Prediction of Skin Penetration Using Artificial Neural Network (ANN) Modeling

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ABSTRACT: Artificial neural network (ANN) analysis was used to predict the skin permeability of selected xenobiotics. Permeability coefficients ($\log k_p$) were obtained from various literature sources. A previously reported equation, which was shown to be useful in the prediction of skin permeability, uses the partial charges of the penetrants, their molecular weight, and their calculated octanol water partition coefficient ($\log K_{oct}$). The equation was used to predict the skin permeability for the set of 40 compounds($r^2 = 0.672$). A successful ANN was developed and the ANN produced $\log k_p$ values that correlated well with the experimental ones($r^2 = 0.997$). The penetration properties of a selection of compounds through human skin that have not been previously investigated, etodolac, famotidine, nimesulide, nizatidine, ranitidine, were investigated. Their permeability coefficients were determined. It was then possible to compare the experimental data with that predicted using the partial charge equation and the trained ANN. ANN modeling for predicting skin permeability was found to be useful for predicting skin permeability coefficients of compounds. In conclusion, the developed and described ANN model in this publication does not require any experimental parameters; it could potentially provide useful and precise prediction of skin penetration for new drugs or toxic penetrants.
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Keywords: artificial neural network; prediction of skin permeability; molecular modeling; diffusion

INTRODUCTION

There are a number of reasons why it would be useful to be able to predict the permeability of xenobiotics through the skin. There is an ongoing interest in transdermal drug delivery for systemic effect. Dermal drug delivery for local effect is still poorly understood with many compounds having very limited bioavailability. The cosmeceutical industry is also interested in active delivery to the various strata of the skin. However, the cosmetic industry often wants to reduce dermal uptake, for example in the use of UV filters. Lastly, it is important to know how much of an industrial or household chemical permeates through the skin if it comes into contact with it. For these reasons, several models have been developed to predict skin permeability from simple physicochemical parameters.

It is important to be able to predict skin permeability and understand the mechanisms of penetration for both (trans) dermal drug application and risk assessment after topical application of xenobiotics. Quantitative structure activity relationships are useful in predicting the behavior

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of novel compounds and may provide insights into the mechanisms of activity. In dermal penetration, the technique is often based on the multiple linear regression analysis (MLA) of molecular features that determines an index of permeation such as the permeability coefficient, k_p, or the diffusion of the permeant across some part of the skin. Early reports[1–3] used a limited data set until Flynn published a collection of more than 90 permeability coefficients and octanol/water partition coefficients (log K_{oct}). These formed the basis of predicting log k_p from log K_{oct}[4] and molecular weight (MW)[5] and subsequently from functional group contributions,[6] solvatochromic parameters,[7] solubility parameters,[8] and partial charges of the penetrant molecules.[9] MLA and principal component analysis[9] have been used to assess the predictors of permeant diffusion across human stratum corneum.

In previous work, artificial neural network (ANN) modeling has been used to assess theoretically derived molecular descriptors of permeant penetration across polydimethylsiloxane membrane.[10] ANN approaches have not been applied to skin permeability data. This publication builds on the use of partial charge, log K_{oct}, and MW data to predict skin permeability using these factors as inputs into an ANN. The results were compared to traditional equations from MLA.

To test the ANN model, a series of compounds were selected (etodolac, famotidine ketoprofen, nimesulide, nizatidine, and ranitidine) and their permeability values were determined experimentally, using Franz-type diffusion cells. Their permeability values were also predicted using a traditional MLA equation and the new ANN model. The predicted and experimental results and the models were then compared.

MATERIALS

Disodium hydrogen phosphate, sodium chloride, sodium hydroxide, potassium hydrogen phosphate, and orthophosphoric acid were obtained from BDH Ltd. (Poole, UK). Etodolac was obtained from Nobel Drug Company (Istanbul, Turkey). Famotidine was obtained from Ilsan Iltas Company, (Istanbul, Turkey). Ketoprofen and nimesulide were purchased from Sigma Chemical Co. (St. Louis, MO). Nizatidine was a gift from Eli Lilly Co. (Indianapolis, IN). Ranitidine was obtained from Fako Drug Company (Istanbul, Turkey). High-performance liquid chromatography (HPLC) grade acetonitrile was from Rathburn Chemicals (Scotland) and J. T. Baker (Deventer, Holland); methanol was from Merck KGaA (Darmstadt, Germany). All buffer components and other chemicals were of standard analytical grade.

METHODS

Software

The ANN program Pythia: The Neural Network Designer version 1.0 was used (Runtime Software LLC; Carson City, NV). Pythia is a computer program for the development and design of neural networks. Neural networks are used to detect hidden relationships in a set of patterns and Pythia uses back propagation networks to achieve this. The network parameters (weights) are initially set to random values. During the training phase, the actual output of the network is compared with the desired output and the error propagated back toward the input of the network. A special feature of the program is the evolutionary optimizer. This module of the software automatically generates suitable networks for a given training data set. The best network model was developed using the optimizer and the ANN that achieved the lowest square deviations. Figure 1 shows the details of the developed ANN model.

A neural network has two phases, commonly referred to as the "training phase" and the "reproduction phase." During the training phase,

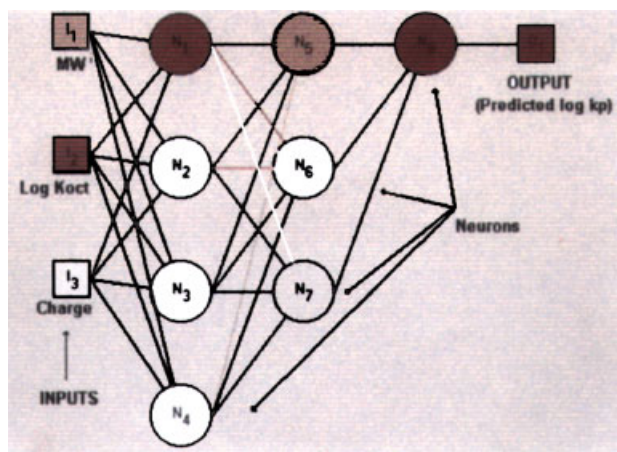


Figure 1. The developed ANN model for predicting skin permeability.

sample data containing both—inputs and desired outputs—are processed to optimize the network's output, meaning to minimize the deviation $(\text{Output}_{\text{Data}} - \text{Output}_{\text{Net}})^2$. $\text{Output}_{\text{Data}}$ is the output value in the training data; $\text{Output}_{\text{Net}}$ is the output value provided by reproducing the input data with the network. During the "reproduction phase," the network's parameters are not changed anymore and the network is used for the reproduction of input data in order to "predict" suitable output data. Figure 1 shows a typical backpropagation network. In backpropagation networks, each neuron has one output and as many inputs as neurons in the previous level. Each network input is connected to every neuron in the first level. Each neuron output is connected to every neuron in the next level. The network's output is the output of the last level's neurons. The network is processed from the left to the right.

Parameter Selection and Evaluation

k_p values were obtained from the literature[11] except atropine, naproxen, and nicotine.[12] $\text{Log}\,K_{\text{oct}}$

Table 1. Molecular Descriptors and k_p Values of Penetrants

Compound	MW	$\text{Log}\,K_{\text{oct}}$	Charge	$\text{Log}\,k_p$
3-Nitrophenol	139,100	2,000	1,227	−2,250
4-Nitrophenol	139,100	1,910	1,235	−2,250
Amobarbital	226,300	1,960	2,680	−2,640
Atropine	389,400	1,830	2,939	−3,250
Barbital	184,200	0,650	2,413	−3,950
Benzyl alcohol	108,100	1,100	1,362	−1,770
4-Bromophenol	170,300	2,590	1,181	−1,440
Butanol	74,120	0,800	1,226	−2,520
2-Chlorophenol	128,600	2,150	1,180	−1,480
Chlorpheniramine	274,800	3,390	2,030	−2,660
Decanol	158,300	4,570	1,778	−1,100
2,4-Dichlorophenol	163,000	3,060	1,205	−1,220
Diethylcarbamazine	218,200	1,750	2,016	−3,089
Ephedrine	165,200	0,930	2,350	−2,220
Estradiol	272,400	4,010	2,680	−2,490
Estradiol	272,400	4,010	2,680	−2,470
Ethanol	46,070	−0,310	1,044	−3,000
2-Ethoxy ethanol	91,100	−0,320	1,556	−3,600
Ethyl ether	74,100	0,930	0,787	−2,800
Heptanol	116,200	2,720	1,502	−1,420
Hexanol	102,200	2,030	1,410	−1,560
Isoquinoline	129,200	2,030	1,007	−1,780
M-Crezol	108,100	1,950	1,222	−1,820
Meperidine	247,400	2,450	1,866	−2,430
Methanol	32,400	−0,770	0,970	−3,000
Methyl4-OH benzoate	152,100	1,900	1,812	−2,040
Naproxen	230,300	3,340	2,161	−2,540
Nicotine	162,200	1,170	1,510	−2,480
Nonanol	144,300	4,260	1,686	−1,220
O-Cresol	108,100	1,950	1,220	−1,800
Octanol	130,200	3,000	1,594	−1,280
P-Cresol	108,000	1,940	1,221	−1,760
Phenol	94,100	1,460	1,171	−1,710
Propanol	60,000	0,250	1,134	−2,850
Propanol	60,000	0,250	1,134	−2,770
Propanol	60,000	0,250	1,134	−2,920
Salicylic Acid	138,100	2,260	2,116	−3,480
Testosterone	287,400	3,320	2,478	−2,660
Thymol	150,100	3,300	1,444	−1,280
2,4,6-Trichlorophenol	197,400	3,690	1,214	−1,230

values were from Medchem (Biobyte, Claremont, CA) and ACD-Log P (Advanced Chemistry Development Inc., Ontario, Canada). Molecular modeling was performed using NEMESIS V1.0 package (Oxford Molecular, Oxford, UK). Conformation analysis using a step size of 30° was used to find the approximate energy minimum conformation, followed by optimization to identify the minimum energy conformation. This two-step approach reduces the risk of finding a local minimum energy form. The program calculates partial charges on atoms on the basis of inductive effects in saturated molecules and Huckel molecular orbital calculations in π systems. The partial charges of the atoms (H, C, O, N, and halogen) constituting the molecule were noted. Various combinations of these charges were tried in the statistical analyses, but none gave superior results to the simple sum of the modulus of the partial charges.

Permeation Studies

Full-thickness human skin was mounted in all-glass Franz-type diffusion cells and thermostated such that the skin surface was at 32°C and the stirred receptor medium at 37°C. The cross-sectional area available for diffusion was 1 cm^2. One milliliter of saturated drug solution was placed into donor phase and the receptor phase was pH 7.4 isotonic saline phosphate buffer solution (~2.5 mL). Samples of the receptor phase were removed periodically (2, 4, 6, 8, 12, 24, 30, 48, 60, and 72 h) and the receptor phase was replenished with fresh solution after each sample. Three replicates were conducted. The steady-state flux values were determined from the linear part of the penetration profile and permeability coefficients were estimated by dividing the steady-state flux by the applied concentration (the aqueous solubility). The concentrations in the donor phase were determined by HPLC analysis. Full-thickness abdominal human skin samples were obtained from the hospital (Plastic Surgery Department, Gazi University Hospital, Besevler-Ankara-Turkey) with appropriate informed consent after surgery. The underlying fatty tissue was removed by blunt dissection and, if not used immediately, the skin was stored at −70°C for no longer than 3 weeks.

HPLC Analysis

HPLC analyses were conducted with a UV detector, pump, injection port, and 20-μL Rheodyne (Hewlett-Packard), series 1050 integrator (Hewlett-Packard), series 3396 pump (Hewlett Packard) or Waters Millipore model 510 pump, 717 plus auto sampler, 996 photo diode array detector (Hewlett-Packard).

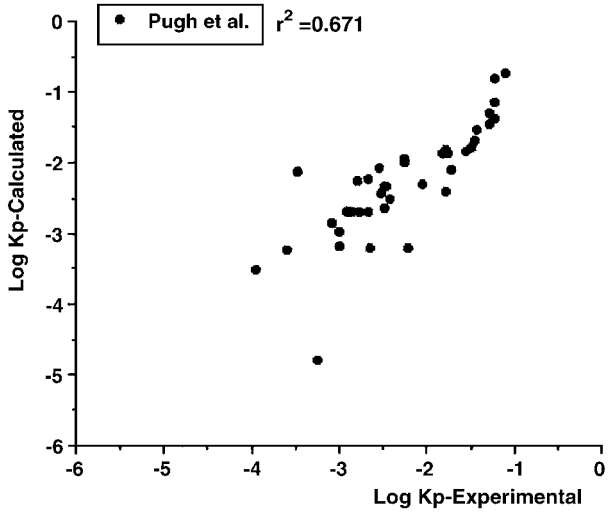


Figure 2. The relationship between predicted log k_p values and experiment results.

RESULTS AND DISCUSSION

Previous MLA models have been reviewed[9] and a successful equation was selected that was capable of predicting k_p from partial charge, log K_{oct}, and

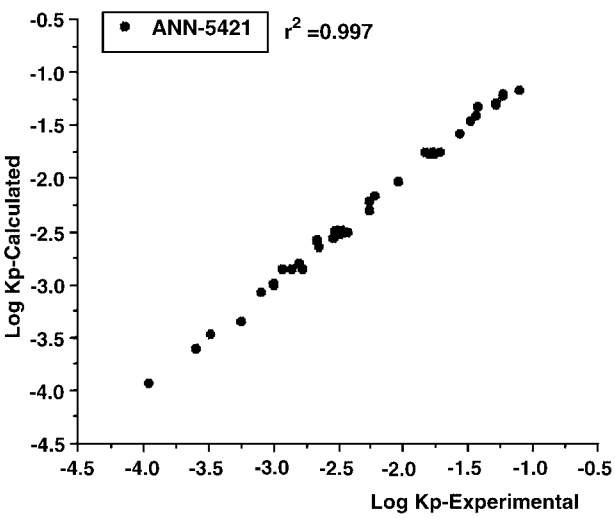
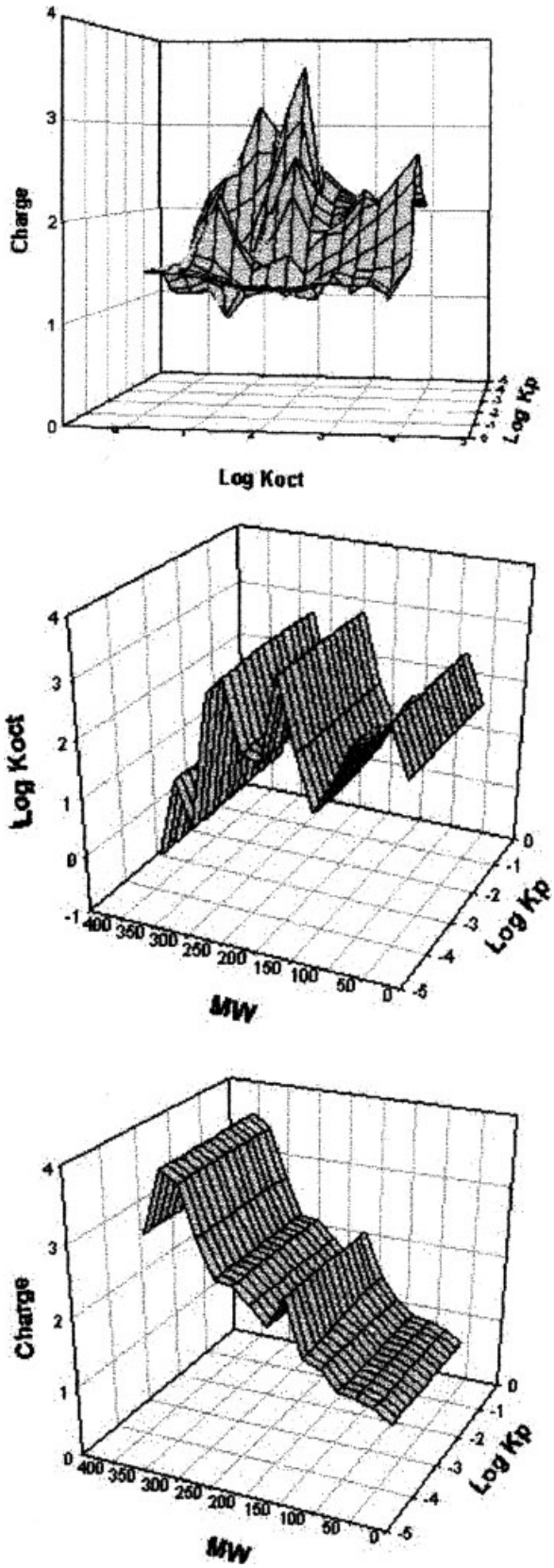


Figure 3. The relationship between predicted log k_p values and experiment results using the ANN model.



molecular weight.

$$\text{Log}\, k_p = -2.644 + 0.59\ \log K_{oct} - 0.00283\ \text{MW} * \text{charge} \qquad (1)$$
$$R^2 = 0.672$$

Charge is the sum of the modulus of the partial charges on the constituent atoms.

Table 1 shows the molecular descriptors and the previously reported k_p values. k_p values were predicted using eq. 1 and Figure 2 shows the relationship between predicted and experimental results.

Pythia was used to construct an appropriate ANN. The optimizer function in the program was used with MW, log K_{oct}, and charge values were used as inputs and the literature log k_p values as the output. The most successful ANN created contained five neurons at level 1, four neurons at level 2, two neurons at level 3, and one neuron at level 4 (model described as ANN-5421). Other configurations were also studied but none gave superior results. The optimization of the model (number of hidden layers and hidden units) was performed automatically and the lowest value of square deviation was obtained with this model (for instance, square deviations were 0.001131 for model ANN-5421, 0.001231 for model ANN-5431, 0.003403 for model ANN-541, 0.005975 for model ANN-5321, 0.004531 for model ANN-5411, and 0.011583 for model ANN-5221). Therefore, the model ANN-5421 was used for further calculations. It is also interesting to note that an ANN model was attempted using inputs of log K_{oct} and MW (the two parameters from the well-established Potts and Guy[4] equation. It was not possible to build an adequate ANN from these two simple inputs.

In the MLA analysis (eq. 1), the r^2 value was calculated as 0.672. This coefficient was highly improved (0.997) when ANN modeling was used. The computer program trained itself (program parameters set as follows: trained until: repetition = 100,000, deviation^2 < 0.000170, time passed = 300; use learn rate = 0.5, automatically adjust; finally: reproduce pattern set and show results in native form). Other parameters such as transfer function, etc. were selected as default. The program trained itself until the square deviations were less then 0.00017 (0.000167 is the

Figure 4. Functional dependence surfaces of descriptors of the ANN model.

Table 2. Experimental Log k_p Values and Theoretically Predicted Values

Compound	Log k_p-Experimental	Log k_p-ANN-5421	Deviation$^2 \times 10^{-3}$	Log k_p Pugh et al.
3-Nitrophenol	−2,250	−2,211	0,141	−1,947
4-Nitrophenol	−2,250	−2,294	0,188	−2,003
Amobarbital	−2,640	−2,642	0,000	−3,203
Atropine	−3,250	−3,343	0,846	−4,803
Barbital	−3,950	−3,927	0,050	−3,518
Benzyl alcohol	−1,770	−1,754	0,023	−2,411
4-Bromophenol	−1,440	−1,404	0,122	−1,685
Butanol	−2,520	−2,496	0,056	−2,429
2-Chlorophenol	−1,480	−1,464	0,023	−1,804
Chlorpheniramine	−2,660	−2,595	0,402	−2,222
Decanol	−1,100	−1,177	0,583	−0,744
2,4-Dichlorophenol	−1,220	−1,204	0,024	−1,394
Diethylcarbamazine	−3,089	−3,071	0,031	−2,856
Ephedrine	−2,220	−2,171	0,225	−3,193
Estradiol	−2,490	−2,489	0,000	−2,344
Estradiol	−2,470	−2,489	0,037	−2,344
Ethanol	−3,000	−2,999	0,000	−2,963
2-Ethoxy ethanol	−3,600	−3,599	0,000	−3,233
Ethyl Ether	−2,800	−2,801	0,000	−2,260
Heptanol	−1,420	−1,332	0,743	−1,533
Hexanol	−1,560	−1,579	0,037	−1,854
Isoquinoline	−1,780	−1,771	0,006	−1,814
m-Crezol	−1,820	−1,759	0,358	−1,867
Meperidine	−2,430	−2,505	0,555	−2,504
Methanol	−3,000	−2,997	0,001	−3,187
Methyl4-OH benzoate	−2,040	−2,030	0,009	−2,302
Naproxen	−2,540	−2,568	0,079	−2,081
Nicotine	−2,480	−2,517	0,137	−2,646
Nonanol	−1,220	−1,212	0,005	−0,819
o-Cresol	−1,800	−1,764	0,125	−1,866
Octanol	−1,280	−1,287	0,005	−1,461
p-Cresol	−1,760	−1,762	0,001	−1,872
Phenol	−1,710	−1,745	0,125	−2,094
Propanol	−2,850	−2,846	0,002	−2,689
Propanol	−2,770	−2,846	0,561	−2,689
Propanol	−2,920	−2,846	0,531	−2,689
Salicylic Acid	−3,480	−3,478	0,000	−2,137
Testosterone	−2,660	−2,581	0,593	−2,700
Thymol	−1,280	−1,300	0,040	−1,310
2,4,6-Trichlorophenol	−1,230	−1,218	0,013	−1,145

lowest value that the program could achieve). Figure 3 shows the relationship between the theoretically calculated log k_p values and experimental results using the ANN model.

The interpretation of effects of each descriptor is difficult because the model is multivariate and nonlinear. However, some insight into the degree of nonlinear behavior of descriptors has been assessed with a functional dependence to understand relationships. The value of input variables was varied through its range, whereas others were held constant. The network output was plotted against two input descriptors to generate a functional dependence surface. This gives an idea and indication of how the network output alters in response to two selected input variables. Figure 4 shows the functional dependence surfaces of the descriptors. Nonlinearity of inputs is clearly evident, suggesting a very complex relationship.

The previously determined MLA result (eq. 1) and the values from ANN modeling were compared

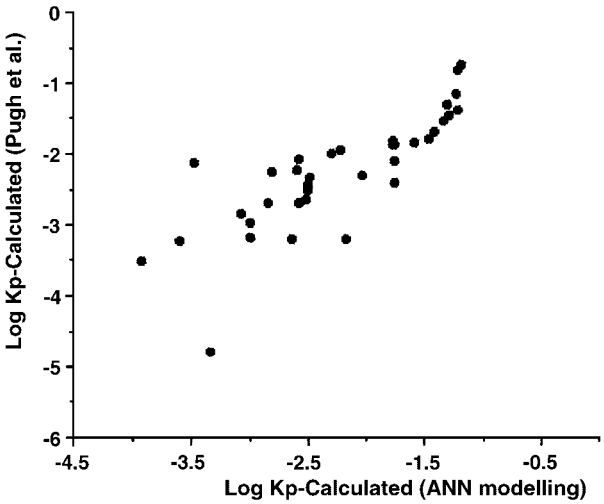


Figure 5. The relationship between previously determined prediction equation and ANN modeling.

(Table 2). Figure 5 shows the relation between them. There was no direct relationship found, indicating that the ANN modeling approach was different from previously determined models.

The r^2 value may not be the most suitable parameter for the comparison because the calculation methods and equations are different. The ANN has one input layer, one or more hidden layers, and the output layer. Each layer is composed of a number of units. The units in neighboring layers are fully interconnected with links. The strengths of the connections between two units are called "weights." In each hidden layer and output layer, the processing unit sums its input from the previous layer and then applies the function to compute its output according to the following equation[13]:

$$Y_i = \sum w_{ij} \cdot x_i \tag{2}$$

$$F(y_i) = 1/[1 + \exp(\alpha - y_j)] \tag{3}$$

Table 3. The Statistical Test Results of the Pugh et al. Model

Regression statistics					
Multiple R	0,819				
R Square	0,671				
Adjusted R square	0,662				
Standard error	0,431				
Observations	40				
	df	SS	MS	F	Significance F
ANOVA					
Regression	1	14,407	14,407	77,556	1,030E-10
Residual	38	7,059	0,185		
Total	39	21,467			

Table 4. The Statistical Test Results of the ANN Model

Regression statistics					
Multiple R	0,998				
R Square	0,996				
Adjusted R square	0,996				
Standard error	0,042				
Observations	40				
	df	SS	MS	F	Significance F
ANOVA					
Regression	1	21,399	21,399	12016,080	3,838E-49
Residual	38	0,067	0,001		
Total	39	21,467			

Where w_{ij} is the weight of the connection between unit i in the current layer j in the following layer, and x_i is the output value from the previous layer. α is the parameter relating to the shape of the function. In fact, it could be useful to use another parameter for testing the model, but ANN modeling uses the previous data over and over to produce the final output value. The technique and the equations are complex; therefore, another parameter such as AIC (Akaike Information Criterion) could not be used for comparison. The final output values can be used for the comparison; therefore, the regression analysis and the analysis of variance (ANOVA) test were used to compare the fitness of the model of Pugh et al. and the ANN. Tables 3 and 4 show the statistical test results for Pugh et al. and ANN modeling, respectively. When all results were compared, the ANN model seemed to be the most suitable model.

The next stage of the evaluation of the ANN was to test the trained model. Compounds were selected that have a range of physicochemical properties and their permeability coefficients were determined using standard techniques (some permeability data of compounds were obtained from the literature[12] to make a better comparison). The results are given in Table 5 [the calculated values of log k_p (from MLA eq. 1 and the ANN) are also given in the table].

The quality of the data has a very important role in modeling; this was particularly important in neural computing.[16] Analysis of published skin permeation data has shown that some compounds seem to have anomalous skin permeability coefficients.[12] Some outliers appear in all prediction equations, and this may be because of the unreliable log k_p values. Their log k_p values may need to be redetermined, but within the range of the compounds tested, ANN modeling gave closer results to experiment results than previously determined models. This may indicate that the penetration of compounds through skin has a very complex mechanism and previous MLA models cannot produce predicted values accurately.

Table 5. Permeability Coefficients for Various Permeants (±SEM, $n = 3$)

Chemicals	MW	Charge	Log K_{oct}	Donor Conc. (mg/mL)	Log k_p (cm · n^{-})			
					Experimental	Literature	Pugh et al.	ANN-5421
Aspirin	180,160	2,675	1,200	1,354 ± 0,030	—	−2,140[12,14]	−3,5204	−2,114
Benzoic acid	122,120	1,605	1,890	0,800 ± 0,015	—	−1,600[12,14]	−3,0119	−1,694
Diclofenac	318,130	3,515	3,550	0,791 ± 0,090	—	−3,450[11]	−4,0967	−3,031
Etodolac	287,260	2,924	3,326	0,755 ± 0,022	−2,127 ± 0,023	—	−3,4562	−2,291
Famotidine	337,430	4,813	−1,020	6,200 ± 0,112	−4,789 ± 0,215	—	−8,3260	−3,761
Ibuprofen	206,280	2,235	3,720	0,389 ± 0,030	—	−1,440[12,14]	−2,3342	−1,879
Ketoprofen	254,280	3,167	2,810	1,406 ± 0,042	−3,212 ± 0,184	—	−3,7609	−3,100
Methyl-nicotinate	137,130	1,553	0,880	34,500 ± 1,550	—	−2,490[15]	−2,9173	−2,230
Nimesulide	308,310	3,382	3,910	0,555 ± 0,012	−2,995 ± 0,094	—	−3,9960	−2,861
Nizatidine	331,450	4,628	1,460	5,500 ± 0,245	−4,425 ± 0,318	—	−6,5823	−3,732
Ranitidine	314,100	3,994	1,280	92,000 ± 3,221	−4,052 ± 0,379	—	−5,8737	−3,865

CONCLUSION

An ANN (5421) model was used for predicting skin permeability for a data set of 40 selected compounds. The r^2 value was calculated as 0.997 when the ANN predicted and experimental log k_p values were correlated. A complex relationship exists between structure of the penetrant and

skin penetration. Unlike many previously determined models, the ANN model developed and described herein does not require any experimental parameters; it could potentially provide a useful and precise prediction of skin penetration for new chemical entities in terms of both therapy and toxicity. It could reduce the need of performing penetration experiments using human skin or other model membranes. The results indicate that the simple predictors investigated to date can be capable of predicting skin penetration.

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