Neuro-Fuzzy Knowledge Representation for Toxicity Prediction of Organic Compounds

Dan Neagu[1], Emilio Benfenati[2], Giuseppina Gini[3], Paolo Mazzatorta[2], Alessandra Roncaglioni[2]

Abstract. Models based on neural and neuro-fuzzy structures are developed to represent knowledge about a large data set containing chemical descriptors of organic compounds, commonly used in industrial processes. The neuro-fuzzy models here proposed include both, QSARs and original numerical values. The developed approaches use various techniques to insert knowledge by training, and to map rules in neuro-fuzzy structures. These possibilities are evaluated and we show that the combination of neuro-fuzzy models, and strategies to insert data in the developed connectionist structures, improve over individual models for toxicity prediction.

1 INTRODUCTION

We are becoming increasingly aware of the need to understand and predict the consequences of chemicals to human health and the environment. The huge number of compounds to be studied makes this especially challenging. In toxicity prediction there are many variables: the toxicological endpoint, the number of molecules in the data set, the homogeneity of the data set, the methods to describe the physico-chemical properties of the molecules, the computational algorithm to produce the statistical relationship, and the validation method.

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. 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 [7], and applied to predict phytotoxicity. A study on the usage of fuzzy logic for descriptors modeling has been presented by Exner [5]. In all cases, the neural network approach of the toxicity prediction is restricted to crisp modeling of data.

In recent years, the neuro-fuzzy systems have drawn increasing research interest [3][6][12][13]. A special focus in neuro-fuzzy processing is to develop some universal computing models, easy customizing to meet wide subjects of particular specifications [10]. For this purpose, it is indispensable to identify generic-processing modules, performing general computations on fuzzy sets, and specific knowledge representation. In this paper, connectionist models based on the MAPI formal neuron [20] are proposed for knowledge representation for toxicity prediction. In section 2, the toxicity prediction problem, and the QSAR problem are emphasized, and some original developed models are presented. In section 3, aspects for data analysis are reviewed.

[1] University "Dunarea de Jos" of Galati, Romania.
[2] Istituto di Ricerche Farmacologiche "Mario Negri" Milano, Italy.
[3] Politecnico di Milano, Italy.

In section 4 is presented the neuro-fuzzy knowledge representation applied for toxicity prediction. The problem is modeled with NIKE (Neural explicit&Implicit Knowledge inference system), a hybrid intelligent system (developed by the first author), based on modular neural/ neuro-fuzzy networks [9][21]. The results show that, combining various models about the same problem will gain better predictions against toxicity (section 5). The paper is ending with conclusions and ideas on future work.

2 DATA DESCRIPTION

The U.S. Environmental Protection Agency [22] provided to build up a data set, starting from a revision of experimental data from literature, referred to acute toxicity 96 hours (LC_{50}), for fathead minnow (*Pimephales promelas*). An accurate analysis of the experimental information will permit to associate besides a mode of toxic action (MOA) to each compound. The data set contains 568 organic compounds, commonly used in industrial processes. This is a large set of compounds belonging to different chemical classes: a positive characteristic is the homogeneity and reliability of this toxicological data. A large number of descriptors was calculated by Istituto di Ricerche Farmacologiche "Mario Negri".

2.1 Molecular descriptors

A set of about 150 descriptors was examined. They were calculated by different software (Hyperchem 5.0-Hypercube Inc., USA, CODESSA 2.2.1-SemiChem Inc., USA, Pallas 2.1-CompuDrug, Hungary). The descriptors are classified (according to CODESSA [11][4][24]), in: *constitutional descriptors* (34), depending on the number and type of atoms, bonds and functional groups; *geometrical descriptors* (14), which give molecular surface area and volume, moments of inertia, shadow area, projections and gravitational indices; *topological descriptors* (38), which are molecular connectivity indices, related to the degree of branching in the compounds; *electrostatic descriptors* (57), such as partial atomic charges and others depending on the possibility for some sites in the molecule to form hydrogen bonds; *quantum–chemicals descriptors* (6), i.e. total energy of the molecule, the energies of the lowest unoccupied and highest occupied orbital (*HOMO* and *LUMO*), ionisation potentials, heat of formation, etc.; and *hydrophobic descriptors* (7), which are *logP, logD*, the expression of lipophilicity of the molecule at various pH.

A pre-processing phase is necessary to make a selection of the variables, to describe better the molecules. Some of these descriptors doesn't add information, but increase the noise making more complex the result analysis. Furthermore using a relatively low number of variables the risk of overfitting is reduced. The descriptors selection was obtained by Principal Components Analysis (PCA) and Correlation Analysis techniques [24] (table 1).

2.2 The QSAR approach

The quantitative structure-activity relationship method has been applied to chemical design and toxicity prediction tasks. Finding a QSAR is essentially a regression process and, historically, linear regression methods have been used. Some regression-based models results in exhibiting instability when trained with noisy data.

For the current set, three original QSAR equations were developed at Istituto "Mario Negri", from a different number of descriptors, using the PLS (Partial Least Squares) algorithm. The variables were normalized using autoscaling procedure for PLS: data were centred and standard deviation made equal to 1.

Two models were obtained with five parameters (QSAR1, 2), while the third model is dependent on 2 descriptors (QSAR3):

$$\log(1/LC_{50}) = 0.7919 + 0.09772*QM6 - 0.2045*C35 + 0.1276*G2 - 0.3509*pH9 - 0.3879*logP \quad (1)$$

$$\log(1/LC_{50}) = 0.8779 + 0.1385*QM6 - 0.06703*C35 - 0.02937*T6 - 0.06165*G12 - 0.6854*logP \quad (2)$$

$$\log(1/LC_{50}) = 0.8237 + 0.1711*QM6 - 0.7974*logP \quad (3)$$

where *logP* is the octanol-water partition coefficient calculated with Pallas software, *QM6 (LUMO)* is the energy of the lowest unoccupied molecular orbital. LC_{50} is expressed in mmoles/l.

In figure 1 is reported the observed versus predicted values for LC_{50} relating to QSAR2, as generated by the specific software used. All the models identified a restricted number of 5 outliers that doesn't satisfy the normal distribution required for residuals. Discharging these compounds, the performance increased reaching accuracy values (for an absolute error level of 0.1) around 70%. Large part of the compounds belong to reactive mode of action.

3 DATA ANALYSIS

Both, the input data set values and the output ones, were fuzzified with respect of the 568 organic compounds descriptors values. The input data set consists of the 17 descriptors (table 1), while the output is toxicity: $\log(1/LC_{50})$.

For fuzzy processing, the membership functions were considered to simplify the calculus and to reduce the number of input neurons: all the descriptors followed a trapezoidal fuzzification. The linguistic variables considered for descriptors, and for toxicity, are characterized by the term sets:

$$D_i = \{Low, Med, High\}, i = 1..17 \quad (4)$$

$$\log(1/LC50) = \{VeryLow, Low, Medium, High, VeryHigh\} \quad (5)$$

Five levels of toxicity are defined for the normalized $\log(1/LC_{50})$: *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 membership functions shapes could be finally chosen from the list of: *Bell*, *Gaussian*, *Pi*, *S*, *Z*, *Triangular*, *Trapezoidal*, and *Sigmoidal*.

3.1 Data preparation

The whole set of available patterns was divided in two independent pattern subsets, each one having its own task in the model training and testing processes (table 2). A pattern is defined as a vector of values of the inputs (descriptors) and values of the output, toxicity. The training set was used for the adjustment of the connections of the neural and neuro-fuzzy networks with the backpropagation [21] (*traingdx*) algorithm.

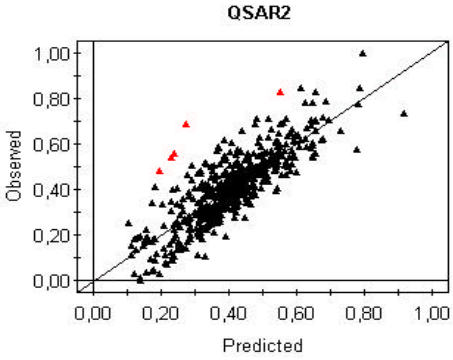


Figure 1. Observed versus predicted values (QSAR2).

Table 1. The selected descriptors.

DESCRIPTORS	CODE
Total Energy (kcal/mol)	*QM1*
Heat of Formation (kcal/mol)	*QM3*
LUMO (eV)	*QM6*
Relative number of N atoms	*C9*
Relative number of single bonds	*C24*
Molecular weight	*C35*
Kier&Hall index (order 0)	*T6*
Average Information content (order 1)	*T22*
Moment of inertia B	*G2*
Molecular volume	*G10*
Molecular surface area	*G12*
TMSA Total molecular surface area	*E13*
FPSA-2 Fractional PPSA (PPSA-2/TMSA)	*E24*
PPSA-3 Atomic charge weighted PPSA	*E28*
FPSA-3 Fractional PPSA (PPSA-3/TMSA)	*E31*
logD pH9	*pH9*
logP	*logP*

Table 2. The distribution of testing + training sets.

Toxicity	VeryLow	Low	Medium	High	VeryHigh
Testing cases	15	66	72	12	2
Training cases	35	156	173	34	3
568 cases	50	222	245	46	5

The network training function *traingdx* updates weight and bias values according to gradient descent momentum and an adaptive learning rate. The same set was used for both, the trained neural and neuro-fuzzy networks.

The data set (568 compounds) was randomly divided, paying attention to conserve the distribution of the five fuzzy values of the output linguistic variable. The algorithm was a 70-30 partitioning, as it is used in the majority of comparative tests for predictive algorithms: 401 training cases and 167 testing cases (table 2).

4 NEURO-FUZZY STRUCTURES FOR TOXICITY REPRESENTATION

The proposed system, NIKE, automates the tasks involved in this process, from the data representation for toxicity measurements, to the prediction of toxicity for given new input. It also suggests how the fuzzy inference produced the result, when required [16][17].

Consequently, we define the *implicit knowledge* as the knowledge represented by neural/ neuro-fuzzy networks, created and adapted by a learning algorithm. We define the *explicit knowledge* as a knowledge base represented by neural networks, which are computationally identical to the I/O relations set, and are created by mapping the given fuzzy rules into hybrid neural networks.

Table 3. Comparison of the accuracy prediction for neural/ neuro-fuzzy structures: the maximum absolute error.

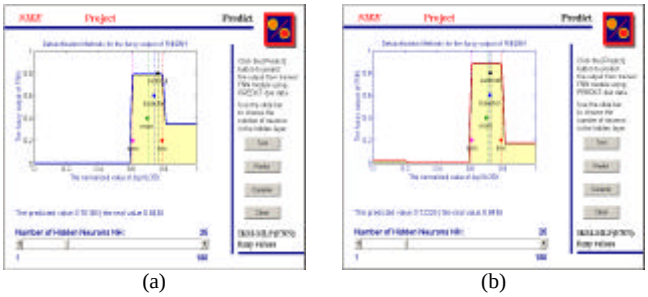
Toxicity	QSAR3	CNN	CNN*	FNN	FNN*
VeryLow	0.2225	0.2425	0.2053	0.2133	0.2086
Low	0.1704	0.1637	0.1662	0.1483	0.1612
Medium	0.3023	0.3181	0.3343	0.2502	0.2551
High	0.3659	0.4451	0.4359	0.4030	0.3496
VeryHigh	0.2726	0.2713	0.2971	0.3258	0.3785

CNN*, FNN*: pre-trained/retrained neural networks.

Table 4. Comparison of the accuracy prediction for neural/ neuro-fuzzy structures: number of cases predicted with absolute error lower than 0.1

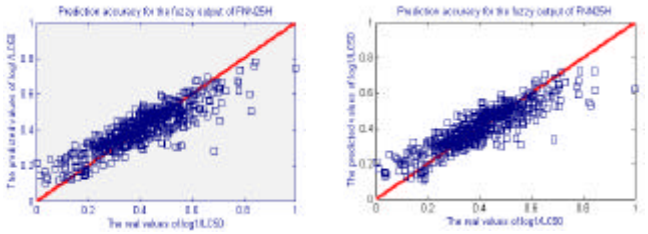
Toxicity	QSAR3	CNN	CNN*	FNN	FNN*
VeryLow	24	24	29	30	30
Low	189	196	203	205	201
Medium	210	200	198	212	219
High	30	28	26	27	31
VeryHigh	3	1	2	2	0

CNN*, FNN*: pre-trained/retrained neural networks.



(a) (b)

Figure 2. Comparing FNN during the application of concept support technique: fuzzy inference result (real value 0.8436, FNN prediction 0.76189 (a), FNN* prediction 0.72325 (b).



(a) (b)

Figure 3. Comparing FNN during the application of concept support technique: predicted versus observed values for FNN (a), and FNN* (b).

4.1 The implicit knowledge representation

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 [2][16]. The MLP model is also used to compare the overall performance of the neurosymbolic system with neuro-fuzzy and QSAR approaches [18].

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 [6], and a defuzzification layer. 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 [6][8][10].

Two steps were used to insert QSAR information in the implicit knowledge representation: This strategy follows an updated form of *concept support techniques* [19], viewing the method used to insert a priori knowledge [14]. The pre-training phase is based on a data collection generated by a selected QSAR function. Then the model is trained with the original data set. The specific results are compared below with the results coming from the normal training procedure, based on a random initialization of the weights of the neural networks. The neural and neuro-fuzzy networks resulted through QSAR insertion in a pre-training phase were retained for further combination of modules. The results in accuracy of prediction (tables 3 and 4) are similar, and better than QSARs. The method is based on inserting the given QSAR2 predictions, and learning the training samples.

For the prediction accuracy, error is calculated as the predicted value from the model minus the actual value, for all observations. The absolute value of each error was then taken. The maximum absolute error was calculated across all 568 observations for each fuzzy value of toxicity (table 3). A second measure to compare the models is determining how many of the 568 observations were high accurately predicted (absolute error less than 0.1), relative to the number of specific cases (table 4). 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. The chosen structures were 23 hidden neurons for CNN, and 25 hidden neurons for FNN.

Since the results are moderately better, the pre-training method is suitable for modular networks in which the expert is interested to insert through the initialization of the start point of learning, some knowledge about the domains with an increased number of outliers. An example of the improving result of prediction inference (for a given test record) is given in figure 2, and the performance for trained FNN and FNN* is shown in figure 3.

4.2 The explicit knowledge representation

The capabilities of MAPI-based neural network to perform fuzzy computing [20] are used to implement the explicit knowledge module. The neural reasoning engine is accorded to multiple premises fuzzy rules using fuzzy connectives.

The extended version of Modus Ponens, proposed in [25]:

$$\begin{array}{l} \text{IF } X_1 \text{ is } A_1 \wedge \ldots \wedge X_j \text{ is } A_j \text{ THEN Y is B} \\ \underline{(X_1 \text{ is } A'_1) \wedge \ldots \wedge (X_j \text{ is } A'_j)} \\ \text{Y is B'} \end{array} \qquad (6)$$

was used to infer results from the developed structures, equivalent to the QSARs given above. This process is performed in four steps: 1) Matching (the compatibility between A' and A), 2) Aggregation (based on triangular norm), 3) Projection: the compatibility of (Y is B') with (Y is B) is obtained as an aggregation function; 4) Inverse-Matching and Defuzzification, performed at the MAPI axonic terminals. Aggregation and projection are performed by generalized aggregative neurons, involving triangular norms or co-norms in Multi Purpose Neural Networks (MPNN) [3][6][20]. There are two different types of relations mapped in MPNNs: empirical fuzzy rules about the descriptors, and QSARs.

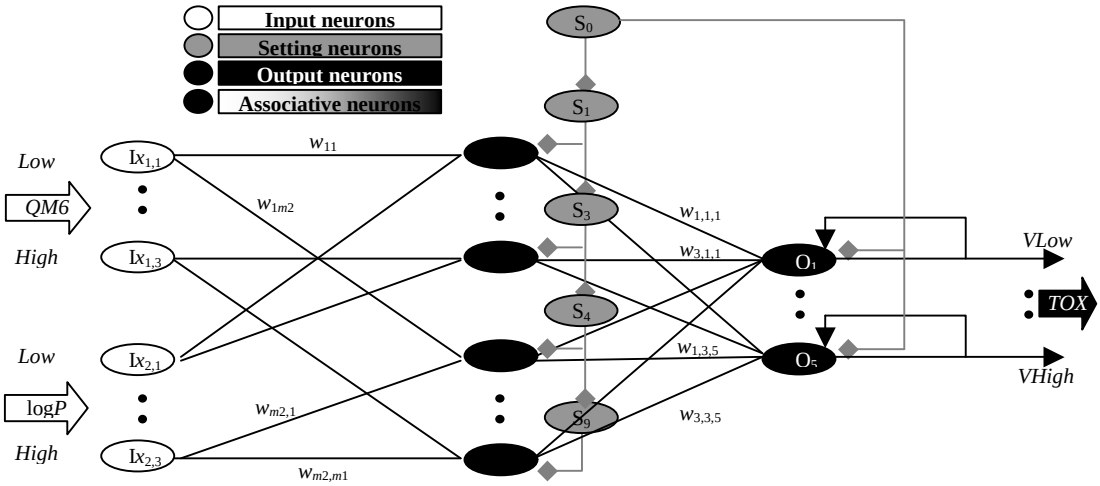


Figure 4. MAPI-based neuro-fuzzy network equivalent with the fuzzy Rule 1 (eq. 7) with two premises.

4.3 Mapping Fuzzy Rules into MPNN

The fuzzy rules are described as a discrete fuzzy rule-based system (DFRBS) [6][20], in order to be mapped in MPNNs. The intrinsic representation of explicit knowledge is based on MAPI fuzzy neurons. The numerical weights corresponding to the connections between neurons are computed using Combine Rules First Method or Fire Each Rule Method [3][6]. We used to insert a single fuzzy rule (Rule 1), an empirically developed relation between toxicity and two of the most important descriptors: *logP* and *QM6*:

IF (*QM6* is *Low*) AND (*logP* is *High*)
THEN log(1/LC_{50}) is *Low* (7)

The implementation of the explicit multi-premise rule (7) in the equivalent neuro-fuzzy network using MAPI neurons [15][17] with fuzzy abilities is shown in figure 4. The weights between input/ associative, respective associative/output neurons are processed according to [15][20]; the setting neurons S_i, i=0,1,...,3*3, provide the synchronism $H_{11}<H_{3,1}<H_{1,3}<H_{3,3}$ ("<" means *fires before*).

For the cases requiring explicit QSAR forms, the approximators given by implicit knowledge modules, will be replaced, following the same mapping procedure as described above, by the explicit knowledge module implementing a first-order Sugeno fuzzy model [23]. The output of MPNN will be a single MAPI neuron, acting as an arithmetical device [20]. This mechanism permit the implementation of neuro-fuzzy modules, equivalent with QSARs.

4.4 The integration of the developed structures: Fire Each Module Strategy

Fire Each Module Strategy (FEM) strategy is the simplest mode to integrate IKM and EKM within the general context of fuzzy processing. A general form of this modular structure is proposed in [9] and shown in figure 5. After off-line training applied to implicit neuro-fuzzy module, the general output of the system is composed as a T-conorm [16][25] of fuzzy outputs of each module: the four-layered IKM structure for global network and the EKM (implemented using combine rules first or fire each rule method).

The system is viewed as equivalent to a set of given fuzzy rules: the overall output is computed using firing (implicit and explicit) rules first method [3][6][17]. The method of combining the specific membership degrees provided by both, IKM and EKM structures, would be done by an aggregating operator, in particular the max fuzzy operator. In the hidden aggregative layer (AL), all the weights are set to one, and the neurons aggregate the computed membership degrees from the implicit, and explicit modules. In our case, the average of the outputs of all the modules is processed by AL+MAPI defuzzifier (figure 5). The final neuron is a MAPI device, which computes the crisp value of the output.

The final structure of the modules is based on the CNN* (the pre-trained version), FNN* (as implicit knowledge structures), and QSAR2 and QSAR3 (as explicit knowledge structures). The final output of the system (based on FEM strategy) is the averaged output of the modules. The overall results are depicted in table 5 (the number of the well predicted cases, and the accuracy of prediction) and figures 6, 7.

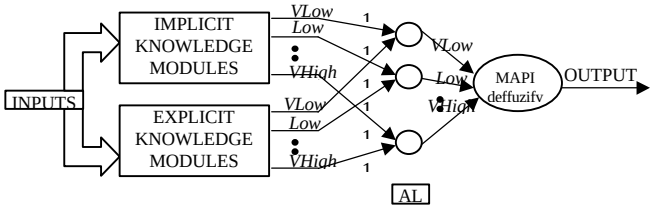


Figure 5. Integration of explicit and implicit knowledge modules in the global architecture of NIKE.

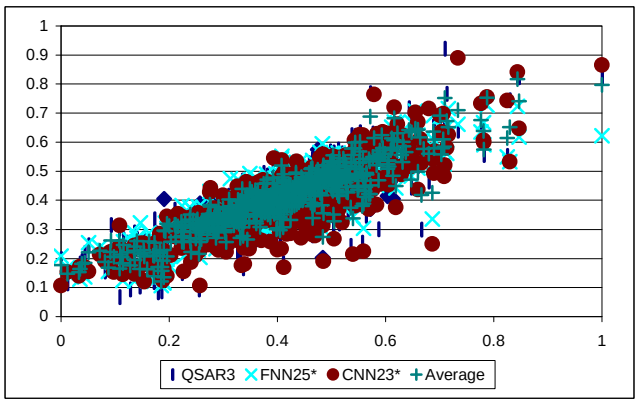


Figure 6. Observed versus predicted values for QSAR3, FNN*, CNN* and the averaging FEM combination.

Table 5. General results for accuracy of prediction (absolute error <0.1).

QSAR2	QSAR3	CNN	CNN*	FNN	FNN*	FEM
447	456	449	458	476	481	507
78.69%	80.28%	79.05%	80.63%	83.80%	84.68%	89.26%

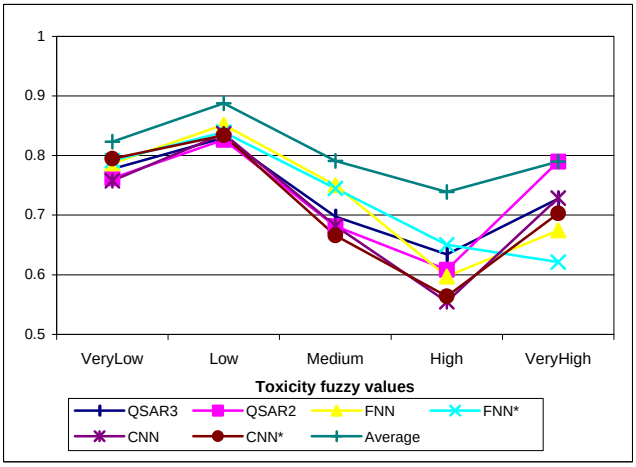


Figure 7. The accuracy of toxicity prediction, by classes (fuzzy values).

5 CONCLUSIONS

Our study wants to contribute to the understanding of the possibilities to represent the knowledge about the toxicity of industrial organic compounds. The present approach represents an example of a hybrid system, combining artificial neural networks (ANN) and QSARs, on the basis of neuro-fuzzy modules implementation. The proposed neuro-fuzzy knowledge representation gives an encouraging alternative to the stochastic models. We proved these kinds of models are able to learn from sophisticated collections of descriptors about industrial organic compounds. In addition, they are capable of representing knowledge acquired from human experts in order to improve the prediction results. Another important feature of our model is its validation with a large test set, which shows a certain capability to generalize.

Classification of the toxicity correlated to the descriptors for organic compounds 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. 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.

The presented evaluation shows that neuro-fuzzy architectures can learn the describing patterns of organic compounds. Further, ANNs can be used to predict the behaviour of such chemicals, and to classify under a toxicity scale. The evaluation shows that these predictions are about 10% more accurate than those of the classical approaches. This offers the possibility of improving the performance of experts by using the neuro-fuzzy combined modules to guide and refine further decisions.

We also evaluated the use of ensembles of ANNs to improve on the error of an individual net on this task. Significant improvement was found, since explicit knowledge was inserted in the connectionist system. This suggests that the 568 training samples used in this study do not provide a best coverage of the problem domain, which is split in contiguous sub domains (since a good model, that does not overfit to training data, could be built with just one ANN. 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.

ACKNOWLEDGMENTS

This work is partially funded by the E.U. under the contract HPRN-CT-1999-00015.

REFERENCES

[1] R. Adamczak, W. Duch, *Neural networks for structure-activity relationship problems*, in Proceedings of the 5th International Conference on Neural Networks and Soft Computing, Zakopane, 669-674, (2000).

[2] J.M. Benitez, J.L. Castro, I. Requena, "Are ANNs Black Boxes?", *IEEE Transactions on Neural Networks*, **8**/**5**, 1157-1164, (1997).

[3] J.J. Buckley, and Y. Hayashi, 'Neural nets for fuzzy systems', *Fuzzy Sets and Systems*, **71**, 265-276, (1995).

[4] J.C. Dearden, 'Physico-chemical descriptors', in *Practical applications of QSARs in environmental chemistry and toxicology*, (Karcher, Devilers, Eds), Kluwer, Dordrecht, 25-29, 1990.

[5] T.E. Exner, and J. Brickmann, 'New Docking Algorithm Based on Fuzzy Set Theory', *Journal Molecular Modelling*, **3**, 321-324, (1997).

[6] R. Fuller, *Introduction to Neuro-Fuzzy Systems*, Advances in Soft Computing Series, Springer-Verlag: Berlin, 1999.

[7] G. Gini, 'Predictive Toxicology of Chemicals: Experiences and Impact of AI Tools', *AI Magazine*, AAAI Press, **21**/**2**, 81-84, (2000).

[8] S. Haykin, *Neural Networks: A Comprehensive Foundation*, New York: Macmillan, 1994.

[9] R.A. Jacobs, M.I. Jordan, and A.G. Barto, 'Task de-composition through competition in a modular connectionist architecture: The what and where vision tasks', *Cognitive Science*, **15**, 219–250, (1991).

[10] J.-S. R. Jang, C.-T. Sun, and E. Mizutani, *Neuro-Fuzzy and Soft Computing*. Englewood Cliffs, NJ: Prentice-Hall, 1997.

[11] A.R. Katritzky, V.S. Lobanov, M. Karelson, *CODESSA Comprehensive Descriptors for Structural and Statistical Analysis. Reference Manual*, version 2.0, Gainesville, 1994.

[12] B. Kosko, 'Fuzzy systems are universal approximators', in *Proceedings of the IEEE Int'l Conf. Fuzzy Systems*, San Diego, CA, 1153–1162, (1992).

[13] C.T. Lin, C.S. Lee, *Neural Fuzzy Systems: A Neuro-Fuzzy Synergism to Intelligent systems*. Englewood Cliffs, NJ: Prentice-Hall, 1996.

[14] C.-D. Neagu, M. Negoiþã, V. Palade, 'Aspects of Integration of Explicit and Implicit Knowledge in Connectionist Expert Systems', *Procs of the 6th Int'l Conf on Neural Information Processing ICONIP'99* (T. Gedeon, et al, Eds.), Perth, **2**, 759-764, (1999).

[15] C.-D. Neagu, V. Palade, 'Fuzzy Computing in a Multi Purpose Neural Network Implementation', *Procs. of the Int'l Conf 6th Fuzzy Days in Dortmund*, (B. Reusch, Ed.), Springer Verlag, 697-700, (1999).

[16] C-D. Neagu, V. Palade, 'An interactive fuzzy operator used in rule extraction from neural networks', *Neural Network World Journal*, **10**/**4**, 675-684, (2000).

[17] C.-D. Neagu, N.M. Avouris, E. Kalapanidas, V. Palade, 'Neural and Neuro-fuzzy Integration in a Knowledge-based System for Air Quality Prediction'', *Applied Intelligence Journal*, Kluwer, (accepted, 2001).

[18] C.-D. Neagu,, A.O. Aptula, G. Gini, 'Neural and Neuro-Fuzzy Models of Toxic Action of Phenols', Procs. IEEE IS2002, (submitted, 2002).

[19] E. Prem, M. Mackinger, G. Dorffner, 'Concept Support as a Method for Programming Neural Networks with Symbolic Knowledge', Tech. Rep. OEFAI04/1993, Austrian Research Inst. for AI, (1993).

[20] A.F. da Rocha, *Neural Nets: A Theory for Brains and Machines*, Lecture Notes in Artificial Intelligence, Springer-Verlag, 1992.

[21] D.E. Rumelhart, and J.L. McClelland, Parallel Distributed Processing, Explanations in the Microstructure of Cognition, MIT Press, 1986.

[22] C.L. Russom, S.P. Bradbury, S.J. Broderius, D.E. Hammermeister, R.A. Drummond. 'Predicting modes of toxic action from chemical structure: acute toxicity in the fathead minnow (*Pimephales promelas*)', *Environ. Toxicol. Chem.*, **16**, (1997).

[23] M. Sugeno, G.T. Kang, 'Structure identification of fuzzy model', *Fuzzy Sets and Systems*, **28**, 15-33, 1988.

[24] R. Todeschini, *Introduzione alla chemiometria: strategie, metodi e algoritmi per l'analisi e il modellamento di dati chimici, farmacologici e ambientali*. Univ. degli studi Milano, EdiSES, 1998.

[25] L.A. Zadeh, 'The role of fuzzy logic in the management of uncertainty in expert systems', *Fuzzy Sets and Systems*,**11**/**3**, 199-227, (1983).