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Modeling of the Swelling Behavior of pH Sensitive Dextran Hydrogels by an Artificial Neural Network

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ABSTRACT

In this study, an artificial neural network model was employed to predict the swelling behavior of cross-linked dextran hydrogels. The predictions from the artificial neural network model were compared with those of the response surface methodology and the nonlinear regression models. The results show that an artificial neural network model gives an excellent correlation with the observed data and it has a good capacity for modeling the phenomena under investigation as compared with traditionally methods such as response surface methodology and non-linear regression models.

Key Words: Dextran hydrogel; pH sensitive hydrogels; swelling behavior; artificial neural network

INTRODUCTION

Hydrogels are crosslinked hydrophilic polymers capable of imbibing large volume of water but insoluble in water because of their network structure. Hydrogels have been examined as potential candidates for the replacement of soft tissue or for other biomedical applications. Among those, pH and thermo sensitive polymers have received much attention because these are the most available environments inside the human body [1,2].

Many synthetic and naturally derived materials have been reported to form well-characterized hydrogels. One such material is dextran, a linear, bacterial polysaccharide. Dextran consists mainly of (1,6) α-D-glucoside linkages with about 5-10% (1,3) α-linked branching, on average, three hydroxyl groups per glucose residue in the structure. Dextrans are colloidal, hydrophilic and water-soluble substances, inert in biological systems and do not affect cell viability [3]. Because of these properties, dextrans have been used for many years as blood expanders to maintain or replace blood volume, and studied for use as a carrier system for a variety of therapeutic agents including antibiotics, anticancer drugs, peptides, proteins and enzymes [4-6].

Hence, an accurate prediction of the swelling behavior under the environmental conditions is an important need in the practical applications of the pH and temperature-sensitive hydrogels.

The swelling behaviors of the hydrogels have been studied with several kinds of models describing the dynamic and equilibrium swelling characteristics proposed in the literature [7-10]. However, they have not been extensive to describe easily the complex physical processes in hydrogels, that is stil an ongoing research area [11].

In our previous work, we have investigated the prediction of swelling behavior of Ca2+-alginate hydrogels by artificial neural networks [12]. It was found that artificial neural network models have a good potential to model non-linear and multi-variable swelling behaviors of highly swellable hydrogels.

In this study, an artificial neural network (ANN) model which was developed for the modeling of swelling behavior of pH sensitive dextran hydrogels.

The performance obtained with this approach was compared with those of response surface methodology (RSM) and nonlinear regression (NLR) models.

MATERIALS AND METHODS

The medical grade Dextran (T-70) was purchased from Sigma (Germany). Its molecular weight characteristics were determined by the manufacturer as the weight average and number average molecular weights of 70000 and 46800 gmol-1, respectively. The crosslinking agents, N,N'-methylenebisacrylamide (MBAm) and epichlorohydrin (ECH) were supplied by Aldrich (Germany). Sodium hydroxide (NaOH), Hydrochloric acid (37%) and 2-amino-2-hydroxymethyl-1,3-propanediol (Tris) used in the swelling studies were obtained from Sigma (Germany). All chemicals were analytical grade and were used as received. Dextran-N,Nı-methylenebisacrylamide (dx-MBAm) and dextran-epichlorohydrin (dx-ECH) hydrogels were synthesized and characterized in previous study [1]. Disc shaped hydrogels of 3 mm diameter and 1.5 mm thickness were placed in distilled water for three days in order to get rid of the impurities (uncrosslinked dextran and/or crosslinker). Washed hydrogels were dried in vacuum at 25oC until no weight loss could be detected.

Swelling experiments

Swelling experiments were performed in the range of pH 2.0-9.0 in tris buffer at 37 ^{o}C. The pH of buffer solutions was adjusted with tris buffer, 0.1 M Hydrochloride acid (HCl) and 0.1 M NaOH using pH meter (pH 30, NEL). The swelling of the hydrogels was expressed as swelling ratio by the following equation:

$$S(\%) = \left(\frac{(M_t - M_0)}{M_0} \right) \times 100 \qquad (1)$$

where, M0 is the dry weight of hydrogel (initial weight), Mt is the weight of swollen gel at any given time.

Artificial Neural Network

Artificial neural networks are based on a simplified modeling of the human brain's biological functions. Therefore, they are very effective in computational systems where complex real world problems are modeled [13]. The analogy between the artificial neuron and the biological neuron is that connections between neurons represent axons and dendrites, connection weights stand for synapses, and the threshold approximates the activity in the soma as illustrated in Figure 1, where yj is the output of the jth neuron, xi is the ith input signal, wi is the connection weight from the ith input neuron to jth neuron, tj is the threshold or bias value of the jth neuron and f(x) is the nonlinear function modeling the system response.

Neural networks can be classified according to their activation phase as feed forward or recurrent, and according to learning phase as supervised or unsupervised.

A multi-layer feed-forward neural network has a layered structure as given in Figure 2. Hidden layers exist between the input and the output layer. Each layer has neurons that receive input from a layer below and send their output to units in a layer above. Activation of a hidden unit is a function of the weighted input and the threshold. A multi-layer feed-forward neural network is trained by a supervised learning algorithm with a set of chosen examples called a training data set and then tested via a data set.

In the supervised learning algorithm, weight and bias factors were determined by minimizing the convergence criteria, i.e. the performance index defined as:

$$\nabla J(\mathbf{w}) = \frac{1}{zN} \sum_{n=1}^{N} \nabla E(\mathbf{w}, n) \qquad (2)$$

The weight and bias updates are proportional to the performance index (∇J) by:

$$\nabla E(\mathbf{w},n) = \left[\frac{\partial E}{\partial w_{11}^{h}} \Lambda \frac{\partial E}{\partial w_{ji}^{h}} \; \frac{\partial E}{\partial w_{11}^{y}} \Lambda \frac{\partial E}{\partial w_{\lambda m}^{y}} \right] \qquad (3)$$

where, N is the number of input and output vectors, z is the number of neurons at the output layer, ∇E(w,n) is the gradient vector of total instantaneous errors that have components associated with the weights of the hidden and output layers Wh and Wy, respectively.

$$\mathbf{W}^{h} = \left[w_{11}^{h} \mathrm{K}\, w_{li}^{h} \mathrm{K}\, w_{ji}^{h} \right] \qquad j = 1,\ldots,s;\; i = 1,\ldots,k \qquad (4)$$

$$\mathbf{W}^{y} = \left[w_{11}^{y} \mathrm{K}\, w_{lm}^{y} \mathrm{K}\, w_{\lambda m}^{y} \right] \quad \lambda = 1,\ldots,z;\; m = 1,\ldots,s \qquad (5)$$

In the error minimization of the gradient descent with momentum learning algorithm, subsequent weight factors were calculated in the steepest descent direction as follows [14]:

$$\mathbf{w}(k+1) = \mathbf{w}(k) - \eta \nabla J(\mathbf{w}) + \alpha \Delta \mathbf{w}\,(\mathrm{k}-1) \qquad (6)$$

where, w(k+1) is the value of the weight vector at the iteration step (k+1), η is the step size or learning rate, α is the momentum coefficient

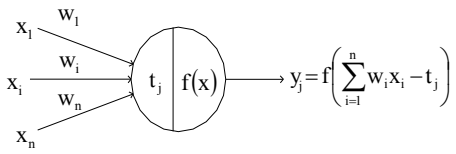

Figure 1. Artificial neuron.

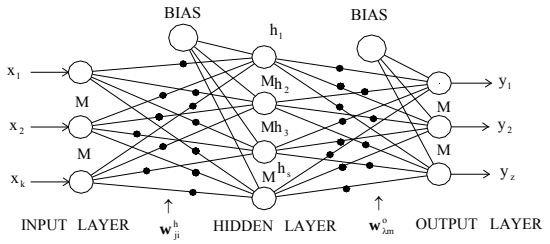

Figure 2. Multi layer feed forward neural network

Response Surface Methodology

Response surface methodology is an experimental strategy consisting of a particular set of mathematical and statistical methods. RSM uses quantitative data from appropriate experimental designs to determine and simultaneously solve multivariate equations graphically represented as response surfaces [15]. It is a tool for understanding the quantitative relationship between multiple input variables and one output variable. When the experimental responses are confounded by unrecorded, uncontrolled factors, RSM has a practical application in analyzing experimental data as a full second order polynomial model as follows:

$$Y = b_0 + \sum_{i=1}^{n} b_i X_i + \sum_{i=1}^{n} b_{ii} X_{ii..}^2 + \sum_{i=1}^{n-1} \sum_{j=1}^{n} b_{ij} X_i X_j \quad (7)$$

where Y is dependent variable, n is the number of independent variables of X, b_0, b_i, b_{ii} and b_{ij} are regression coefficients for the intercept, linear, quadratic and interaction coefficients respectively.

Application of ANN model to experimental data

This section presents the application of multilayer feed forward neural network described before was developed to determine the equilibrium water content of high level swellable hydogels based on cross-linked dextran. Appropriate neural network structure which was designed as $x_3h_{10}y_1$ employs three inputs or neurons corresponding to the process type of dextran-N,N[1]-methylenebisacrylamide (dx-MBAm) and dextran-epichlorohydrin (dx-ECH) hydrogels, and pH value and time to predict the swelling ratio as output of the network. The *230* observed data of Imren [16] was divided into two subsets randomly: training set (80 %) and testing set (20 %), respectively. Training set was used in learning phase while testing set was used to check the generalization capabilities of the model. The range of the parameters in the data set used training is given in Table 1. Neural network was trained by using gradient descent with momentum learning algorithm.

Table 1. The range of the parameters in the data set used training

Process type	Range	Process Parameter						
		Time (min)	S (%)					
			pH 2.0	pH 3.0	pH 6.0	pH 7.0	pH 8.0	pH 9.0
Dx-MBAm	Minimum	15	310.71	203.71	215.05	288.15	280.35	380.66
	Maximum	1800	1212.09	1222.69	1325.24	1427.96	1698.69	2658.49
Dx-ECH	Minimum	15	176.10	179.00	157.99	273.18	365.30	456.94
	Maximum	1800	929.08	947.49	988.89	1261.36	1359.36	1401.85

The bipolar sigmoid function was allocated for hidden units and linear functions were employed for output units for neural network structure. Learning rate and momentum coefficients were obtained as 0.1 and 0.5, respectively, by the trial and error procedure employed with various combinations for the network structure. The minimum mean square errors of computations (MSE) were used as the performance criteria. MSE value was obtained as 0.00167 at iteration number of 10000.

RESULTS AND DISCUSSION

Swelling of the hydrogel structures in suitable solvent is the most important parameter for controlled drug delivery systems. The results obtained from ANN model show that the model has a good capacity for modeling the dextran hydrogel swelling. Testing results were given in Table 2 by mean errors (ME) and determination coefficients (r) as follows:

$$ME = \frac{1}{n} \sum_{i=1}^{n} \left| x_i - \hat{x}_i \right| \qquad (8)$$

$$r = 1 - \frac{\sum_{i=1}^{n} (x_i - \hat{x}_i)^2}{\sum_{i=1}^{n} (x_i - \bar{x})^2} \qquad (9)$$

where $\hat{x}_i$: predicted value, $\bar{x}$: mean of the real data. Determination coefficients are the main performance indicators in the testing stage of neural networks [17].

S values were also predicted by RSM (RSM1 and RSM2) and nonlinear regression models (NLR1 and NLR2) which were evaluated by the polynomial function of order four:

$$Y = b_0 + \sum_{i=1}^{n} b_{1i} X_i + \sum_{i=1}^{n} b_{2i} X_i^2 + \sum_{i=1}^{n} b_{3i} X_i^3 + \sum_{i=1}^{n} b_{4i} X_i^4 \quad (10)$$

These models were described in Table 2 and their regression coefficients were given in Tables 3 and 4. The regression coefficients were obtained by the Levenberg-Marquardt algorithm [18]. The RSM1, RSM2, NLR1 and NLR2 models were tested in the similar procedure to the neural network model given in Table 2.

Table 2. Testing results for the models of artificial neural network, response surface methodolgy and nonlinear regression models

Model	Hydrogel	ME	r
ANN	Dx-MBAm Dx-ECH	58.18	0.971
RSM1	Dx-MBAm	159.81	0.861
RSM2	Dx-ECH	138.70	0.763
NLR1	Dx-MBAm	146.21	0.876
NLR2	Dx-ECH	102.95	0.898

As it can be seen from Table 2 and Figures 3-8, the ANN model significantly outperforms the RSM1, RSM2, NLR1 and NLR models in terms of the mean errors and determination coefficients.

As an example, the ANN produces lower ME value than the RSM1 and the NLR1 and this gives an improvement in the ME of 174.68 % and 151.30 % when compared with the RSM1 and the NLR1 models, respectively. This indicates that ANN models is more suitable and can be applied to the prediction of the swelling ratio of the hydrogels under investigated. It is also clearly seen that the S values of all dextran hydrogels formed are increased by time and pH. Furthermore, after a certain period they show constant swelling behavior, and process is transformed to equilibrium state.

These hydrogels exhibited a significantly higher S at pH 7.0 than acidic medium. Because that dextran-based hydrogels are pH-sensitive and highly swelling materials. It has been argued that for extensive swelling, neither the diffusion coefficient not the thickness of the disc remain constant, and therefore Fickian diffusion should not apply.

The results show that an artificial neural network model which can be proposed as an alternative approach for modeling of swelling characteristics. Because there are many possible nonlinear patterns in the data and nonlinear parametric models may not capture all the nonlinerities in the data. On rhe other hand, ANN is a data driven model as multivariate, nonlinear, nonparametric, stochastic approximation with dynamic feature extraction.

CONCLUSIONS

In this study, the ANN models were applied as new techniques to model the swelling behavior of the dextran hydrogels. The results show the good agreement between the predictions and observations was found in the comparisons and ANN models perform better than RSM models. This paper shows that ANN models have a good potential to model non-linear and multi-variable swelling behaviors of highly swellable dextran hydrogels.

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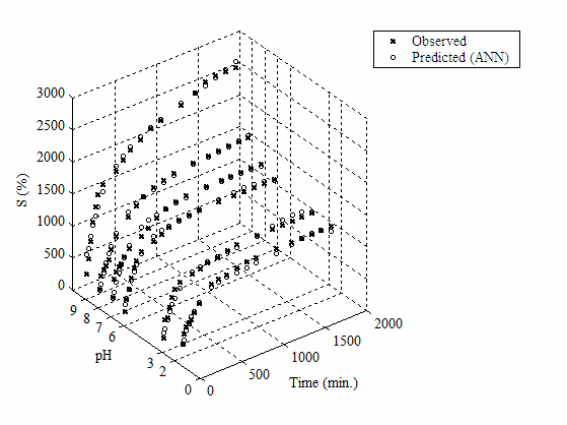

Figure 3. Comparing the predicted S values by ANN model with the observed data for dx-MBAm hydrogels

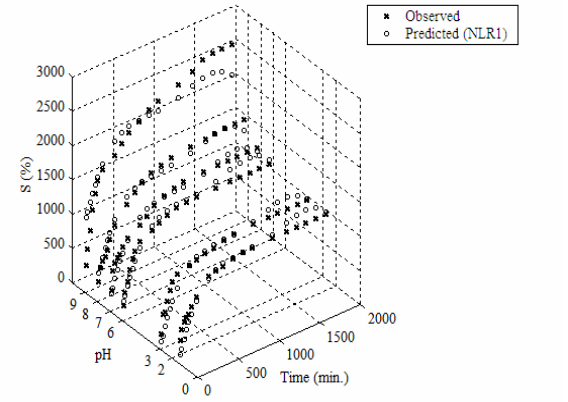

Figure 5. Comparing the predicted S values by NLR1 model with the observed data for dx-MBAm hydrogels

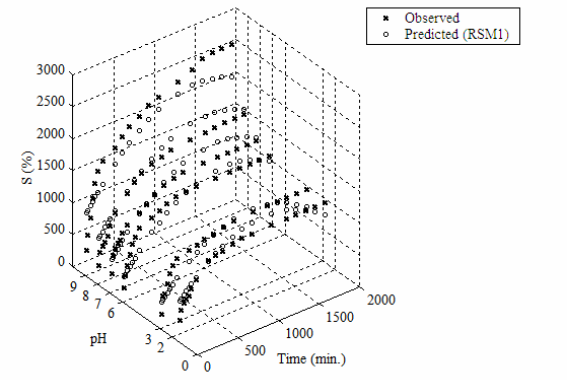

Figure 4. Comparing the predicted S values by RSM1 model with the observed data for dx-MBAm hydrogels

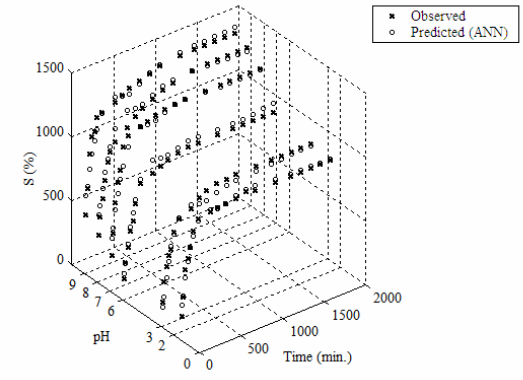

Figure 6. Comparing the predicted S values by ANN model with the observed data for dx-ECH hydrogels

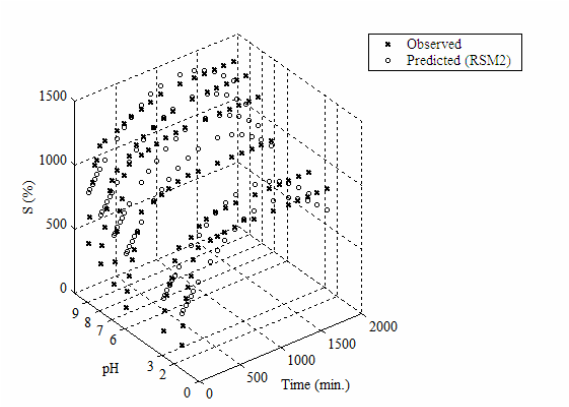

Figure 7. Comparing the predicted S values by RSM2 model with the observed data for dx-ECH hydrogels

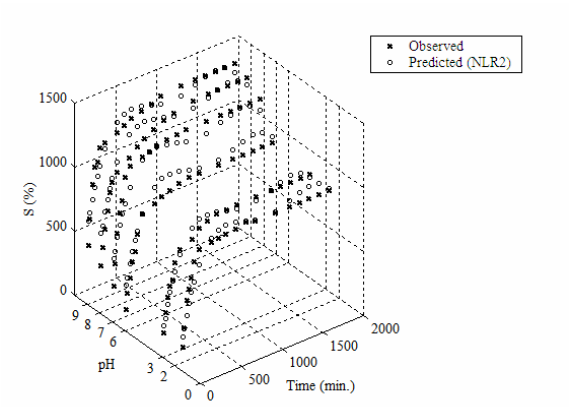

Figure 8. Comparing the predicted S values by NLR2 model with the observed data for dx-ECH hydrogels

Table 3. The coefficients of the models of RSM1 and RSM2

Term	RSM1		RSM2	
	Coefficient	Standard error	Coefficient	Standard error
b_0	988.027	145.970	422.467	88.230
b_1	-307.547	53.425	-22.619	18.240
b_2	1.405	0.1960	1.086	0.136
b_{11}	0.058	0.0151	0.0052	0.001
b_{22}	33.602	4.950	7.597	3.619
b_{12}	-0.0007	0	-0.0005	0

Table 4. The coefficients of the models of NLR1 and NLR2

Term	NLR1		NLR2	
	Coefficient	Standard error	Coefficient	Standard error
b_0	1182.880	392.765	-61.555	41.440
b_{11}	-1431.240	435.632	360.868	294.830
b_{12}	5.019	0.594	3.878	0.356
b_{21}	567.489	153.165	-161.441	105.982
b_{22}	-0.008	0.001	-0.007	0.001
b_{31}	-86.975	21.385	26.791	14.860
b_{32}	0	0	0	0
b_{41}	4.594	1.025	-1.379	0.709
b_{42}	0	0	0	0