models during the both training and testing steps due to a

Table 5. Performance of the RSM models during the training and testing steps.

| Parameter | Diameter | Maximum strength | Porosity |
|-----------|----------|------------------|----------|
|           | Train    | Test             | Train    | Test    |
| MSE       | 0.007    | 0.002            | 0.011    | 0.003 |
| $R^2$     | 0.854    | 0.899            | 0.804    | 0.845 |
| GV        | 1.847    | 1.899            | 1.793    | 1.842 |
| TGV       | 1.852    | 1.797            | 1.681    | 1.796 |

Table 6. The coefficients and offset values of the RSM models.

| Coefficient | Diameter | Maximum strength | Porosity |
|-------------|----------|------------------|----------|
| a0          | -0.360   | -0.489           | -0.440   |
| a1          | -0.657   | -0.199           | 1.567    |
| a2          | 1.324    | 2.728            | -0.078   |
| a3          | 0.521    | 0.764            | 1.757    |
| a4          | 0.046    | -0.296           | 1.658    |
| a5          | 1.158    | 0.752            | 0.665    |
| a12         | -0.289   | 0.162            | -0.811   |
| a13         | -0.194   | -0.083           | 0.151    |
| a14         | 0.793    | 0.928            | -0.153   |
| a15         | 1.778    | 1.655            | 0.364    |
| a23         | 0.067    | 0.009            | 0.566    |
| a24         | -0.369   | -0.460           | -0.752   |
| a25         | -0.555   | -0.247           | 0.068    |
| a34         | -0.431   | -0.600           | -0.245   |
| a35         | -0.894   | -0.843           | -0.429   |
| a45         | -0.614   | -0.759           | -0.926   |
| a11         | 0.649    | -0.182           | -1.834   |
| a22         | -1.123   | -2.889           | 0.372    |
| a33         | -0.028   | -0.172           | -1.845   |
| a44         | 0.358    | 0.832            | -0.844   |
| a55         | -0.680   | -0.314           | -0.195   |
better correlation between normalized experimental and predicted values. Table 7 quantitatively outlines the performance of the ANN models.

As it can be seen in Table 7, the ANN models provide the same performance during the testing and training steps which indicates the high precision of its prediction in comparison to the RSM models. The weights and biases values of the best-performed network of 300 runs for diameter, maximum strength and porosity are summarized in Tables 8–10.

By using the same weight and bias values given in Tables 8–10, the same ANN-based model to predict the diameter, maximum strength and porosity of samples could be constructed. Besides, When the ANN models are trained, the effect of input variables on the diameter, maximum strength and porosity of the NFCM is considered using a sensitivity analysis method based on the weights of networks. To assess the relative importance of different input variables \( R_i \) on the output of networks, equation (20) is used.

\[
R_i(\%) = \frac{\sum_{j=1}^{nH} \left| \frac{Z_{ij}}{V_j} \right|}{\sum_{i=1}^{nI} \sum_{j=1}^{nH} \left| \frac{Z_{ij}}{V_j} \right|} \times 100
\]  

(20)
According to equation (20), the higher value will result in a bigger impact of the input variable on the output of the network. The results of the relative importance of input parameters on the output of networks are compared in Figure 6.

According to Figure 6, it can be found that the shell flow rate, as well as core flow rate, are the most sensitive parameter affecting the diameter of nanofiber with almost the same
value as 27.12% and 26.47%, respectively. Similarly, these two parameters are also the highest ones in the case of the maximum strength of 25.87% and 26.34%, respectively. Meanwhile, in addition to shell and core flow rate, PVP and zeolite concentration have almost the same importance on the porosity of the mat. Besides, voltage has the lowest percentage for all three responses. Based on the obtained results, the ANN models are chosen for the optimization step as objective functions.

**Optimization results**

In the optimization step using the GA, the important parameter that determines the optimal design is the cost value. Table 11 summarizes the cost value of the samples based on the corresponding squared difference of responses.

According to Table 11, sample 40 is the closest one to the target sample with a cost value of 0.113. Based on the information in Table 3, GA stops when the cost value is lower

| Weight | Bias |
|--------|------|
| Z      |      |
| -0.927 | -0.605 | -1.019 | -2.564 | -1.264 | 1 | 1.582 |
| -0.061 | -1.327 | -1.006 | -1.981 | -1.769 | 1 | -1.585 |
| 1.331  | -0.886 | -0.057 | 1.442  | 1.400  | 1 | -0.861 |
| -0.772 | 0.212  | -0.757 | -1.151 | -0.417 | 1 | 0.190  |
| 1.014  | -1.347 | 0.565  | 0.836  | -2.463 | 1 | -1.358 |
| -1.406 | -1.910 | -1.572 | 0.828  | 0.436  | 1 | -0.372 |
| -0.366 | 1.798  | -0.844 | -1.022 | -2.880 | 1 | 0.792  |
| -0.393 | 0.564  | -0.442 | 1.355  | -1.689 | 1 | 1.540  |
| 1.729  | -0.423 | 0.645  | 1.090  | -0.450 | 1 | 1.449  |
| 1.810  | 0.552  | -0.049 | -0.204 | -1.229 | 1 | 2.191  |
| V      | 1.287  | 0.442  | 1.162  | -1.211 | -0.650 | 1.090 | -0.834 | 0.478 | -0.589 | 2 | -0.079 |

| Weight | Bias |
|--------|------|
| Z      |      |
| 1.874  | 0.919 | -1.154 | 1.375 | 3.603 | 1 | -3.824 |
| -2.271 | -1.655 | 0.604 | 0.143 | -2.369 | 1 | -0.112 |
| 1.197  | 0.031 | -0.677 | -2.353 | -0.327 | 1 | 1.723  |
| 0.112  | -2.963 | -0.010 | 1.710  | -2.512 | 1 | -2.143 |
| -1.256 | -0.685 | -0.108 | 0.546  | 3.815  | 1 | -0.819 |
| -1.717 | 3.551  | -0.724 | 4.854  | 0.945  | 1 | -0.102 |
| 1.236  | -0.159 | -2.459 | 1.385  | -1.472 | 1 | 3.661  |
| -0.890 | 3.430  | -0.349 | -2.387 | -1.108 | 1 | -2.878 |
| -1.845 | 2.719  | -2.082 | -1.021 | 1.055  | 1 | 3.049  |
| 0.234  | -1.906 | -0.536 | 3.806  | -0.979 | 1 | -2.859 |
| V      | 1.605  | -0.191 | -0.168 | -0.965 | -0.327 | -0.514 | 1.033 | -0.500 | -0.434 | 1.210 | 2 | 0.934 |

**Table 8.** The weight and bias values of diameter ANN model.

**Table 9.** The weight and bias values of maximum strength ANN model.
than 1e-6 or the generation number reaches the determined value. In order to check the diversity of optimization, the variation of cost value during the different generations under various population sizes is shown in Figure 7.

Based on Figure 7, it can be found that the population converges when generations pass in which the means scores in term of cost value is descended. It is difficult to avoid local minima while keeping convergence low or postponing is better to find global minima. On the other hand, the diversity of the population would result in better search space for GA. Without exception, the defined optimization problem has the capability of finding the solution with any precision of optimization. Table 12 shows the trend of precision increasing during the increase of population size. Besides, because the GA is a stochastic algorithm, the reported data are based on the minimum cost value of 10 runs.

Despite sample 4, it can be said that increasing the population size would result in higher precision of optimization. The optimization problem has been defined that how to allow GA not only to improve search space with a higher population size but also provide a proper diversity to find a better individual. However, increasing the population size would result in a higher computation cost. In addition, the performance of GA with 1 generation number and 10 population size demonstrates that the optimization algorithm

Table 10. The weight and bias values of porosity ANN model.

| Weight | Bias |
|--------|------|
| 1.429  | 0.373|
| 1.148  | 0.035|
| 2.015  | -0.285|
| 2.188  | 0.662|
| 0.946  | -0.648|
| 0.193  | 0.326|
| -0.431 | 1.560|
| 1.879  | -1.718|
| -1.273 | -0.588|
| 1.935  | 1.449|

Figure 6. Relative importance of each input variables in ANN models.
| Sample | Squared difference of $d$ | Squared difference of $\sigma$ | Squared difference of $\phi$ | Cost value |
|--------|--------------------------|-------------------------------|--------------------------|------------|
| 1      | 0.095                    | 0.137                         | 0.000                    | 0.482      |
| 2      | 0.102                    | 0.148                         | 0.001                    | 0.502      |
| 3      | 0.089                    | 0.144                         | 0.018                    | 0.501      |
| 4      | 0.016                    | 0.050                         | 0.014                    | 0.285      |
| 5      | 0.100                    | 0.122                         | 0.000                    | 0.472      |
| 6      | 0.075                    | 0.085                         | 0.024                    | 0.430      |
| 7      | 0.107                    | 0.122                         | 0.004                    | 0.484      |
| 8      | 0.040                    | 0.053                         | 0.002                    | 0.309      |
| 9      | 0.083                    | 0.115                         | 0.010                    | 0.457      |
| 10     | 0.000                    | 0.000                         | 0.016                    | 0.128      |
| 11     | 0.110                    | 0.244                         | 0.028                    | 0.620      |
| 12     | 0.060                    | 0.108                         | 0.000                    | 0.411      |
| 13     | 0.110                    | 0.173                         | 0.042                    | 0.570      |
| 14     | 0.002                    | 0.000                         | 0.031                    | 0.187      |
| 15     | 0.115                    | 0.205                         | 0.076                    | 0.630      |
| 16     | 0.067                    | 0.153                         | 0.004                    | 0.474      |
| 17     | 0.018                    | 0.027                         | 0.012                    | 0.241      |
| 18     | 0.091                    | 0.003                         | 0.029                    | 0.353      |
| 19     | 0.120                    | 0.287                         | 0.059                    | 0.683      |
| 20     | 0.006                    | 0.000                         | 0.007                    | 0.116      |
| 21     | 0.088                    | 0.081                         | 0.015                    | 0.429      |
| 22     | 0.009                    | 0.001                         | 0.019                    | 0.176      |
| 23     | 0.129                    | 0.274                         | 0.084                    | 0.698      |
| 24     | 0.011                    | 0.001                         | 0.044                    | 0.240      |
| 25     | 0.122                    | 0.221                         | 0.098                    | 0.664      |
| 26     | 0.070                    | 0.009                         | 0.021                    | 0.319      |
| 27     | 0.120                    | 0.224                         | 0.041                    | 0.621      |
| 28     | 0.097                    | 0.021                         | 0.008                    | 0.357      |
| 29     | 0.122                    | 0.234                         | 0.005                    | 0.602      |
| 30     | 0.004                    | 0.000                         | 0.009                    | 0.119      |
| 31     | 0.124                    | 0.249                         | 0.001                    | 0.612      |
| 32     | 0.026                    | 0.064                         | 0.002                    | 0.305      |
| 33     | 0.096                    | 0.108                         | 0.045                    | 0.500      |
| 34     | 0.160                    | 0.032                         | 0.159                    | 0.593      |
| 35     | 0.036                    | 0.357                         | 0.160                    | 0.744      |
| 36     | 0.159                    | 0.382                         | 0.019                    | 0.749      |
| 37     | 0.013                    | 0.042                         | 0.002                    | 0.241      |
| 38     | 0.006                    | 0.001                         | 0.012                    | 0.143      |
| 39     | 0.005                    | 0.007                         | 0.029                    | 0.206      |
| 40     | 0.000                    | 0.011                         | 0.001                    | 0.113*     |
| 41     | 0.135                    | 0.207                         | 0.053                    | 0.629      |
| 42     | 0.001                    | 0.006                         | 0.020                    | 0.169      |
| 43     | 0.013                    | 0.000                         | 0.008                    | 0.146      |
| Minimum| -                        | -                             | -                        | 0.113      |
Figure 7. The optimization performance of GA with different population sizes.
is able to find the best individual (sample 40 of Table 11) with minimum time and computation cost. After the optimization process, all seven samples of Table 12 were produced to check their actual cost value. Among the new samples, sample 4 of Table 12 demonstrated much better results than sample 40 of Table 4.

Comparing sample 4 of Table 12 to 40 of Table 4, it can be found that there are two sharp contrasts including higher voltage (32.326 > 18.500) and lower core flow rate (1.022 < 3.100), which resulted in the reduction of diameter due to increasing of electrostatic force acting on fibers and decreasing the viscosity of solution. Figure 8 compares the SEM of mentioned samples. Eventually, it can be seen that there is an improvement not only in the case of diameter but also in the case of porosity. Thus, optimization was able to preset a sample that outstrips all other samples.

**Cell proliferation assay**

Researchers examined the cytotoxicity of PES/PVP/ZSM NFCM because of the worries about the possible negative impact of zeolite particles on the health of human. The silicate materials’ cytotoxicity is complicated, and it is principally dependent on the size of the particle, surface functional group, and the zeolite percentage used in nanofiber composite for toxicity survey. In the study by Neidrauer at Drexel University usefulness of a combination of nitric oxide and zeolite in wound healing was revealed. Bioceramics imitate the bone tissues and zeolites are regarded as bioceramics materials and their properties are similar. Thus, it is possible to use them as scaffolds for bone tissue engineering. Zeolite Y biomaterial-hydroxyapatite composite was synthesized in 2014, and based on the 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) test results, the scaffold with 10% zeolite showed higher cell viability compared to other samples.

Considering the morphology of L929 fibroblasts on nanofibers as shown in Figure 9, there is cell attachment to the surface of the nanofibers, and it presents the cellular compatibility of the scaffolds. Upon the contact of cells with materials, they undergo morphological changes to adapt to the surface of cellular materials.

![Table 12](image)

Table 12. The obtained solutions of GA under different population sizes.

| Sample | Population size | Combination | Cost value |
|--------|-----------------|-------------|------------|
|        | A               | B           | C          | D          | E          |          |
| Generation=1 | 10             | 12.015      | 19.052     | 18.625     | 3.002      | 1.210     | 0.092    |
| 1      | 10              | 16.597      | 26.786     | 5.449      | 1.598      | 2.025     | 0.010    |
| 2      | 20              | 23.795      | 29.658     | 12.262     | 0.362      | 1.496     | 0.009    |
| 3      | 30              | 15.374      | 12.315     | 25.308     | 0.353      | 1.015     | 0.003    |
| 4      | 40              | 14.726      | 21.959     | 32.326     | 1.022      | 1.363     | 0.006    |
| 5      | 50              | 13.984      | 16.071     | 5.330      | 0.040      | 1.992     | 0.003    |
| 6      | 100             | 10.772      | 13.911     | 25.308     | 0.256      | 1.183     | 0.001    |
| 7      | 1000            | 17.482      | 17.373     | 30.776     | 0.662      | 1.774     | 0.001    |
| Minimum| —               | —           | —          | —          | —          | —         | 0.001    |
Based on Figure 9, it can be found that sample 4 of Table 12 with 21.96% zeolite as the optimal sample selected in the optimization step, demonstrates strong and good cell proliferation on the scaffold surface after 24 h of culture compared to sample 40 of Table 11 with 20% zeolite and also sample 35 which has no zeolite. Generally, it has been realized that hydrophobic nano fiber membranes impose an anti-adhesion impact compared to ultra-hydrophilic or hydrophilic membranes. The hydrophilic membranes are more promising because of their proliferation performance and cell adhesion. Additionally, ultra-hydrophilic ones show an easy attachment to fats.\textsuperscript{54,55} Hence, the present work showed that PES/PVA/ZSM core-shell nano fiber membrane could be a suitable nano-fibrous membrane for cell proliferation and adhesion due to its average hydrophilic surface.

**Conclusion**

This work presents an optimization algorithm based on RSM-GA or ANN-GA using a novel goodness function to develop the models and then find the optimal design of NFCM
for scaffold application according to experimental information provided by RSM design. In the modeling step, the lack of correlation of RSM models during the training and testing steps has indicated the low performance based on their goodness values (≈ 1.780). In fact, the relationship between inputs and outputs variables is more complicated than the considered equation of RSM. In addition, the ANN models have shown the most accurate results with a goodness value close to the ideal one (≈ 1.999). These results highlight the capability of ANN-based models to predict any relationship with complex non-linearity. Tuning to the optimization step, the proposed ANN-GA algorithm is capable of finding global minima with desirable cost value (0.006). In other words, such an algorithm can provide a tool to engineer the structure of scaffolds using Nanofibrous materials for specific applications. Ultimately, the selected sample as the best individual has a strong and good cell proliferation as a scaffold which demonstrates good feedback from the proposed optimization algorithm. In spite of presenting the best individual through implementing the considered method in this work, it provides a time-efficient and cost-efficient procedure to develop a scaffold with engineered properties.

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**ORCID iDs**

Hajir Bahrami  [https://orcid.org/0000-0001-5777-8428](https://orcid.org/0000-0001-5777-8428)

Jalal Barzin  [https://orcid.org/0000-0002-4860-5805](https://orcid.org/0000-0002-4860-5805)

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