Neural and Neuro-Fuzzy Models of Toxic Action of Phenols

Ciprian-Daniel N. NEAGU, Aynur O. APTULA, and Giuseppina GINI

***Abstract*—The problem of describing the bio-chemical action of different classes of chemical compounds through relations dependent on their structures is known as the quantitative structure-activity relation (QSAR) problem. Development of toxicity models of phenols using neural and neuro-fuzzy models is here proposed. A dataset about the inhibition of growth determined by phenolic compounds to the protozoan ciliate *Tetrahymena pyriformis* was used to produce QSAR and connectionist models. The results are promising, and suitable for further research.**

***Index Terms*—Neural Networks, Neuro-Fuzzy Networks, Fuzzy Inference, QSAR.**

I. Introduction

In recent years, the neuro-fuzzy systems have drawn increasing research interest. This approach has been successfully used in various areas [3][16][18], such as speech/natural language understanding [25], industrial and medical diagnosis, and financial applications [11][20]. The reason for studying and applying artificial neural networks (ANN) approaches is a way to develop subsymbolic knowledge representation systems, as the ones based on the neuro-fuzzy networks paradigm [24].

The hydroxy-substituted aromatic compounds (phenols) form a large and structurally diverse group. These are interesting from a toxicological point of view, since the phenols are widely used organic compounds. They elicit a number of toxicities to different species [10][22]. Thus, there has been much interest in quantitative structure-activity relationships (QSARs) for phenols, due to their ubiquitous nature and the various toxicities they may have [23]. However, for acute toxicity, the elucidation of mechanism of action (MOA) is required. In many cases, in the toxicity problem, successful QSAR analysis depends on the identification of MOA of the compounds [8].

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Until now, several research papers have been published, discussing the role that artificial intelligence (AI) tools could play in the problem of toxicity prediction and QSAR modeling. Adamczak and Duch [1] applied neural networks to analyze two QSAR series and to compare the results with other three AI-related approaches. A hybrid expert system approach was done by Gini [11], and applied to predict phytotoxicity. A study on the usage of fuzzy logic for descriptors modeling has been presented by Exner and Brickmann [7]. In all cases, the neural network approach of the toxicity prediction is restricted to crisp modeling of data.

This paper is a contribution to the area of modeling the toxicity of phenols and of analysing the correlations between chemical descriptors and related MOA. Results obtained using neuro-fuzzy techniques for descriptors analysis, toxicity modeling, and prediction are encouraging and show that the method is worthy of further research as an application of ANNs to real problems.

The aim of the proposed investigation was to perform a neural and neuro-fuzzy analysis of 225 phenolic toxicity data (described in section 2) to *Tetrahymena pyriformis*. The two most successful architectures of the developed neural and neuro-fuzzy models (proposed in section 4) were applied for MOA classes of phenols, in order to obtain specific models and to compare with the traditional QSAR approach (reviewed in section 3). Further, the analysis was performed in an attempt to give more light on the mechanisms of toxic action (sections 5). The developed models were validated by using a test set of compounds and compared for descriptors interpretation and significance (section 6). Additionally, the results were compared with some QSAR approaches (section 7).

II. Data description

A. Biological data

The 2D ciliate (*Tetrahymena pyriformis*) population growth impairment (IGC50) data were processed from TETRATOX database [6][22], described by Schultz, Sinks, and Cronin [23]. All chemicals and their updated toxicity values are available as IMAGETOX data sets [2][5]. Toxicity was quantified as the log of the inverse of potency. Potency values (reported as millimoles, mM) were normalized to their extremes of the set.

B. Molecular Descriptors

A total of 158 2D and 3D descriptors were calculated for each compound. Hydrophobicity with and without correction for ionization (log*P*, log*D*), acidity constant (*pKa*) and energy

of the lowest unoccupied molecular orbital (E_{LUMO}) are the most cited entry variables for the problem of toxicity prediction in our case. Some of them were rejected, due to the zero values for most of the chemicals. Finally, 43 descriptors were used as inputs in ANNs, and the output was toxicity as $\log(1/IGC_{50})$. From these, a number of 7 descriptors built the second set of entries, to study their significance in a final reduced size model of toxicity and correlation with MOA.

The mode of action (MOA) of the phenols is coded in the following classes: MOA=1, (153 polar narcotics: 4-hydroxyphenylaceticacid, 1,3,5-trihydroxybenzene, etc.), MOA=2 (18 respiratory uncouplers: 2,4,6-trinitrophenol, 2,4-dichloro-6-nitrophenol, etc.), MOA=3 (27 pro-electrophiles: 2,4-diaminophenol2HCl, 3-methylcatechol, etc.), MOA=4 (23 soft electrophiles: 3-nitrophenol, 4-hydroxy-3-nitrobenzaldehyde, etc.) MOA=5 (4 pro-redox cyclers: tetrabromocatechol or tetrafluorohydroquinone).

Logarithms of the 1-octanol/water partition coefficient ($\log P$) and *pKa* values were calculated using the ACD/Labs© software[1]. The distribution coefficient ($\log D$) at *pH*=7.35 was calculated according to the following expression:

$$\log D = \log P - \log(1 + 10 \times pH - pKa) \quad (1)$$

Other descriptors were calculated with Chem-X ver.2000.1, TSAR ver.3.3[2] and QSARis© ver.1.1)[3].

2D structures of the chemicals, in SMILES notation [26], were converted automatically to three-dimensional (3D) structures through the use of Chem-X 2D-3D Builder. The 2D-3D Builder uses a parameter file for building chains and a fragment database for building rings and functional groups. Converted structures were subsequently optimized by means of MOPAC version 6.49, implemented in Chem-X using the all-valence electron semi-empirical Hamiltonian. By default, in QSARis© the structures were entered into the 2D Editor, which were converted to the 3D structures, and 2D as well as 3D descriptors were calculated.

III. The QSAR approach

A structure-activity relationship (SAR) relates features of physico-chemical structure to a property, effect, or biological activity associated with that chemical. In so doing, there can be both qualitative and quantitative considerations. A qualitative relationship is a general rule-type of relationship, which provides either yes/no, or at best, A<B<C information. Such relationships can be developed with noncontinuous, or categorical data. Quantitative structure-activity relationships (QSARs), however, can be developed only using continuous, or quantitative, data.

The premise of structure-toxicity modeling is that, changes in the structure of a chemical may influence the type and potency of its toxic action. This principle is a continuation of the concept that all chemical-toxicological effects are the result of an interaction between the chemical and one or more components of the living system. Over the past fifteen years, schemes for structure-toxicity modeling have changed from the congeneric series approach through the chemical class-based approach, multiple regression or AI-based approaches. Recently, many attempts have been made for modeling the toxicity of phenolic compounds as the QSAR analysis on the described dataset [2][5][10][23]. Major available data are for the inhibition of growth to the protozoan ciliate *Tetrahymena pyriformis*.

For example, a two-parameter QSAR, or response-surface, was developed by Cronin and Schultz [5] based on parameters for hydrophobicity and electrophilicity for the toxicity of a limited selection of these compounds (QSAR2):

$$\log(IGC_{50})^{-1} = 0.67(0.02)\log P - 0.67(0.06)LUMO - 1.123$$
$$n = 120, R^2 = 0.90, R^2_{CV} = 0.89, s = 0.26, F = 523 \quad (2)$$

where IGC_{50} is the concentration in millimoles causing 50% inhibition of growth, after 40 hours, to *Tetrahymena pyrformis*, P is the octanol-water partition coefficient, *LUMO* is the energy of the lowest unoccupied molecular orbital, n is the number of observations, R^2 is the coefficient of determination, R^2_{CV} is the leave-one-out cross-validated coefficient of determination, s is the standard error of the estimate, F is the Fisher statistic. Figure in parentheses are the standard errors on the coefficients.

Garg, Kurup, and Hansch [10], obtained, on the same dataset, a similar relationship (QSAR3), replacing *LUMO* with Hammett constant (σ):

$$\log(IGC_{50})^{-1} = 0.64(0.04)\log P - 0.61(0.12)\sigma + 1.123(0.13)$$
$$n = 119, R^2 = 0.90, R^2_{CV} = 0.89, s = 0.265 \quad (3)$$

Cronin and Osman [5], working with a greater number of phenols to *Tetrahymena pyriformis*, demonstrated that the $\log D$ and *LUMO* are the most successful descriptors in modeling (QSAR4) of phenols toxicity (correlation coefficient between $\log D$ and *LUMO* is 0.396):

$$\log(IGC_{50})^{-1} = 0.60(0.021)\log D - 0.69(0.058)LUMO - 0.81(0.054)$$
$$n = 161, R^2 = 0.84, R^2_{CV} = 0.83, s = 0.33, F = 420 \quad (4)$$
$$T - values: \log D = 28.3, LUMO = 12.0$$

Recently, Aptula [2] obtained, for the classification of 221 phenols, with respect to 4 pre-assigned MOA, based on 5 structural and physico-chemicals descriptors, a correct classification of 89.1% of the compounds (absolute error 0.3).

IV. The connectionist approach

We used connectionist models as powerful tools to process knowledge, to build models, for multidimensional data scaling, and because explicit rules are not available.

NIKE (Neural explicit&Implicit Knowledge inference systEm) is a hybrid system [20], developed in Matlab©6 (MathWorks Inc.) for prediction, based on modular neural and neuro-fuzzy networks.

[1] ACD/Labs© (1995, Advanced Chemistry Develop.Inc.,Toronto, Canada).
[2] Chem-X ver.2000.1, TSAR ver.3.3 (Oxford Molecular Ltd, Oxford, UK).
[3] QSARis© version 1.1 (SciVision-Academic Press, San Diego, CA).

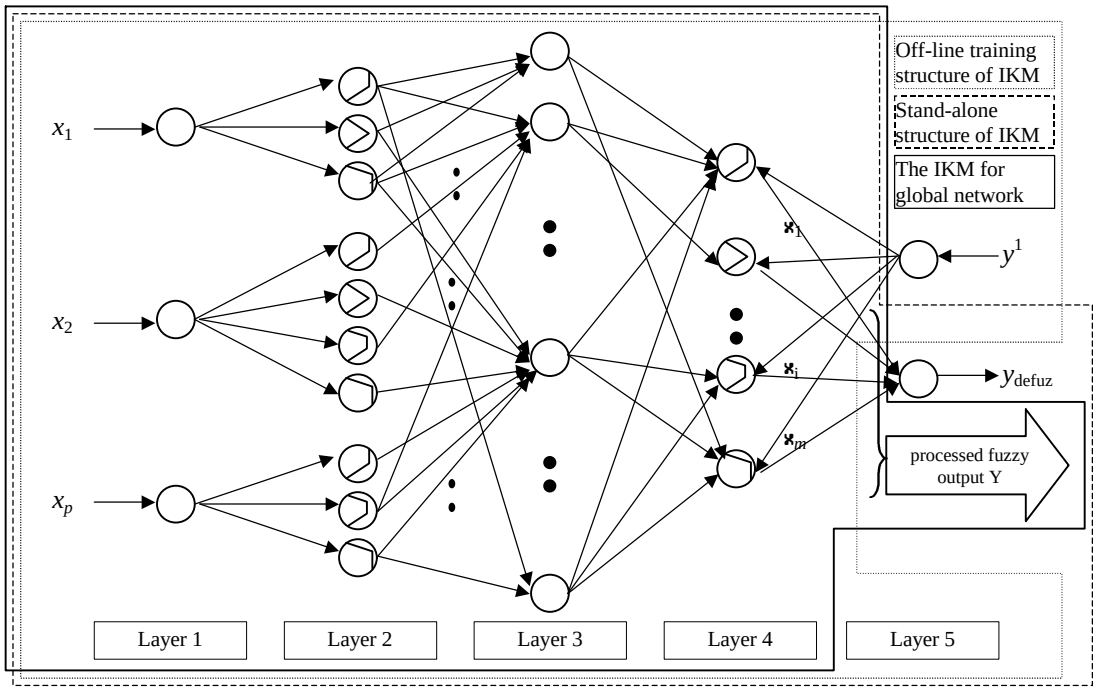


Fig. 1. Implicit Knowledge Module implemented as FNN2.

NIKE system automates the tasks involved in this process, from the data representation for toxicity measurements, to the establishment of a prediction of a given new input. It also suggests how the fuzzy inference produced the result, when required. At present, NIKE contains two modules that could be used individually, and operate on the same inputs in order to model and to predict the toxicity. We define the *implicit knowledge* as the knowledge represented by neural/ neuro-fuzzy networks, created and adapted by a learning algorithm. The representation of implicit knowledge is based on the numerical weights of the connections between neurons.

The first module, called IKM-CNN (Implicit Knowledge Module-based on Crisp Neural Networks), takes charge of modeling the data set as a multilayer perceptron (MLP [21]), for which a procedure of extracting an equivalent fuzzy rules system is added, based on the interactive fuzzy operators [4][19]. The MLP model is also used to compare the overall performance of the future neurosymbolic system with neuro-fuzzy and QSAR approaches.

The second module, called IKM-FNN (Implicit Knowledge Module-based on Fuzzy Neural Networks) is implemented as a multilayered neural structure with an input layer, establishing the inputs to perform the membership degrees of the current values, a fully connected three-layered FNN2 [9], and a defuzzification layer [20] (fig.1). The weights of the connections between layer 1 and layer 2 are set to one. The linguistic variable X_i is described by m_i fuzzy sets, A_{ij}, having the degrees of membership performed by the functions $\mu_{ij}(x_i)$, j=1,2,...,m_i, i=1,2,..,p., (in our case, on the descriptors and toxicity values). Since the layers 1 and 5 are used in the fuzzification process in the training and prediction steps, the layers 2-4 are organized as a feedforward network to represent the implicit rules through FNN training [9][19].

The methodology proposed to build the connectionist approach, based on the two described neural and neuro-fuzzy architectures, consists on the following steps, for which the results will be discussed in the next sections:

- *Step 1*: the identification of input and output linguistic variables. The set of data was normalized relative to the values of the 225 compounds descriptors. The variables are represented by continuous values and fuzzy sets, and mapped in the NIKE input units through specific formatted files.
- *Step 2*: the IKM modules are represented as MLP and FNN networks (parameterized by the number of hidden neurons). We build and train each IKM described, in order to assure for each one a crisp specific output. The best CNN and FNN networks are chosen to be used in the next steps, as neural and neuro-fuzzy models.
- *Step 3*: the contribution of each descriptor, from a short list of the ten most interesting to be studied for their influence in toxicity and MOA variations, was measured using the strategy outlined by Gori [12]. All the input values corresponding to the descriptor under evaluation were zeroed. Models for the reduced data sets are developed.
- *Step 4*: The initial data set was split in the MOA classes 1 and 5 (already easy to model by well known QSARs) and classes 2-4, more difficult to analyze through classical approaches. The idea is to insert in the future development of the hybrid intelligent system NIKE, the explicit knowledge about classes 1 and 5 (specific QSARs), as equivalent fuzzy rules, and the trained ANN models for the rest.

V. Data analysis

Both, the input data set values and the output ones, were normalized and fuzzified with respect of the 225 phenols descriptors values. The input data set consists of 43 descriptors, while the output is toxicity: $\log(1/IGC_{50})$.

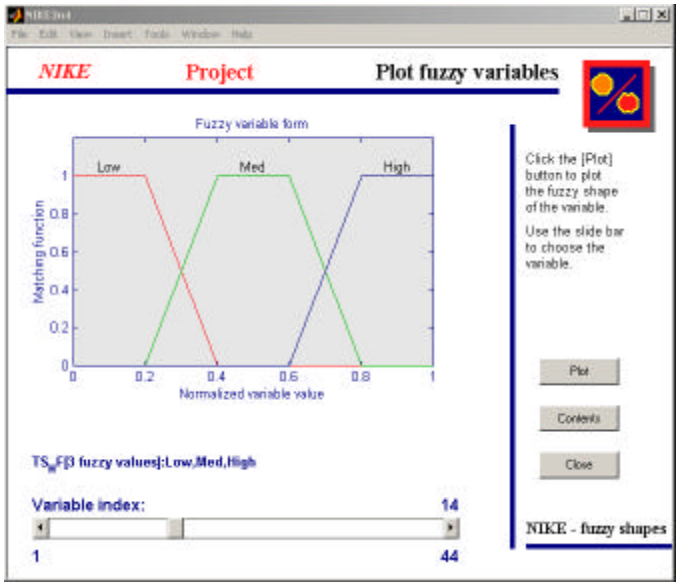


Fig. 2. Fuzzy shapes of a generic descriptor D_i.

For the FNN processing, the membership functions were considered to simplify the calculus and to reduce the number of involved input neurons. All the descriptors followed a fuzzification trapezoidal-triangular-trapezoidal (fig. 2). Consequently, the linguistic variables considered for descriptors inputs are characterized by the term sets:

$$D_i = \{Low, Med, High\}, i = 1..43 \quad (5)$$

The fuzzy shapes of the normalized values of the toxicity considered as linguistic variable are presented in fig. 3, while the terms set is:

$$\log(1/IGC50) = \{VeryLow, Low, Medium, High, VeryHigh\} \quad (6)$$

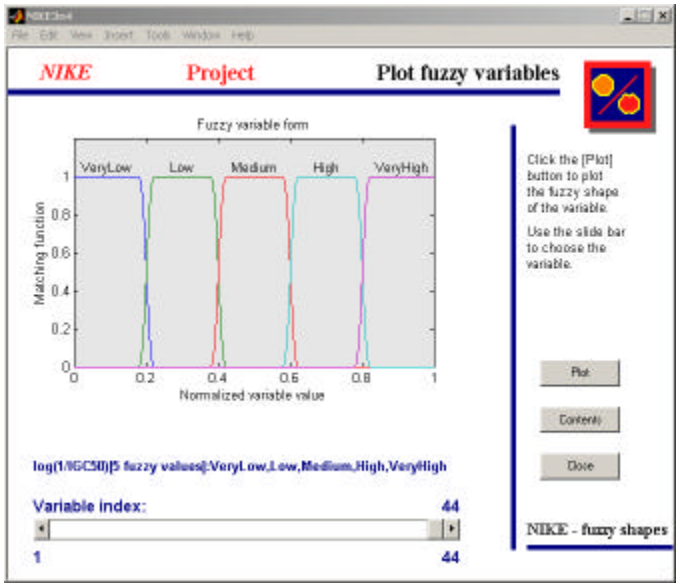


Fig. 3. Fuzzy shapes of the output linguistic variable *Toxicity* (log(1/IGC50)).

Five levels of toxicity are defined for the normalized $\log(1/IGC_{50})$: *VeryLow* (0-0.2), *Low* (0.2-0.4), *Medium* (0.4-0.6), *High* (0.6-0.8), and *VeryHigh* (0.8-1). The slopes of the shapes were considered in order to interpret the outputs as classification or as continuous values. The membership functions shapes could be chosen from the list of: *Bell*, *Gaussian*, *Pi*, *S*, *Z*, *Triangular*, *Trapezoidal*, and *Sigmoidal*.

A. *Data Base Preparing*

The whole set of available patterns was divided in two independent sets, each one of them having its own task in the model training and testing processes (table I). A pattern is defined as a vector of values of the input features (selected descriptors) and values of the output, toxicity of phenols.

The training set was used for the adjustment of the connections of the neural and neuro-fuzzy networks with backpropagation (traingdx) algorithm; *traingdx* is a network training function that updates weight and bias values according to gradient descent momentum and an adaptive learning rate. The testing set was used for testing both, the trained neural and neuro-fuzzy networks. In order to determine the performance of the overall best model, the same testing set was used as a production set of data.

TABLE I

THE DISTRIBUTION OF TESTING AND TRAINING SETS.

Tox. / MOA	VeryLow	Low	Medium	High	VeryHigh
MOA=1: 153 cases	3+8	14+34	16+36	12+23	2+5
MOA=2: 18 cases	0+0	0+1	1+4	2+5	1+4
MOA=3: 27 cases	0+1	1+2	3+8	2+7	1+2
MOA=4: 23 cases	0+0	0+0	4+9	2+7	0+1
MOA=1: 4 cases	0+0	0+0	0+1	1+1	1+0
Total:	3+9	15+37	24+58	19+43	5+12

The values are: (number of testing values)+(number of training values).

The data set (225 compounds) was divided paying attention to conserve the distribution of the 5 classes of MOA, as well as the five fuzzy values of the output linguistic variable (fig. 4). The algorithm was a 70-30 partitioning, as it is used in the majority of such kind of comparative tests between predictive algorithms: 159 training cases and 66 testing cases (table I).

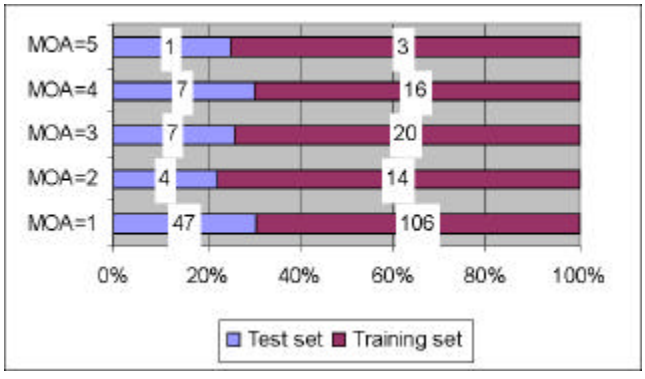


Fig. 4. The distribution of training/testing sets against the MOA classes.

VI. THE IMPLICIT KNOWLEDGE MODELS

The neuro-fuzzy network is a multi-layered structure with the 43x3 above described fuzzy inputs and 5 fuzzy output neurons, the toxicity linguistic variable $\log(1/IGC_{50})$. The number of hidden neurons parameterized the neural and neuro-fuzzy networks: a medium number of hidden units is desirable.

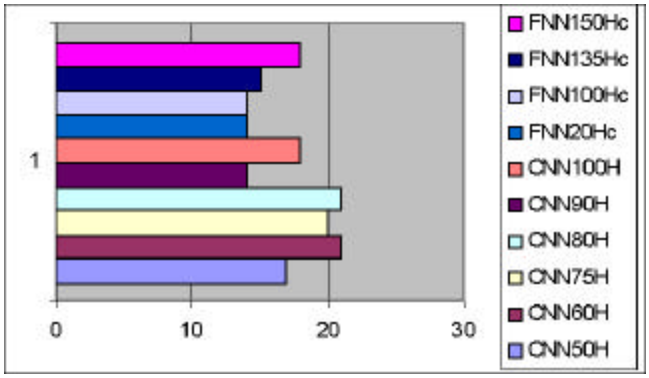


Fig. 5. The number of outliners with an absolute error prediction greater than 0.15, for the different IKM-CNN and IKM-FNN (step 2).

For an ANN, to be able to generate closed decision regions, the minimum number of hidden units must be greater than the number of input units [12]. To derive the maximum number of hidden units in the network, results based on Kolmogorov's theorem were used. Hecht-Neilson [13][17] established that the maximum number of hidden neurons needed to represent any function of *n* variables is less than twice the number of inputs 2x*n_input*+1.

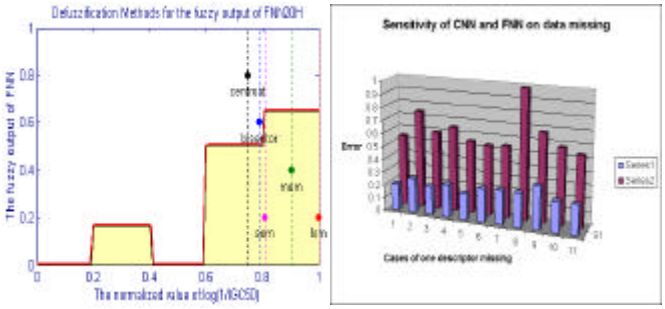
The backpropagation algorithm was used for training [21]. A learning rate of 0.7 and a momentum term of 0.9 were used (a relatively high learning rate ensures rapid finding of the error function minimum, and a high momentum term prevents too many oscillations of the error function). The networks were trained up to 5000 epochs, giving an error about 0.005 (*step 2*). The same context was applied for CNN training. The most relevant rules were extracted from the IKM structures [14][15], using Relative Rule Strength, or Causal Index Method for FNN implementation, respectively interactive fuzzy operators [19] for IKM-CNN implementation. Finally, the 90 hidden neurons IKM-CNN (CNN90H), and 20 hidden neurons IKM-FNN (FNN20H) were considered (fig.5).

The list of the most trusty fuzzy rules extracted from the 20 hidden neurons FNN20H is:

```
IF TS_HOMO is:Low THEN log(1/IGC50) is:Low
(100.00%)
IF QS_Gmin is:High THEN log(1/IGC50)
is:Medium (83.24%)
IF QS_MaxNeg is:Med THEN log(1/IGC50)
is:Low (82.27%)
IF TS_Dip is:Med THEN log(1/IGC50)
is:Medium (79.13%)
```

The performances of the models were evaluated on the testing data set. The outputs of the explicit and implicit modules, viewed as an inference results, are computed for a given testing pattern. A typical model performance is shown in fig. 6a (predicted value: 0.74745, the real toxicity: 0.75902).

Consequently, the connectionist approaches were used as descriptors correlation test tool (*step 3*). The descriptors for the reduced data set are: *CX_EPM20*, *MO_Dmax*, *MO_Amax*, *TS_LUMO*, *TS_HOMO*, *QS_SHHBd*, *QS_SHBa*. Good results were obtained for this step, with the major observation that all the connectionist networks were more difficult to train, and the number of outliners was bigger (fig. 7).



(a) (b)

Fig. 6. (a) The prediction of toxicity as a fuzzy inference on IKM-FNN. (b) The sensitivity of CNN (back) and FNN (front) on data missing, relative to the error of prediction.

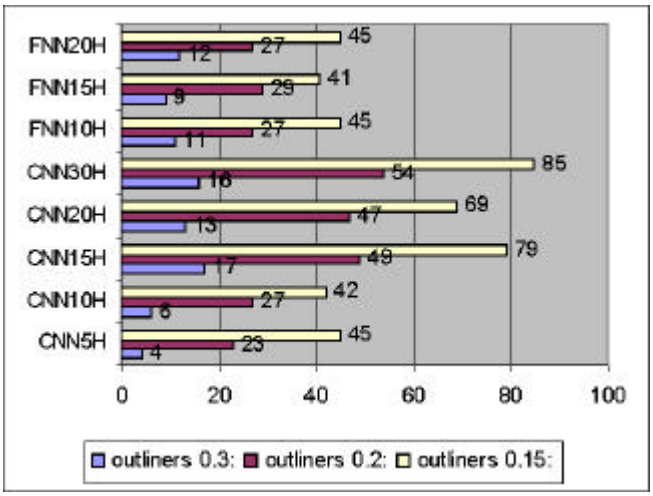
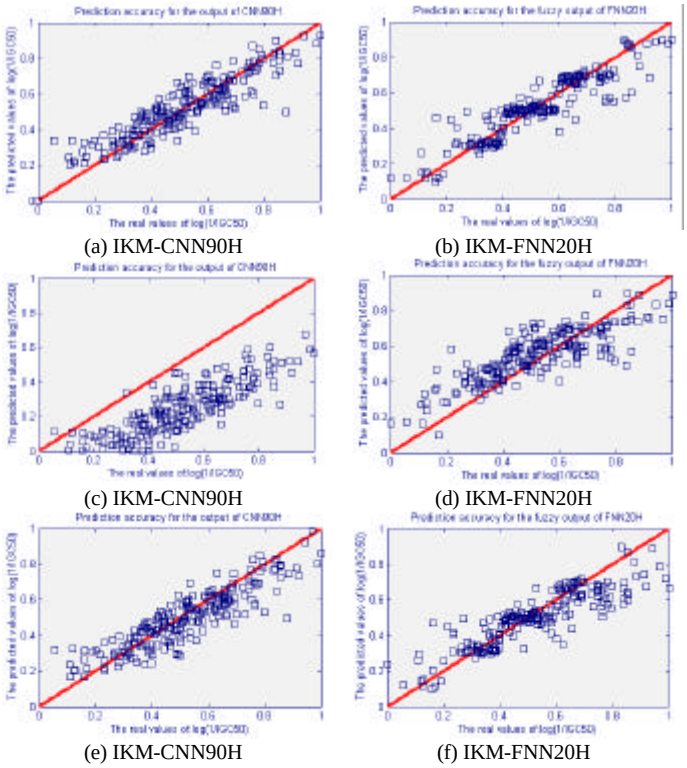


Fig. 7. The number of outliners with an absolute error prediction greater than 0.15, for the IKM-CNN and IKM-FNN, the reduced data set case (step 3).

The most spectacular and immediate result, is the consequence of the two developed models applied in the steps 1-3, for the already trained FNN20HN and CNN90HN, for the descriptors significance study. One of the important tasks in phenols analysis is the examination of the relevance of the descriptors in the general context of toxicity prediction, in a closed correlation to MOA. This is a tedious task, more a data mining one, considering the big number of descriptors and compounds to be studied. With NIKE, modifying the test data set, according to [12], through zero columns on studied descriptor, we obtained two important results (fig. 8):

- The IKM-CNN models are more sensible to the noisy data (fig.6b), as described, which make them a very important indicator of the significance of the descriptors to toxicity and MOA correlation. As depicted in the fig. 8, CNN demonstrates two behaviors about missing descriptor, other than a normal small increasing of absolute error prediction: a translation of the predictions (fig. 8c), which announce a linear dependence with the absent descriptor, or a proportional magnify of the error, consequence of a nonlinear relation between some of the current inputs.
- The IKM-FNN models, as already known from other applications, are more robust to noisy data (fig. 8d,f): this recommends it as more suitable for toxicity prediction task.



(a) IKM-CNN90H (b) IKM-FNN20H

(c) IKM-CNN90H (d) IKM-FNN20H

(e) IKM-CNN90H (f) IKM-FNN20H

Fig. 8. Performance validation (predicted data set versus real data values) for: (a,b) complete test data set; (c,d) significant (D3: ACD_LogD); (e,f) not significant (D11: MO_Amax) descriptor missing in test data set.

VII. Conclusions and Future Work

Classification of the toxicity correlated to MOA for phenols requires a high degree of experience from computational chemistry experts. Several approaches were described to generate suitable computer-based classifiers for these patterns. The described classifiers range from a QSAR to a neuro-fuzzy system, through classical ANN architectures (table II). The main problem regarding the symbolic approach is the difficulty of improvement and correlation analysis, due to the existence of limitations in knowledge elicitation, as this is a complex domain. Several implicit knowledge models with different number of neurons on the hidden layer were trained and analyzed for better results.

TABLE II
THE DISTRIBUTION OF TESTING AND TRAINING SETS.

.	QSAR2	QSAR3	QSAR4	CNN90H	FNN20H
Accuracy1	0.5622	0.5660	0.5471	0.9377	0.9377
Accuracy2	0.7283	0.7433	0.7358	0.9822	0.9511
Accuracy3	0.9471	0.9433	0.9433	0.9955	1.0000

The values are: Accuracy1 is relative to absolute error>0.15, Accuracy2: to absolute error>0.2, Accuracy3: to absolute error>0.3.

Future work will be carried out following the outlined new possibilities of neural and neuro-fuzzy integration of implicit knowledge with explicit QSARs into the hybrid system NIKE.

VIII. Acknowledgments

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