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Prediction of skin permeability using an artificial neural network

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Transdermal drug delivery has many advantages. It can provide steady-state plasma levels of drug and long-term therapy from a single dose, avoid the hepatic first-pass metabolism associated with oral administration, and allow easy termination of drug input. It would be desirable that the skin permeability could be predicted computationally with an accuracy that allows the early rejection of unsuitable candidates.

Artificial neural networks are being increasingly used in pharmaceutical research to predict pharmacokinetic parameters [1–4]. They are especially useful when there are non-linear relationships between predictors and pharmacokinetic parameters. In this paper, we divided the data set constructed by Abraham et al. [5] into two subsets: training set and test set, and used an artificial neural network to derive a model predicting the permeability coefficients through human skin *in vitro*.

The backpropagation algorithm with a modified learning rule, normalized cumulative delta was used to train the network. A tanh function was used as the transfer function. The neuronet model was four-layer network that included an input layer, two hidden layers, and an output layer. Inputs to the neural network consisted of the molecular volume (V, nm^3), the energy of the highest occupied molecular orbital (E_{HOMO}, eV), the energy of the lowest unoccupied molecular orbital (E_{LUMO}, eV), the sum of the absolute values of the net atomic charges of oxygen and nitrogen atoms which were hydrogen-bond acceptors ($Q_{O,N}$), and the sum of net atomic charges of hydrogen

Table 1: Permeability coefficients through human skin *in vitro* and structural parameters for training set

						log P (P, cm/s)	
Compound	V	Q_H	$Q_{O,N}$	E_{HOMO}	E_{LUMO}	Obs.[a]	Calc.[b]
Diethylether	0.1273	0.0000	0.2827	−10.3931	2.9816	−5.35	−5.19
Butanone	0.1164	0.0000	0.2897	−10.5414	0.8776	−5.90	−5.88
Formic acid	0.0528	0.2418	0.6815	−11.8200	0.9578	−7.08	−6.97
Propanoic acid	0.1001	0.2429	0.6829	−11.5019	1.0235	−7.01	−6.83
Butanoic acid	0.1239	0.2428	0.6837	−11.5020	1.0285	−6.46	−6.55
Pentanoic acid	0.1474	0.2429	0.6836	−11.4831	1.0298	−6.14	−6.15
Heptanoic acid	0.1945	0.2427	0.6835	−11.2985	1.0298	−5.27	−5.43
Octanoic acid	0.2182	0.2428	0.6835	−11.2396	1.0285	−5.18	−5.36
Methanol	0.0520	0.1954	0.3260	−11.1349	3.7783	−6.56	−6.62
Ethanol	0.0757	0.1966	0.3296	−10.8752	3.5649	−6.56	−6.62
1-Propanol	0.0994	0.1972	0.3296	−10.8461	3.4888	−6.41	−6.49
1-Butanol	0.1230	0.1972	0.3292	−10.8460	3.4246	−6.16	−6.25
1-Hexanol	0.1700	0.1972	0.3291	−10.8475	3.3692	−5.44	−5.38
1-Heptanol	0.1934	0.1972	0.3291	−10.8488	3.3533	−5.05	−4.94
1-Octanol	0.2308	0.2008	0.3278	−7.4406	0.5175	−4.84	−4.99
1-Nonanol	0.2408	0.1973	0.3292	−10.8495	3.3363	−4.78	−4.68
1-Decanol	0.2643	0.1973	0.3292	−10.8493	3.3320	−4.66	−4.76
2-Ethoxyethanol	0.1350	0.2033	0.6170	−10.4883	2.6445	−7.16	−7.01
Benzene	0.1150	0.0000	0.0000	−9.6530	0.5548	−4.51	−4.43
Toluene	0.1382	0.0000	0.0000	−9.3307	0.5203	−3.56	−3.76
Ethylbenzene	0.1608	0.0000	0.0000	−9.2984	0.5376	−3.48	−3.66
Phenol	0.1222	0.2173	0.2526	−9.1144	0.3978	−5.64	−5.64
2-Methylphenol	0.1448	0.2170	0.2537	−8.9648	0.3965	−5.36	−5.23
4- Methylphenol	0.1455	0.2168	0.2527	−8.8804	0.4347	−5.31	−5.26
3,4-Dimethylphenol	0.1677	0.2166	0.2526	−8.8561	0.4559	−5.00	−4.99
4-Ethylphenol	0.1672	0.2165	0.2532	−8.8171	0.4067	−5.01	−4.99
2-Isopropyl-5-methylphenol	0.2124	0.2146	0.2528	−8.8716	0.3915	−4.83	−4.68
2-Chlorophenol	0.1399	0.2211	0.2369	−9.1896	0.0656	−5.04	−5.12
4-Chlorophenol	0.1406	0.2201	0.2482	−9.1246	0.0947	−5.00	−5.14
4-Chloro-3-methylphenol	0.1626	0.2197	0.2490	−9.0559	0.0894	−4.82	−4.92
4-Chloro-3,5-dimethylphenol	0.1851	0.2191	0.2493	−8.9889	0.1258	−4.79	−4.79
2,4-Dichlorophenol	0.1584	0.2236	0.2331	−9.2308	−0.1969	−4.78	−4.88
4-Bromophenol	0.1480	0.2212	0.2469	−9.1892	0.0204	−5.00	−5.04
2-Nitrophenol	0.1492	0.0000	0.5846	−9.9110	−1.1846	−4.56	−4.56
3-Nitrophenol	0.1504	0.2277	0.9531	−9.9656	−1.1662	−5.81	−5.61
4-Nitrophenol	0.1496	0.2290	0.9613	−10.0718	−1.0650	−5.81	−5.83
Methyl 4-hydroxybenzoate	0.1804	0.2238	0.8831	−9.5357	−0.3969	−5.60	−5.84
2-Naphthol	0.1778	0.2173	0.2518	−8.5697	−0.3443	−5.11	−4.88
Resorcinol	0.1294	0.4366	0.4973	−8.9825	0.2747	−7.18	−7.08
Benzyl alcohol	0.1453	0.2015	0.3262	−9.3606	0.4792	−5.78	−5.65
Progesterone	0.4194	0.0000	0.5957	−10.0206	0.0074	−4.92	−4.92
Testosterone	0.3820	0.1982	0.6164	−10.0129	0.0143	−6.21	−6.11
Aldosterone	0.4318	0.4493	1.5564	−10.1454	−0.1017	−7.79	7.80
Estradiol	0.3500	0.4136	0.5717	−8.7874	0.4460	−5.95	−5.95
Dexamethasone	0.4574	0.6426	1.5276	−10.1421	−0.4457	−7.75	−7.87

[a] From reference [5] [b] From the network

Table 2: Predicted permeability coefficients through human skin *in vitro* for a test set

Compound	V	Q_H	$Q_{O,nN}$	E_{HOMO}	E_{LUMO}	log P (P, cm/s) Obs.[a]	Pred.[b]	Pred.[c]
Acetic acid	0.0766	0.2433	0.6826	−11.6254	0.9701	−7.01	−6.94	−6.50
Hexanoic acid	0.1709	0.2428	0.6836	−11.3797	1.0300	−5.42	−5.73	−6.18
1-Pentanol	0.1466	0.1972	0.3293	−10.8470	3.3911	−5.78	−5.87	−5.90
Styrene	0.1503	0.0000	0.0000	−8.9979	0.0192	−3.75	−3.62	−3.92
3- Methylphenol	0.1453	0.2170	0.2533	−9.0521	0.3733	−5.37	−5.21	−5.19
2,4,6-Trichlorophenol	0.1767	0.2348	0.2264	−9.3906	−0.5015	−4.78	−4.81	−4.86
2-Phenylethanol	0.1680	0.1996	0.3302	−9.3903	0.4395	−5.68	−5.55	−5.23
Corticosterone	0.4341	0.4230	1.2448	−10.0195	0.0286	−7.08	−7.29	−6.78

[a] From reference [5] [b] From the network [c] From equation (1)

atoms attached to oxygen or nitrogen atoms (Q_H). These molecular structural parameters were greatly related with molecular volume, lipophilicity, and hydrogen bond-forming ability of a compound which were considered to be the main factors determining skin permeability [6], and were obtained from the semiempirical self-consistent field molecular orbital calculation AM1 method [7]. The atomic radii used to calculate molecular volumes were those used by Clark [8]. The two hidden layers both consisted of four neurons. The output layer consisted of a single neuron which was the permeability coefficient through human skin in vitro (log P). This network architecture is shown in the Fig.

The neural network was trained for 100000 cycles. The calculated log P values for the training set from the trained network were shown in Table 1 and they were in good accordance with the experimental values. To further assess the predictive ability of the network, we predicted the log P values of 8 compounds outside the training set (shown in Table 2). The mean prediction error was 2.6% for the test set. It was satisfying.

If the multiple linear regression analysis was used for the training set with the same predictors, the following regression equation was obtained.

$$\log P = -4.762 + 3.691V - 2.856Q_H - 2.194Q_{O,N} - 0.03267E_{HOMO} - 0.2196E_{LUMO}$$
$$n = 45 \quad r = 0.8553 \quad s = 0.5369 \quad F = 21.26 \qquad (1)$$

In this equation, n is the number of samples, r is the correlation coefficient, s is the standard deviation, F is the F-statistic. The predicted log P values for the test set of 8 compounds from eq. (1) were shown in Table 2. Their mean prediction error was 32.09%.

The neural network model showed much more accurate prediction than multiple regression analysis, indicating that there were complex nonlinear relationships between the permeability coefficient through human skin and the predictors used in this paper. Because the predictors can be easily calculated, it is convenient to predict the skin permeability using the network model.

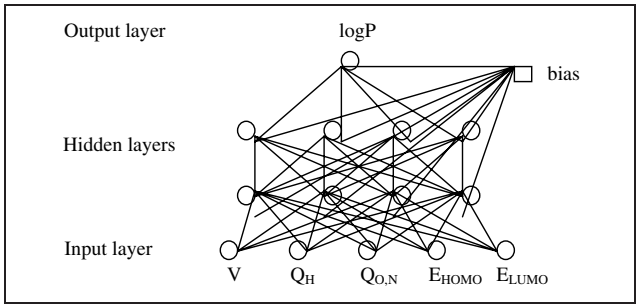

Fig.: Structure of the neural network

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Received February 4, 2002
Accepted March 16, 2002

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