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Prediction of the electrophoretic mobilities of some carboxylic acids from theoretically derived descriptors

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Abstract

A 4-4-1 artificial neural network was constructed and trained for the prediction of the electrophoretic mobilities of some aliphatic and aromatic carboxylic acids based on quantitative structure–property relationships. The inputs of this network are theoretically derived descriptors that were chosen by the stepwise variables selection techniques. These descriptors are: shape factor, molecular surface area, the maximum value of electron density on atom in molecule, and the sum of atomic polarizability. In order to assess the accuracy and predictability of the proposed model, the cross-validation test was employed. The results obtained showed the ability of developed artificial neural network to prediction of electrophoretic mobilities of aliphatic and carboxylic acids. Also result reveals the superiority of the artificial neural network over the multiple linear regression models.

Keywords: Neural networks, artificial; Structure–property relationships; Electrophoretic mobility; Regression analysis; Molecular descriptors; Carboxylic acids

1. Introduction

Capillary electrophoresis (CE) provide high efficiency separations of samples of very diverse nature (pharmaceutical, biological, environmental, . . .) [1–4]. It has been considerable advantage over chromatographic techniques in terms of higher efficiency, reduced analysis time, smaller amounts of sample required, and lower cost. The key parameter for separation of analytes are their electrophoretic mobilities. There are many factors that influence on the electrophoretic mobilities of solutes [5–8]. According to Max Born's model two fundamental frictional factors are found to be important in the electrophoretic mobilities of analytes; the hydrodynamic friction factor (f_h) and the dielectric friction factor (f_{dl}) [9–11]. These factors related to the electrophoretic mobility (μ_0) by the following equation:

$$\mu_0 = \frac{q}{f_h + f_{dl}} \quad (1)$$

where q is the charge on the solute. The hydrodynamic friction factor associated with moving of the solute through a continuum solvent of finite viscosity and relate to molecular volume and/or mass of solute. The dielectric friction is caused by the orientation of the solvent dipoles in response to ionic charge. After ion passes, energy is dissipated during the relaxation of the solvent to its equilibrium polarization. This factor is related to the charge distribution within the solute.

During method development in CE to develop an optimized separation the analytes generally have to employ a large number of experiments, which is often costly and time-consuming. Numerous empirical models have been developed for the calculation/prediction of electrophoretic mobilities [12–14]. It has been established experimentally that the electrophoretic mobility is proportional to the charge q and inversely proportional to the molecular mass M to the power $-b$:

$$\mu_0 = aqM^{-b} \quad (2)$$

where a and b are constants. Jokl [15] using paper electrophoresis found $b = 0.5$ whereas Offord [16] on basis of an extensive study of peptides determined $b = 2/3$.

Some reports have investigated the quantitative correlation between the molecular parameters and the obtained re-

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sponses in CE. Fu and Lucy [17] developed non-linear expressions to correlate/predict the absolute mobilities of 34 monoamines using experimental data collected from conductimetric measurements. They used molecular mass and average hydration number as independent variables in their equations. The average percentage error in the best model produced by these authors for correlating the mobility of 34 aliphatic amines was 3.7%. Lucy and coworkers [18] also developed an equation based on Max Born model for correlating the mobility of some aliphatic carboxylic acid based on their molar volume (V) and their p-function of dissociation constant. This study investigated that the pK_a value can be used as a relative measure of the dielectric friction and molecular volume demonstrate the effect of hydrodynamic friction. The obtained percentage error in calculation of electrophoretic mobilities of 15 aliphatic carboxylic acids using this equation was 3.7%. Jouyban et al. [19] developed an equation for calculating the electrophoretic mobility of amines with respect to the concentration of organic modifier in mixed-organic modifier running buffer which derived from mixture response surface methodology. Also, Wronski used charge and hidden mass of the solute in a non-linear equation for the calculation/prediction of the electrophoretic mobility of a diverse series of peptides and organic acids [20].

Quantitative structure–property relationships (QSPRs) have extensively been used to explain separation mechanisms and predict retention behaviour in analytical chemistry [21–25]. Liang et al. [26] correlated the electrophoretic mobility of flavonoids to topological indices but with relatively high prediction error (10%). Jalali-Heravi and Garkani-Nejad correlated the electrophoretic mobility of some sulfonamides with their structural parameter using QSPR techniques [27]. They have correlated the mobility of analytes with the heat of formation, molecular surface area, p-function of dissociation constant and partial charge on the most positive atom in the molecule.

The main aim of the present work was to development of a QSPR model using artificial neural networks (ANNs) to prediction of electrophoretic mobilities of some mono functional aliphatic and aromatic carboxylic acids and to determine the underlying factors governing their mobilities. In the first step, a multiple linear regression (MLR) model was constructed. Then for inspection of non-linear interactions/relation between different parameters in the model, an artificial neural network was generated for the prediction of the electrophoretic mobility of organic acids.

2. Methods

2.1. Data set

The electrophoretic mobilities of 58 anions of weak organic acids were taken from Ref. [20], that were be used as data set. The compounds in the data set (Table 1) consist of aliphatic and aromatic monofunctional carboxylic acids with various groups, heteroatoms and structural isomers. The electrophoretic mobilities of these compounds were obtained in the same conditions. The mobilities of compounds in data set fall in the range of 23.2–43.9 (10^{-4} cm^2 s^{-1} V^{-1}) for *p-tert*-butylbenzoic acid and fluoroacetic acid, respectively. The data set was randomly divided in two groups, a training set and a prediction set consisting of 48 and 10 molecules, respectively. The training set was used for the model generation and the prediction set was used for the evaluation of the generated model.

2.2. Descriptors

The electrophoretic mobility of molecule related to molecular structure in a complex way. The molecular structure and chemical properties of the solute and solvent determine the electrophoretic mobility of solute. Due to the diversity of the molecules studied in this work different descriptors were calculated. These descriptors encoded different aspects of the molecular structure and consist of electronic, geometric, and topological descriptors. Geometric descriptors were calculated using optimized Cartesian coordinates and the van der Waals radius of each atom in the molecule [28,29]. Electronic descriptors were calculated using the MOPAC package (version 6) [30] and topological descriptors were calculated using two-dimensional representation of the molecules. Some of these molecular descriptors were calculated by Dragon package [31] on the basis of the minimum energy molecular geometries optimized by HYPERCHEM package [32]. Dragon is a new, freely available software (by Milano Chemometrics and QSAR Research Group) for the calculation of more than 800 molecular descriptors. The generated numerical descriptors were responsible for encoding important features of the structure of molecules.

2.3. Regression analysis

The main goal of the generation of the MLR model was to choose a set of suitable descriptors that can be used as inputs for generation of the ANN model. Some of descriptors generated for each compound encoded similar information about the molecule of interest. Therefore, it was desirable to test each descriptor and eliminate those that show high correlation ($R > 0.95$) with each other. Subsequently, the method of stepwise multiple linear regression was used for the selection of important descriptors and MLR model construction. The best MLR model is one that has high correlation coefficient and F-value, low standard error and high prediction power. The constructed MLR model is presented in Table 2.

2.4. Artificial neural network construction

A detailed description of theory behind artificial neural networks have been adequately described elsewhere

Table 1
Data set and corresponding observed and predicted values of the electrophoretic mobilities (10^{-4} cm^2 s^{-1} V^{-1})

Number	Name	μ_{EXP}	μ_{ANN}	μ_{MLR}	E_r (%)
Training set					
1	Fluoroacetic acid	43.9	43.7	42	−0.45
2	3-Iodopropionic acid	34.9	34.3	35	−1.72
3	Benzoic acid	34.4	35.7	34.3	3.78
4	Gallic acid	34.4	33.9	31.9	−1.45
5	Phenoxyacetic acid	27.8	27.2	29.3	−2.16
6	*o*-Aminobenzoic acid	31.6	31.6	33	0
7	2-Hydroxybutyric acid	34.2	33.8	35.2	−1.17
8	Bromoacetic acid	38.8	38	39.4	−2.06
9	3,5-Dinitrobenzoic acid	29.1	30.1	29.6	3.44
10	*p*-Hydroxybenzoic acid	34	35	33.7	2.94
11	Vanillic acid	27.1	28.2	29.5	4.06
12	Chloroacetic acid	41.9	42	40.8	0.24
13	*p*-Fluorobenzoic acid	33.4	33.6	33.5	0.6
14	Pyruvic acid	40.4	40.4	37.7	0
15	2-Nitro-3-chlorobenzoic acid	31.3	30.3	29.1	−3.19
16	Trichloroacetic acid	36.2	36.5	36	0.83
17	Glycolic acid	42.3	43.1	41.6	1.89
18	*p*-Nitrobenzoic acid	32.1	32.7	32.1	1.87
19	Nicotinic acid	34.6	34.9	34.5	0.87
20	2-Nitro-3-bromobenzoic acid	28.2	28.5	28.3	1.06
21	Glucutonic acid	26.6	27.1	27.5	1.88
22	4-Bromobutyric acid	32.8	32.9	32.6	0.3
23	3,4-Dibromofluoroacetic acid	36.9	36.4	35.8	−1.36
24	*o*-Isopropylbenzoic acid	24.7	24.7	24.2	0
25	Trifluoroacetic acid	42.5	42.7	41.8	0.47
26	Cinnamic acid	28.3	28.5	29.5	0.71
27	*p*-Methoxybenzoic acid	28.3	29.2	30.6	3.18
28	2-Chlorobutyric acid	32.8	33.5	34.1	2.13
29	Gluconic acid	27.2	26.7	26.6	−1.84
30	*p*-Bromobenzoic acid	31.5	32.1	32	1.9
31	Iodoacetic acid	40.2	39.1	38.2	−2.74
32	Salicylic acid	35.4	35.2	33.8	−0.56
33	Lactic acid	36.5	36.1	38.2	−1.1
34	Dichloroacetic acid	39.4	38.5	37.9	−2.28
35	2,3-Dimethylbenzoic acid	27.1	27.7	28.5	2.21
36	*p*-Chlorobenzoic acid	33.4	33.8	32.9	1.2
37	5-Bromovaleric acid	30.8	31.6	31.7	2.6
38	Trichloroacetic acid	34.2	34.8	35.1	1.75
39	*p*-*tert*-Butylbenzoic acid	23.2	23.9	21.7	3.02
40	5-Iodovaleric acid	30.8	30.1	29.6	−2.27
41	2-Bromobutyric acid	30.8	31.4	33.5	1.95
42	3,4-Dihydroxybenzoic acid	34.4	33.8	32.8	−1.74
43	Chlorodibromoacetic acid	34.9	35.1	34.4	0.57
44	*p*-Toluic acid	29.1	29	30.3	−0.34
45	Glyoxalic acid	37.8	37.8	41.3	0
46	Tribromoacetic acid	34.9	34.2	33.7	−2.01
47	Glyceric acid	36.3	36.2	37.6	−0.28
48	2-Bromopropionic acid	33.4	33.7	36.2	0.9
Prediction set					
49	3-Chloropropionic acid	36.8	37.6	38.1	2.17
50	2,3-Dibromopropionic acid	32.3	33.4	34	3.4
51	4-Iodobutyric acid	32.9	33.3	32.4	1.22
52	2-Chloro-3-hydroxybutyric acid	32.9	32.6	33.1	−0.91
53	*p*-Ethylbenzoic acid	26.5	27.2	27.9	2.64
54	2,4,6-Trimethylbenzoic acid	24.7	24	25.8	−2.83
55	2,4-Dihydroxybenzoic acid	32	33.7	33.2	5.31
56	*p*-Ethoxybenzoic acid	26.6	25.9	28.5	−2.63
57	5-Chlorovaleric acid	30.8	31.8	31.8	3.25
58	Phenylacetic acid	31.7	32.3	31.2	1.89

Table 2
Specification of multiple linear regression models

Descriptor	Notation	Coefficient
Shape factor	SF	1.1 (±0.4)
Maximum values of electron density on atom in the molecule	MED	18 (±8)
Molecular surface area	MSA	−0.024 (±0.018)
Sum of atomic polarizability	SAP	−1.4 (±0.2)
Constant		−67 (±5)

[33–39]. In addition, we reported some relevant principles of the ANNs in previous papers [40–47]. An ANN program was written in FORTRAN 77 in our laboratory. This network was feed-forward fully connected that has three layers with sigmoidal transfer function. Descriptors appearing in the MLR models were used as inputs of network and signal of the output node represent the electrophoretic mobility of interested compound. Thus, this network has four nodes in input layer and one node in output layer. The value of each input was divided into its mean value to bring them into dynamic range of the sigmoid transfer function of the network. The back-propagation algorithm was used for the training of the network. The initial values of weights were randomly selected from a uniform distribution that ranged between −0.3 and +0.3. The initial values of biases were set to be 1. These values were optimized during the network training. Before training, the network parameters would be optimized. These parameters are: number of nodes in the hidden layer, weights and biases learning rates, and the momentum. Procedures for the optimization of these parameters were reported in our previous papers [42,45]. Then the optimized network was trained using training set for the adjustment of weights and biases values. Also cross-validation test was performed to evaluate the performance and prediction power of the generated ANN model.

3. Results and discussion

Table 1 shows the data set and corresponding observed MLR and ANN predicted values of electrophoretic mobilities of all molecules studied in this work. The selected MLR models are presented in Table 2. It can be seen from this table that four descriptors appeared in the MLR model. These descriptors are: shape factor (SF), molecular surface area (MSF), maximum value of electron density on atom in the molecule (MED), and the sum of atomic polarizability (SAP). The numerical values of these descriptors are shown in Table 3. These variables encode different topological, geometrical, and electronic aspect of molecular structure. As mentioned earlier, two fundamental frictional factors are found to be important in the electrophoretic mobility of a solute in capillary electrophoresis. These factors are the hydrodynamic friction factor, which is related to the molecular size and/or mass of solute, and the dielectric

Table 3
The values of the descriptors that were used in this work[a]

Number	SF	SF	MED	SAP
1	1.5413	84.852	6.352	4.36
2	1.6214	127.62	6.357	8.85
3	2.5667	132.912	6.365	10.19
4	2.7496	159.426	6.364	11.55
5	2.3955	171.36	6.351	12.85
6	2.272	147.492	6.408	11.19
7	1.3563	129.456	6.351	8.40
8	1.4252	100.026	6.342	5.78
9	2.9170	187.074	6.337	12.50
10	2.7215	143.010	6.370	10.64
11	2.4073	173.520	6.367	12.85
12	1.6928	94.680	6.357	5.29
13	2.7316	139.176	6.317	10.12
14	1.2637	102.726	6.272	5.88
15	1.8795	180.054	6.341	12.20
16	1.0934	125.298	6.305	7.01
17	1.6514	87.822	6.367	4.88
18	2.9338	159.696	6.349	11.34
19	2.5468	130.158	6.315	9.43
20	1.9354	184.752	6.337	12.70
21	1.4207	186.426	6.348	12.98
22	1.4207	186.426	6.362	9.30
23	1.0856	127.566	6.300	7.07
24	1.2638	195.876	6.368	15.46
25	1.1628	39.168	6.283	4.24
26	3.3163	166.446	6.362	13.70
27	2.5829	165.42	6.371	12.40
28	1.2901	133.074	6.330	8.80
29	2.1175	205.704	6.340	13.74
30	2.7464	154.944	6.360	11.54
31	1.8317	104.022	6.355	7.09
32	2.5918	140.418	6.379	10.64
33	1.2306	110.772	6.369	6.64
34	1.1690	111.798	6.320	6.15
35	2.2611	167.040	6.370	13.70
36	2.8239	151.488	6.360	11.04
37	1.6825	160.020	6.358	11.06
38	1.0901	125.622	6.256	7.01
39	1.6194	215.100	6.367	17.22
40	1.9925	171.468	6.360	12.36
41	1.3922	140.742	6.341	9.30
42	2.7683	151.326	6.365	11.10
43	1.0461	135.720	6.310	7.99
44	2.2851	153.594	6.320	11.94
45	1.8910	80.802	6.269	4.13
46	1.0617	139.608	6.310	8.49
47	1.4314	119.736	6.370	7.10
48	1.2969	121.518	6.337	7.54
49	1.9709	114.984	6.354	7.04
50	1.5364	140.094	6.329	8.89
51	1.8809	149.922	6.357	10.60
52	1.5097	143.118	6.310	9.26
53	2.1558	178.596	6.366	13.70
54	2.2954	185.454	6.379	15.46
55	2.7802	149.814	6.384	11.10
56	2.8449	184.536	6.371	13.78
57	1.5715	157.914	6.357	10.56
58	2.4224	154.026	6.360	11.94

The numbers refers to the number of the molecules given in Table 1.
[a] The definitions of the descriptors are given in Table 2.

friction factor, which is related to the charge distribution within the solute [9–11]. In organic acid, the charge distribution of carboxylate anion significantly influences the acid dissociation constant. Hence, the pK_a value is an effective measure of the charge distribution within a fully deprotonated carboxylate ion, so each parameter that affected on pK_a value can influenced on the electrophoretic mobility of solute. The maximum value of electron density on a atom in molecule and the sum of atomic polarizability can influenced on the pK_a values of solutes and can be affected on the dielectric friction term and plays important roles in the migration behavior of carboxylate ions. The third parameter that appeared in the MLR model is molecular surface area. It is obvious that the hydrodynamic friction force in CE is related to the size of molecule. As the MSA increase the electrophoretic mobility decreases. This is due to the frictional factor that may arise from shear across a small element of liquid close to the migration solute, which depends on the molecular surface area of solute. Another descriptor appearing in the MLR model is shape factor. This parameter indicates the compactness and degree of branching of the molecule. In the structural isomers as the branching of molecule increase the value of this parameter decreases. The inclusion of this parameter in the model considerably improves the ability of the model to true prediction of the electrophoretic mobility of structural isomers. Another reason for appearing of this descriptor in the model is that the steric effects influence the acid dissociation constants. Bulky chain around the carboxyl group makes salvation of the carboxylate ion more difficult, resulting in an increase in the pK_a value and alter the electrophoretic mobility. These results are in agreement with Max Born's model and Lucy experiments [17,18].

The next step was to construct the artificial neural network. Before training the network, the parameters of the number of nodes in the hidden layer, weights and biases learning rates and momentum values were optimized. Table 4 shows the architecture and specifications of the optimized network. After optimization of the network parameters, the network was trained for the adjustment of weights and biased values. To control the over fitting during training after each 100 training iterations the network was used to calculation of the electrophoretic mobilities of molecules included in the test set. To maintain the predictive power of the network at a desirable level, training was stopped when the standard errors of prediction for the test set started to increase. Obtained results showed that after 73 700 iterations, the values of standard error of prediction started to increase and over fitting began. Based upon the high values of iterations two points may arise. First, the architecture of the generated ANN was correctly designed and second, the descriptors appeared in the MLR model have been adequately chosen.

Table 4
Architecture and specification of the generated ANN

Number of nodes in the input layer	4
Number of nodes in the hidden layer	4
Number of nodes in the output layer	1
Weights learning rate	0.19
Biases learning rate	0.50
Momentum	0.50
Transfer function	Sigmoid

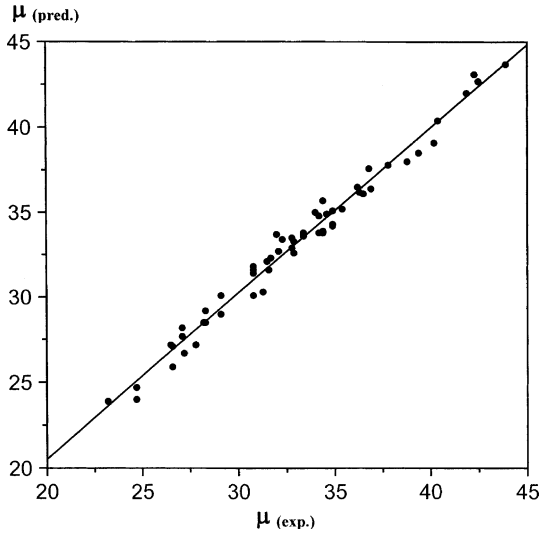

Fig. 1. Plot of the ANN predicted electrophoretic mobilities against the experimental values.

In order to evaluate the credibility of the obtained ANN model, the cross-validation method was used [48]. In this method, 10 molecules were removed randomly from the data set each time and the model was generated with the remaining molecules (leave-10-out procedure). Then the electrophoretic mobilities of removed molecules were predicted using the generated model. This procedure was continued until each molecule was predicted once. As a result, six rounds of run were needed (in one of these runs the validation set has eight molecules). The obtained ANN predicted values of the electrophoretic mobilities of data set are shown in Table 1 and Fig. 1 and the statistical results obtained are included in Table 5. As can be seen from this table, the results do not depend on the molecules in training and prediction set. In the case of ANN model, the maximum and minimum absolute relative errors for the predicted electrophoretic mobilities are 5.31 and 0%, respectively.

Table 5
Comparison of the SEC and SEP of the selected model with the test models obtained using different molecules

Model	Predicted molecule	S.E.	*R*	*F*
Test model I	1–10	0.8237	0.9856	271
Test model II	11–20	0.5930	0.9947	743
Test model III	21–30	0.5097	0.9906	998
Test model IV	31–40	0.5762	0.9947	753
Test model V	41–48	0.4788	0.9877	238
Test model VI	49–58	0.6354	0.9867	295

Table 6
Statistical parameters obtained using the ANN and MLR models[a]

Model	SEC	SEP	R_t	R_p	F_t	F_p
ANN	0.6017	0.7201	0.992	0.987	3004	292
MLR	1.4799	0.9730	0.953	0.973	458	142

R is the correlation coefficient; F is the statistical F value; SEC and SEP are referring to standard error of calibration and prediction, respectively.
[a] t is referring to the training set; p is referring to the prediction set.

The average percent of deviation (APD) were calculated for ANN and MLR predicted value of electrophoretic mobility [49]. The APD for calibration and prediction set for the ANN model are 1.56 and 2.63%, which should be compared with the values of 3.59 and 3.64%, respectively, for the MLR model. Comparison between these values and also other statistical results of these two models in Table 6 indicates that obtained results using ANN are better than those obtained using MLR model. This is believed to be due to the non-linear capabilities of the ANN.

Fig. 1 shows the plot of the ANN predicted against the experimental values of electrophoretic mobilities for the molecules included in the data set. The correlation coefficient and standard error of this plot are 0.991 and 0.65, respectively. Also, the propagation of points in both sides of linear regression line indicates that no systematic error exists in the development of the ANN model.

Li et al. [50] reports a QSPR model for the prediction of electrophoretic mobilities of aliphatic carboxylates and amines. They use molecular mass, molecular volume, the code (+1 or −1) for acid and base, and pK value as descriptors in their model. In comparison with results obtained by Li and coworkers they used an experimentally determined parameter (pK) in their model, but in the present work only theoretically derived descriptors were used. In QSPR studies, it is preferred to use theoretical derived descriptors over experimental parameters. Because the determinations of these parameters are usually expensive and time consuming, need pure compounds and some instrumental facilities, and also these values may have some experimental uncertainties. In addition, the credibility and predictive power of the present work evaluate carefully with cross-validation test.

4. Conclusion

The results of this study demonstrate that QSPR method using the artificial neural network techniques can generate suitable model for the prediction of electrophoretic mobilities of carboxylic acids in capillary electrophoresis. The key strength of the neural networks is their ability to allow for flexible mapping of the selected features by manipulating their functional dependence implicitly, unlike regression analysis. Neural network handles both linear and non-linear relationships without adding complexity to model. This capability offset the larger computing time required and complexity of the ANN method with respect to MLR. Descriptors that appear in the MLR models and included in ANN, provide information related to the different molecular properties that can participate in the physiochemical process that occurs in capillary electrophoresis.

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