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# Quantitative structure-binding relationships (QSBR) and artificial neural networks: improved predictions in drug: cyclodextrin inclusion complexes

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**Abstract**

The application of the principal neural network architecture, namely the multilayer perceptron (MLP), have been developed for obtaining sufficient quantitative structure-binding relationships (QSBR) with high accuracy. To this end a dataset of 17 barbiturates as guests complexing to α- and β-cyclodextrins was examined and the results compared to that of Lopata et al (J. Pharm. Sci., 74, (1995)) who studied the same problem using multiple regression analysis. A series of new and improved algorithms other than the 'old fashion' and problematic steepest descent were examined for training the MLP networks. The proposed methods led to substantial gain in both the prediction ability and the computation speed of the resulting models. A specific ANN architecture (4–4–1) trained with the Levenberg–Marquardt algorithm diminished the number of outliers, during its implementation to unseen data (barbiturates), to zero.


*Keywords:* QSBR; Artificial neural networks

The interest in studies dealing with the complexation of drugs with cyclodextrins (CDs; Loukas et al., 1994) has been increased dramatically over the last years. In these studies the major aim is the improvement of some characteristics of drugs due to complexation (Loukas et al., 1995a). Almost in all of these studies much effort is concentrated on the calculation of the binding (stability) constants (Loukas et al., 1995b), a value, which characterize the stability of the complex. In literature several models have been described, from linear to nonlinear ones (Loukas 1997a,b, 1998), in order to calculate these values as accurate as possible. In the present study the application of ANN is described, Fig. 1 based on advanced algorithms, to the prediction of the binding constant values in complexation of homologous series of drugs with cyclodextrins.

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In the present study we used the dataset of 17 barbiturates (Fig. 2a) acting as complexing agents to α- and β-cyclodextrins (Fig. 2b) and as inputs the four descriptors proposed by Lopata et al. (1985); Table 1). As far as the input variables and the dataset were selected the next step was the division of the dataset in three subsets namely the training, validation and test subsets. The main requirement during training is the data representativity, means that the samples in the data set should be (evenly) spread over the expected range of data variability. In order to avoid the risk of not selected representative samples during training, we evaluated two different strategies of training set design namely the D-optimal design and the Kohonen self-organizing map approach.

For the training we used two backpropagation training algorithms: gradient descent and gradient descent with momentum. These two methods are often too slow for practical problems. To overcome this problem we examined several high performance algorithms, which can converge from 10 to 100 times faster than the algorithms examined previously. All of these algorithms train faster and fall into two main categories. The first category uses heuristic techniques, which were developed from an analysis of the performance of the standard steepest descent algorithm. Such heuristic modifications include the use of momentum, variable learning rate backpropagation, and resilient backpropagation. The second category of fast algorithms uses standard numerical optimization techniques such conjugate gradient, quasi-Newton and Levenberg–Marquardt (Table 2).

We have performed a QSBR study for the complexation of α- and β-cyclodextrins by 17 barbiturates using the data in Table 1. This data set, even if it is of limited size, the subsequent small number of inputs could assure accurate predictions as Tetko et al. (1993) concluded also in their study of 16 mitomycin derivatives. The neural network systems were simulated using Matlab Neural Network Toolbox (MathWorks Inc., unknown) running on a Pentium II platform. Training continued until there was no further decrease in overall error after a period of 500 cycles and the average training time for each run was few minutes for the examined feedforward networks. The quality of the examined QSBR models was assessed by the term MSE (Table 2).

$$\mathrm{MSE} = \sum_{i=1}^{N}\sum_{j=1}^{g}\frac{(y_{ij} - \mathrm{out}_{ij})^2}{Ng}$$

where $N$ is the number of objects in the examined data set (train, validate or test), $g$ is the number of output variables, $y_{ij}$ is the element of target matrix $\mathbf{y}$ $(N \times g)$ for the data considered (ie training, validate or test set) and $\mathrm{out}_{ij}$ is the element of the output matrix **out** $(N \times g)$ of the ANN. The examined algorithms are presented in Table 2 together with the training error (MSE), the training correlation coefficient $R$ and the number of outliers in the unseen (test) data set of five compounds.

The ability of the examined models to predict the outputs in unseen data (test data set) is called generalization. In Table 3 is calculated the root-mean-square error of predictions (RMSEP), a statistical term for comparing the performance of the examined models in the same data set:

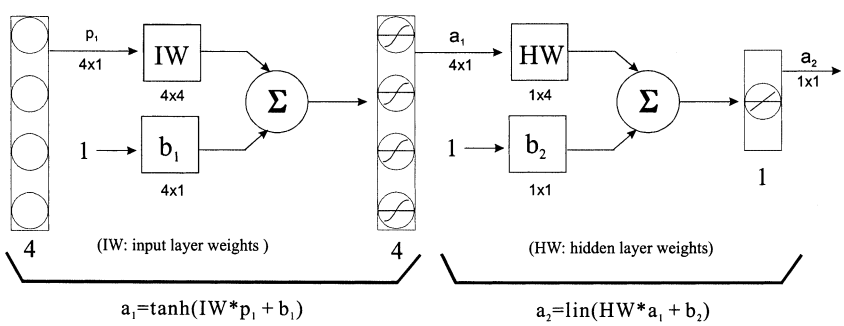


Fig. 1. Schematic representation of the architecture and the way of processing of the examined MLP network.

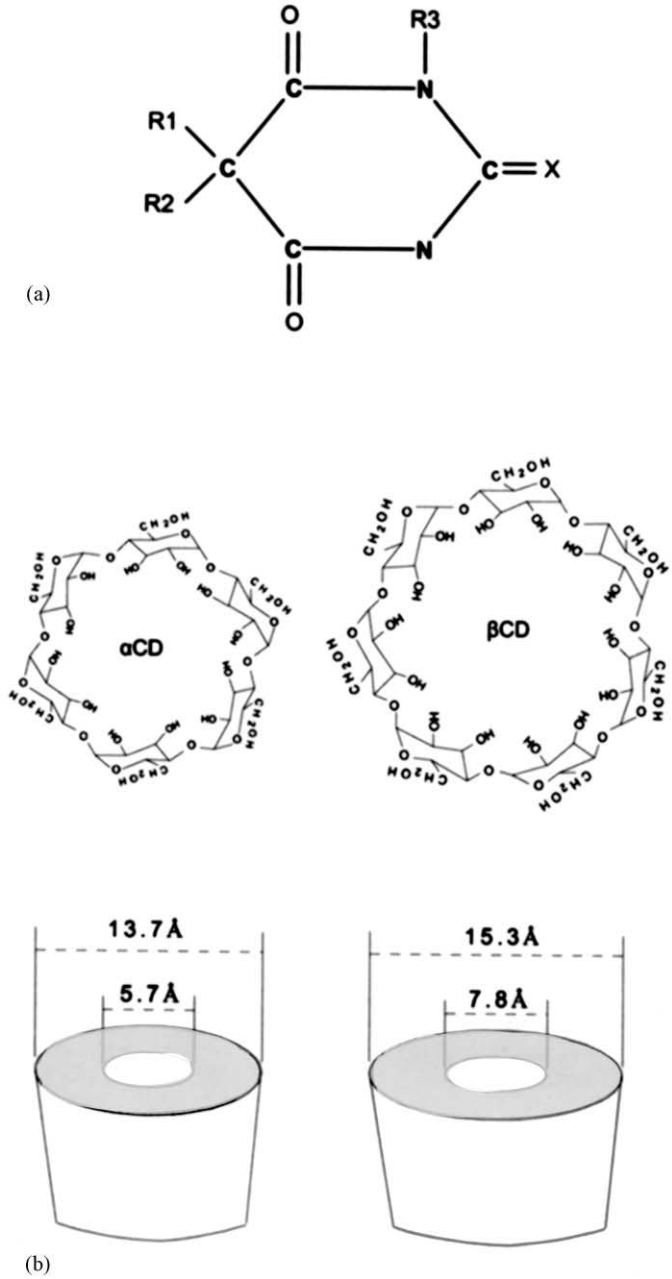


Fig. 2. (a) Structure of barbiturates and (b) structure of α- and β-cyclodextrin.

$$\mathrm{RMSEP} = \sqrt{\frac{\sum_{1}^{n} |y_{\mathrm{obs}} - y_{\mathrm{pred}}|^2}{n}}.$$

The importance of the inputs, derived from sensitivity analysis, was the following (from the most to the least important): $c_1$ (contribution of group $R_1$ to hydrophobicity, Fig. 2a), $\sigma_1^*$ (Taft substituent constant—electronic effect of $R_1$), $MR_1'$ (molar refractivity-steric bulk of $R_1$) and $P_c$

(chloroform—water partition coefficient). These results of this analysis indicate that, within the examined barbiturate series, steric bulk is not an important factor in binding to cyclodextrins. The influence of the hydrophobicity constant $c_1$ confirms the presence of a hydrophobic binding site. The current observations highlight the mechanism of complexation procedure between barbiturates and cyclodextrins suggesting an entrance of the barbiturates from their $R_1$ side. Thakkar and Demarco (1971), Thakkar et al. (1972) drowned the same conclusions based on their $^1$H NMR obser-

Table 1
Structures, physicochemical parameters and observed binding constant values of the barbiturate derivatives

| | $R_1$ | $R_2$ | $R_3$ | $X$ | $P_c$[a] | $c_1$[b] | $s_1$[c] | MR$'_1$[c] | Log $K_\alpha$ | Log $K_\beta$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $(CH_2)_2CH_3$ | $CH_2CH_3$ | H | 0 | 2 | −0.773 | −0.12 | 1.496 | 2.724 | 2.114 |
| 2 | $(CH_2)_3CH_3$ | $CH_2CH_3$ | H | 0 | 9.67 | −0.147 | −0.13 | 1.959 | 2.633 | 2.681 |
| 3 | $(CH_2)_4CH_3$ | $CH_2CH_3$ | H | 0 | 38.6 | 0.389 | −0.16 | 2.424 | 2.94 | 3.114 |
| 4 | $(CH_2)_5CH_3$ | $CH_2CH_3$ | H | 0 | 78.5 | 0.784 | −0.17 | 2.89 | 3.384 | 3.456 |
| 5 | $(CH_2)_6CH_3$ | $CH_2CH_3$ | H | 0 | 334 | 1.408 | −0.17 | 3.355 | 3.618 | 3.715 |
| 6 | $CH(CH_3)(CH_2)_2CH_3$ | $CH_2CH_3$ | H | 0 | 28 | 0.334 | −0.23 | 2.424 | 2.613 | 3.196 |
| 7 | $(CH_2)_2CH(CH_3)_2$ | $CH_2CH_3$ | H | 0 | 28.3 | 0.336 | −0.16 | 2.424 | 2.146 | 3.243 |
| 8 | Phenyl | $CH_2CH_3$ | H | 0 | 4.4 | −0.422 | 0.6 | 2.536 | 2.23 | 3.27 |
| 9 | Phenyl | $CH_2CH_3$ | $CH_3$ | 0 | 191 | −0.422 | 0.6 | 2.536 | 2.398 | 3.22 |
| 10 | Cyclohex-3-enyl | $CH_3$ | $CH_3$ | 0 | 153 | −0.518 | −0.12 | 2.956 | 2.342 | 3.185 |
| 11 | $CH_2CH_3$ | $CH_2CH_3$ | H | S | 11.1 | −1.132 | −0.1 | 1.03 | 2.699 | 2.477 |
| 12 | $(CH_2)_2CH_3$ | $CH_2CH_3$ | H | S | 27.9 | −0.773 | −0.12 | 1.496 | 2.875 | 2.732 |
| 13 | $(CH_2)_3CH_3$ | $CH_2CH_3$ | H | S | 103 | −0.147 | −0.13 | 1.959 | 2.778 | 2.839 |
| 14 | $(CH_2)_4CH_3$ | $CH_2CH_3$ | H | S | 306 | 0.389 | −0.16 | 2.424 | 3.267 | 3.324 |
| 15 | $(CH_2)_5CH_3$ | $CH_2CH_3$ | H | S | 926 | 0.784 | −0.17 | 2.89 | 3.458 | 3.684 |
| 16 | $CH(CH_3)(CH_2)_2CH_3$ | $CH_2CH_3$ | H | S | 326 | 0.334 | −0.23 | 2.424 | 2.447 | 3.38 |
| 17 | Phenyl | $CH_2CH_3$ | H | S | 63.9 | −0.422 | 0.6 | 2.536 | 3.519 | 3.549 |

[a] Uekama et al. (1978).
[b] Obtained from Free–Wilson analysis.
[c] Hansch and Leo (1979).

Table 2
Algorithms used for training the mlp networks and the resulted MSE, post training correlation coefficient $R$ and the number of outliers

| Algorithm | MSE | Post train $R$ | Outliers[a] |
|---|---|---|---|
| Levenberg–Marquardt backpropagation | 0.028 (0.033)[b] | 0.958 (0.939) | 0 (1) |
| BFGS quasi-Newton backpropagation | 0.035 (0.041) | 0.949 (0.921) | 1 (1) |
| Polak–Ribiere conjugate gradient backpropagation | 0.040 (0.049) | 0.921 (0.920) | 1 (2) |
| Scaled conjugate gradient backpropagation | 0.051 (0.058) | 0.889 (0.905) | 1 (1) |
| Powell–Beale conjugate gradient backpropagation | 0.043 (0.055) | 0.929 (0.935) | 3 (2) |
| Fletcher–Powell conjugate gradient backpropagation | 0.04 (0.049) | 0.930 (0.941) | 3 (3) |
| Gradient descent w/momentum and adaptive lr backprop | 0.085 (0.079) | 0.871 (0.899) | 4 (3) |
| Gradient descent w/adaptive lr backpropagation | 0.11 (0.09) | 0.819 (0.850) | 4 (3) |
| One step secant backpropagation | 0.047 (0.055) | 0.939 (0.922) | 4 (4) |
| Resilient backpropagation ($R_{prop}$) | 0.053 (0.065) | 0.895 (0.902) | 4 (4) |
| Gradient descent backpropagation | 0.2 (0.25) | 0.67 (0.71) | 4 (4) |
| Gradient descent w/momentum backpropagation | 0.25 (0.33) | 0.63 (0.65) | 5 (4) |

[a] An outlier had $|\text{binding}_{obs} - \text{binding}_{pred}| > 0.1$.
[b] Numbers in parentheses correspond to binding values of barbiturates with β-cyclodextrin.

Table 3
Test set of five barbiturates, the observed (experimental) binding constants, the predicted ones from the 4–4–1 network trained with the LM algorithm, and the published ones

| Barbiturate derivatives | Observed | Predicted ANN | Published results (Lopata et al., 1985) |
|---|---|---|---|
| 3 | 2.94 (3.114)[a] | 2.960 (3.040) | 3.133 (3.063) |
| 4 | 3.384 (3.456) | 3.344 (3.401) | 3.326 (3.406) |
| 7 | 2.146 (3.243) | 2.125 (3.320) | 2.311 (3.063) |
| 12 | 2.875 (2.732) | 2.796 (2.800) | 2.750 (2.690) |
| 14 | 3.267 (3.324) | 3.186 (3.300) | 3.133 (3.373) |
| RMSEP | | 0.055 (0.063) | 0.142 (0.091) |

[a] Numbers in parentheses correspond to binding values of barbiturates with β-cyclodextrin.

vations, that during complexation β-cyclodextrin includes the $R_1$ substituent of barbiturates. It could be concluded also, that the hydrophobic effects of specific substituents rather than the hydrophobicity of the entire molecule favor the complexation. The sensitivity analysis concerning complexation of barbiturates with αCD supported the same conclusions.

The cyclodextrin:barbiturates inclusion complexation is a representative sample from the population of host:guest (or ligand:substrate) interactions where it is necessary to model the binding procedure and to predict the binding constant values. In the category of the host:guest interactions the interaction of certain drugs with specific receptors could be added also. The algorithms for training the feed-forward networks such as the LM or BFGS improved the predictions to unseen data and the networks reached a significant level of accuracy.

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