Neural Modelling for the Condensing Process of the Hydrazides of Sulphonamidated Phenoxy-alchyl Carboxylic Acids with Transitional Metal Salts

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Is is well known that the complexes of phenoxyacetic acids with transitional metals are very interesting due to their broad spectrum of biological and pharmaceutical activities. By condensing the hydrazides with transitional metal salts (Cu, Fe, Cr, Co, Mn), a series of metal complexes are obtained that have been showed to be efficient for treating various diseases. A complete description of metallic complexes synthesis has been made by the means of direct and reversed modelling using an established artificial neural network. The main parameters that influence the process are: molar ratio, temperature and reaction time. The experimental data were employed in the design of the feed forward neural networks in order to predict the yield of the process for different reaction conditions (direct modelling) or the process conditions for a predetermined yield (inverse modelling).

Keywords: phenoxyacetic acid hydrazides, transitional metal salts, neural networks, direct modelling, inverse modelling

Acidic hydrazides and their corresponding condensing products – acylhydrazones - lately catch the eyes of the specialists in organic and inorganic chemistry due to their various biological actions. Their complexes with transitional metals were considered to be very interesting due to their broad spectrum of biological and pharmaceutical activities, such as: anti-cancer, anti-tumour, anti-oxidant and, inhibition of lipid peroxydation [1, 2].

This fact increased our interest in this class of compounds, so we started to study a series of complexes combination with the following general formula:

Me= Cu, Ni, Cd, Co, Sn, Cr, Mn, Fe, Ti;

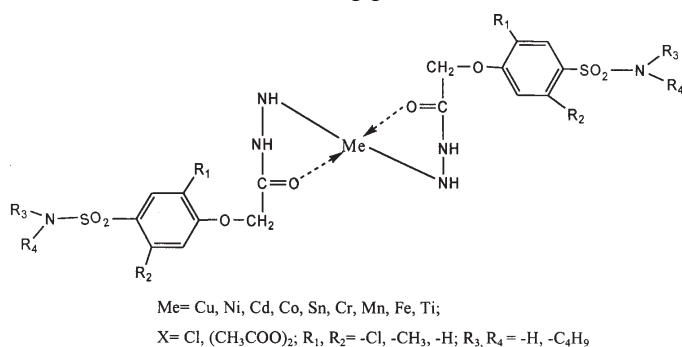X= Cl, $(CH_3COO)_2$; R_1, R_2= -Cl, -CH_3, -H; R_3, R_4 = -H, -C_4H_9

Fig.1. General formula for metal complexes

By condensing the hydrazides with transitional metal salts (Cu, Fe, Cr, Co, Mn), a series of metal complexes are obtained that have been showed to be efficient for treating various diseases [3-5]. Drugs that include Cu complexes are used for inflammatory processes, for treating ulcers, convulsions, cancer and diabetes. Fe is an element required for cells to live and is a constituent of hemoglobin and other ferments included into enzymes. Co is a bioactive element included in B_{12} vitamin and is required in blood formative processes. Cr is necessary for the body to act as a stimulator, participating in nucleic acids transformations, in lipids and fermentative processes. Mn is part of some ferment and activates destructive processes for proteic substances.

The design of control and process monitoring systems is currently driven by a large number of requirements imposed by energy and materials costs and the demands for robust fault-tolerant systems. These considerations introduce extra needs for effective process modelling techniques. Many systems are not amenable to conventional modelling approaches due to the lack of precision, formal knowledge about the system, due to strongly nonlinear behavior, high degree of uncertainty, or time-varying characteristics. The Artificial Neural Network (ANN) has been recognized as a power tool which has the remarkable ability to derive meaningful information from complicated or imprecise data. It can be used to extract patterns and detect trends, which are too complex to be noticed by other computational techniques [6].

The objective of this study is to predict the optimum yield for many working conditions by direct neural network modelling. Further, by inverse neural modelling, for an imposed yield value, the reaction parameters were determined.

Overview on ANN
Neural networks, inspired by the information processing strategies of the human brain, are proving to be useful in a variety of engineering and, especially, chemical engineering applications [6, 7, 11].

ANN may be viewed as paralleled computing tools comprising of highly organized processing elements called neurons which control the entire processing system by developing association between objects in response to their environment. The researches have proposed many architectures of the network. The most popular neural network architecture in engineering investigations is the multilayer perception (MLP) [12, 13].

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A typical MLP, consists of a layer of input neurons being as a data gateway to the network, one or more hidden layers of neurons processing the data received from the input layer and finally a layer of output neurons receiving the processed data and providing the final responses. The network is trained how to correlate the input and output through numerous data in a supervised training process. In this study, the back propagation training algorithm has been utilized in feed-forward the one hidden layer [14]. Back-propagation algorithm, as one of the most well-known training algorithms for multilayer perception, is a gradient descendent technique to minimize the error for a particular training pattern in which it adjust the weights by a small amount at the time [13].

Once the network is trained, it can be tested on a different set of data than that used for training. It is a good approach to divide the given input/output data into two parts: one part ($\geq 70\%$) issued for training, whereas the other part is used for testing the neural network model. The testing data set is reserved to validate the trained network [15].

In order to make the statistical analysis of the performance (prediction capacity) for the neural model, the following parameters have been used:
- Medium Square Error (MSE) that must be as close as possible to zero:

$$MSE = \sqrt{\frac{1}{n+1} \cdot \sum_{i=1}^{n} \left(x_i - \bar{x}\right)^2}$$

and: $\bar{x} = \frac{1}{n} \cdot \sum_{i=1}^{n} x_i$

where:
x_i is the measured value in experiment i (experimental)
n - number of experimental sets
x - average value for experimental results.
- Linear Correction Coefficient, r, between the experimental data and neural predictions that is calculated with the following relation:

$$r = \frac{n \sum_{i=1}^{n} x_{exp,i} \cdot x_{ANN,i} - \sum_{i=1}^{n} x_{exp,i} \cdot \sum_{i=1}^{n} x_{ANN,i}}{\sqrt{n \cdot \sum_{i=1}^{n} x_{exp,i}^2 - \left(\sum_{i=1}^{n} x_{exp,i}\right)^2} \cdot \sqrt{n \cdot \sum_{i=1}^{n} x_{ANN,i}^2 - \left(\sum_{i=1}^{n} x_{ANN,i}\right)^2}}$$
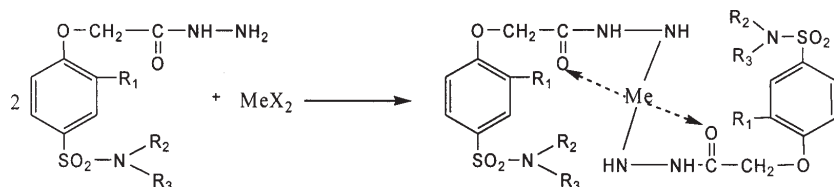
For a better correlation, r must be as close as possible to the unit (1).
- Percentage Relative Error:

$$e_r(\%) = \frac{x_{ANN,i} - x_{exp,i}}{x_{exp,i}}$$

Neural modelling has been made by using the *Neurosolutions* applications.

Results and discussions

Starting from the hydrazides of sulfonamidated phenoxyacetic acids and by taking their biological action into account we've obtained some metal complexes by treating the hydrazides with chloride or acetate of some transitional metals. In order to synthesize the complexes, the ligand (hydrazide) is treated with metal salt in organic solvent, under heating. The experimental method has been previously printed [8-10].

The obtaining reaction is presented in figures 2 and 3.

For direct modelling, the input parameters are: the molar ratio α-(2-chloro-4-sulphonamido-fenoxy) propyonil hydrazide/cobalt acetate (x_1), the reaction time (x_2), and the temperature (x_3). As output parameter the global yield (y) has been considereded. Thus, the resulting architecture MLP will have 3 neurons in the input layer. The experimental data required for the mentioned parameters have been collected [9].

The parameters for the molecular modelling are:
-activation function SigmoidAxon,
-learning algorithm (learning-rule) Levenberg-Marquardt,
-number of epochs– 20.000 epochs,
-precision 0.00001 (threshold value).
The best neuronal model has been determined through the trial-error method and it is MLP (3:4:1). Network training exhibit a good statistical characterization, as concluded from table 1.

Table 1
STATISTICAL CHARACTERIZATION FOR TRAINING *MLP(3:4:1)*

Performance	y
Mean Squared Error, MSE	4.4501e-23
Mean Absolute Error, MAE	5.41816e-12
Linear Correlation Coefficient, r	1

Me= Cu, Ni, Cd, Co, Sn, Cr, Mn, Fe, Ti;
X= Cl, $(CH_3COO)_2$
R_1 = -Cl, -CH₃, -H;
R_2, R_3 = -H, -C_4H_9,

Fig.2. Complexes obtained from hydrazides

Fig.3. Reaction scheme for synthesis of our complexes
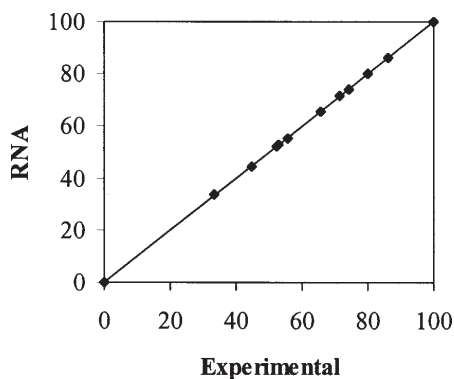
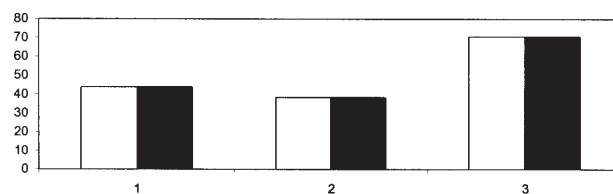Fig.4. Predictions of *MLP(3:4:1)* compared to the experimental data for the training stage

Fig. 5. Comparations between experimental data and MLP (3:4:1) predictions for the validation stage: □ - experimental , ■ - RNA.

Training performances are clearly observed in the diagram presented in figure 4.

For validation a new set of experimental data have been used to train the network. The MLP (3:4:1) network generated the values for global yield (the answer) for the studied system. The obtained results (table 2) showed that the neural model exhibit a good prediction capacity and is able to generalize the connections between input variables and the output ones (fig. 5).

The good results obtained during the validation step enable us to use the neural model in order to make the corresponding predictions for other values for the reaction parameters, different from those used in experimental protocol. In order to verify this ipothesis, values for the independent variables around the optimum 97.08% for global yield have been considered. The obtained result are presented in figure 6 and table 3.

Obtained data confirm that the variation of the molar ratio α-(2-chloro-4-sulphonamido-fenoxy) propyonil hydrazide/cobalt acetate (M) strongly influences the global yield, while reaction time and temperature, respectively, have less effect. About the molar ratio, it is observed that it exhibit an optimal value that assure the maximum global yield for the chemical reaction.

As previously shown, the predictions are in very good correspondency with the experimental data. The predicted values inside and outside the experimental range abide by the tipical conduct for the studied process [9].

For the inverse neural modeling the values for the global yield, reaction time and temperature have been dictated and the value for the molar ratio have been determined, because the molar ratio has the stonger influence for the global yield.

The same parameters have been used as in the direct modelling, as shown above. Using the mentioned conditions, the neural model obtained has been MLP (3:7:1).
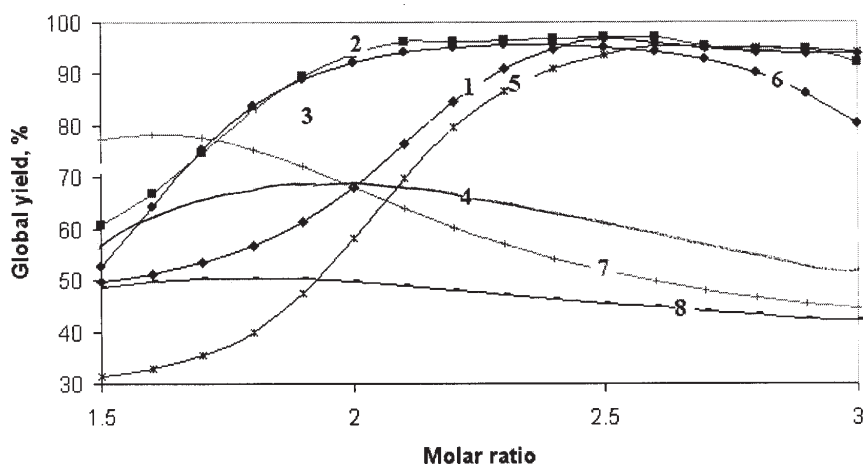
Table 2

EXPERIMENTAL DATA FOR VALIDATION OF THE NETWORK

Performance	y
Mean Squared Error, MSE	3.609e-06
Mean Absolute Error, MAE	0.00112382
Linear Correlation Coefficient, r	0.999999996

Fig. 6. Estimated curves by the means of direct neural modeling for time=10 and molar ratio (M): 1- M=25, 2-M=30, 3-M=35, 4-M=40 ; time=20 and 5- M=25, 6-M=30, 7-M=35, 8-M=40.

Table 3
PREDICTIONS OF MLP
(3:4:1)

Temperature/molar ratio (M)	Time=10				Time=20			
	25	30	35	40	25	30	35	40
1.5	49.87928	60.64848	71.76198	56.79201	31.56872	52.62877	77.34586	48.65963
1.6	51.30338	66.893	76.85226	62.1763	32.89022	64.19834	78.33543	49.73568
1.7	53.43934	74.72163	80.55157	65.86286	35.38023	75.2756	77.55747	50.30735
1.8	56.67579	82.86332	82.65435	67.96691	39.92807	83.67096	75.33121	50.43167
1.9	61.47752	89.52833	83.33686	68.81231	47.49398	89.08942	72.02275	50.19034
2	68.16	93.84376	82.88283	68.71471	58.08265	92.29705	68.09442	49.67237
2.1	76.34439	96.19593	81.56026	67.92422	69.74826	94.11331	64.03363	48.96286
2.2	84.53201	96.36061	79.6035	66.63034	79.7447	95.08624	60.2231	48.13656
2.3	90.90989	96.52007	77.2157	64.97952	86.76106	95.51609	56.87022	47.25477
2.4	94.84049	96.67107	74.56501	63.08966	91.13166	95.53409	54.02828	46.36465
2.5	96.90341	**97.08**	71.78074	61.05905	93.71954	95.15115	51.65998	45.50015
2.6	95.8	96.98152	68.95638	58.9707	95.23752	94.26989	49.69327	44.68383
2.7	95.12	95.39843	66.15812	56.89375	95.13345	92.67289	48.05356	43.92907
2.8	94.2	94.48686	63.43418	54.88365	94.96202	90.0195	46.67681	43.24233
2.9	94.02	94.87409	60.82168	52.98204	94.86335	85.92662	45.51224	42.62507
3	93.79039	92.19629	58.3501	51.21736	94.11326	80.22266	44.52078	42.07546

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Performance	x
Mean Squared Error, MSE	0,000605543
Mean Absolute Error, MAE	0,017898657
Linear correlation coefficient, r	0,999347546
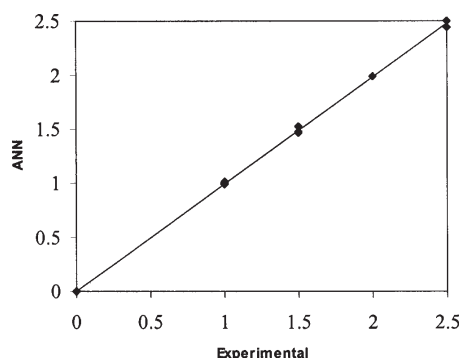
Fig.7. Performances of training *MLP(3:7:1)*

Fig.8. Testing performances: white- experimental, grey- models prediction

Yield, %	Temperature, °Celsius	Reaction time, min	Molar ratio	
37	40	15	2	
48	30	20	1	**Table 5**
59	45	10	1.9	PREDICTIONS
62	30	15	3	PROVIDED BY
77	35	20	1.8	MLP(3:7:1)
83	40	10	2	
89	35	15	2	
96.9	30	10	2.5	
97	30	10	2.5	
97.08	**30**	**10**	**2.5**	

Statistical parameters that testify the quality of the established neural model are presented in table 4.

Performances of the neural model are marked in figure 7.

The results for the validation step are shown in figure 8.

Model MLP(3:7:1) have been used to establish reaction parameters required in order to obtain a maximum global yield of 97.1%. The obtained results are gathered in table 5.

As shown in table 5, the obtained results confirm the fact that for the studied reaction the global yield value of 97.08% is obtained for a molar ratio α-(2-chloro-4-sulphonamido-fenoxy) propyonil hydrazide/cobalt acetate equal to 2.5, a reaction time of 10 min and temperature of 30°C.

Conclusions

For the studied condensing reaction a study of direct and inverse neural modeling has been made, for which the following experimental parameters were considered: the molar ratio α-(2-chloro-4-sulphonamido-phenoxy) propyonil hydrazide/cobalt acetate (x_1), the reaction time (x_2) and the temperature (x_3). As output parameter the global yield (y) has been considered.

Neural networks were designed by testing more topologies and by evaluating their performances.

Neural model for the direct modelling is type MLP (3:4:1), and for the inverse one is MLP (3:7:1).

Direct neural modeling showed the maximum value for the yield (the optimum) to be 97.08%.

Inverse neural modelling provided us with the required experimental values for the parameters in order to obtain the maximum yield which are: molar ratio α-(2-chloro-4-sulphonamido-phenoxy) propyonil hidrazide/cobalt acetate = 2.5, a reaction time of 10 min and temperature of 30°C.

Optimum stability analysis made by using the neural model MLP (3:4:1) showed that the found optimum value is stable for temperature variations between ±5°C, variations for molar ratio of ±0.1 and reaction time of ± 2 min.

Thus, the precise predictions obtained using simulations on the neural model are complete information, certain and necessary in order to optimally lead organic synthesis processes.
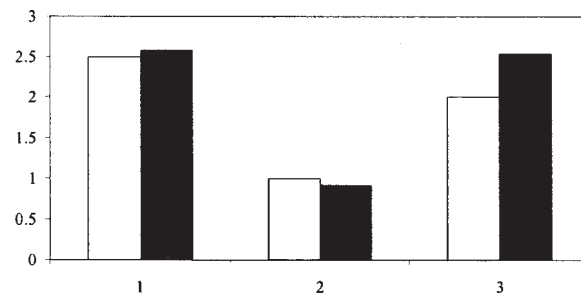
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