Neural network based modeling of N^1-[α-(2-chloro-4-sulphonamido-phenoxy)]propionyl-N^2-(2,4-dinitro-benzylidene) hydrazone synthesis

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Abstract

The last step in the synthesis of a novel sulphonamidated α-phenoxy-propionyl hydrazone with potential herbicide and auxin properties consists of the condensation between α-(2-chloro-4-amidosulphonyl-phenoxy) propionyl hydrazide and 2,4-dinitro-benzaldehyde, which is influenced by three main parameters: molar ratio between the reagents, temperature and time. In order to establish the optimum reaction conditions, a planned factorial experiment of first-degree order was accomplished, in which the real values of the parameters and their limits of variation were chosen arbitrarily. Feedforward neural networks with a single hidden layer were used in direct and inverse modeling of the process, to predict the yield of the reaction for different reaction conditions and, on the other hand, the reaction conditions for a pre-established yield. The neural modeling of the condensation process enabled to settle the optimum values of the parameters for a maximum yield in N^1-[α-(2-chloro-4-sulphonamido-phenoxy)] propionyl-N^2-(2,4-dinitro-benzylidene) hydrazone. A real and complete characterization of the condensation process was accomplished by neural network based modeling.

Keywords: sulphonamidated α-phenoxypropionic acid derivatives, azomethine of α-phenoxypropionyl hidrazide, neural networks, mathematical modeling.

Introduction

The phenoxyalkane carboxylic derivatives include some of the most efficient and selective herbicidal agents, being used on annual and evergreen dicotyledonous plant in the haulm crops. There are three main classes of phenoxyalkane acid type pesticides: phenoxyacetic acids (1), α-phenoxypropyonic acids (2), and γ-phenoxybutyric acids (3) (Scheme 1).

Scheme 1. The main classes of phenoxyalkane acid type pesticides

These compounds, as well as some of theirs derivatives (esters, amides, hydrazides), are also used as auxins, at small doses [1]. By introducing a sulphonamidated moiety on the aromatic ring both herbicidal and growth regulatory actions of the compounds are improved, the toxicity toward humans and mammiferous becoming insignificant. For example, Asfac® induces an augmentation of the production of about 40 %, when applied on beet sugar crops, and does not produce toxic wastes [1-6].

In order to obtain a new class of herbicides, we synthesized a series of derivatives with general formula (4) (Scheme 2), in which the sulphonamidated phenoxyalcan carboxylic residue is linked to a 2,4-dinitro-benzylidene residue, through a hydrazine segment [7]. We anticipated that this kind of compounds might have

synergic herbicidal actions due to both sulphonamidated phenoxyalcan carboxylic and 2,4-di-nitrophenyl residues (also present in herbicides such as: *Dinoterb*® and *Medinoterb*®), and additionally, auxin actions [1].

Scheme 2. A new class of herbicides

Since the last step in the synthesis of compounds (4) (see figure 1 below) is characterized by low yields, we carried out the reaction under different conditions by varying the main parameters influencing the process under study.

In recent years, neural networks have been much studied because of their capability to approximate any continuous nonlinear functions. Neural networks possess the ability to learn what happens in the process without actually modeling the physical and chemical laws that govern the system.

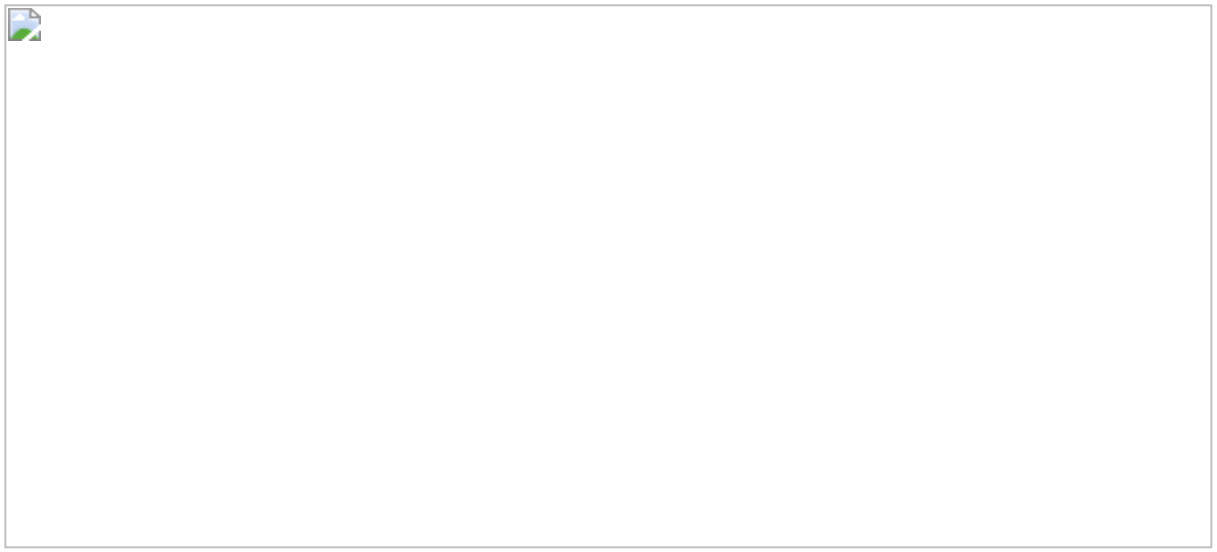
The use of neural networks has become increasingly recommended for applications where the mechanistic description of the interdependence between variables is either unknown or very complex. They are now the most popular artificial tool with applications in areas such as pattern recognition, classification, process control, optimization [8-12]. Different types of neural network applications are reviewed in our precedent work [13].

The aim of this paper is to present an important example of how artificial neural networks can help with the modeling and optimization of the condensation process between ethyl *α*-(2-chloro-4-amidosulphonyl-phenoxy)propionate and 2,4-dinitro-benzaldehyde. The reaction yield is predicted for different working conditions (*direct neural network modeling*) and the reaction conditions are determined to lead to an imposed yield (*inverse neural network modeling*). In this way, some experiments are avoided, saving time and materials. The novelty of the paper consists
in a new modeling methodology for the last condensation in N^1-[*α*-(2-chloro-4-sulphonamido-phenoxy)] propionyl-N^2-(2,4-dinitro-benzylidene) hydrazone obtaining process, modeling that provides useful information for the synthesis.

Materials and methods

N^1-[*α*-(2-chloro-4-sulphonamido-phenoxy)] propionyl-N^2-(2,4-dinitro benzylidene) hydrazone synthesis was carried out starting from ethyl *α*-(2-chloro-phenoxy) propionate (5 in
Scheme 3) which, by cholorosulphonation, gives the ethyl *α*-(2-chloro-phenoxy-4-chlorosulphonyl) propionate (6 in Scheme 3). By amidating (6) with ammonia, ethyl *α*-(2-chloro-4-amidosulphonyl-phenoxy) propionate (7) is obtained and submitted subsequently to the reaction with hydrazine to the hydrazide (8). [14-16].

The reaction of the last with 2,4-dinitro-benzaldehide provides the hydrazone (9) (Scheme 3).



Scheme 3. Synthetic route for N^1-[α-(2-chloro-4-sulphonamido-phenoxy)] propionyl-N^2-(2,4-dinitro phenoxy-methylene) hydrazone obtaining

The general experimental procedure applied for the synthesis of the compound (9): over 0.293 g α-(2-chloro-4-sulphonamido-phenoxy)propionyl hidrazide (0.001 mole) dissolved in about 15 ml acetone were added various amounts of 2,4-dinitrobenzaldehyde (as noticed in the factorial experiment, *i.e.* molar ratio toward the ester: 0.75 (0.147 g), 1 (0.196 g), and 1.25 (0.245 g) diluted by 10 ml ethanol, and 3 drops of anhydrous acetic acid. The reaction mixture was then stirred at the temperature 35 °C, 40 °C, and 45 °C, respectively, and for the duration 35, 40, and 45 minutes as prescribed in the factorial experiment. The hydrazone (9) was isolated by recrystallisation from ethanole. The product resulted as a white powder melting at 154-158°C.

IR (KBr pellets, cm^{-1}): ν_{CO-NH} amidic valence vibrations (the bands denoted by amide I and amide II, respectively): 1651.06 cm^{-1} and 1535.33 cm^{-1}, $\nu_{C=N}$ valence vibration 1651.05 cm^{-1}, $\nu_{Caromatic-O-C aliphatic}$: 1062.78 cm^{-1} ($\nu_{C-O symmetric}$) and 1274.94 cm^{-1} ($\nu_{C-O asymmetric}$), ν_{NH} valence vibration: 1585.48 cm^{-1}, ν_{SO2}: 1161.14 ($\nu_{SO2 symmetric}$) cm^{-1} and 1309.66 cm^{-1} ($\nu_{SO2 asymmetric}$), $\nu_{C=S}$: 1076.28 cm^{-1}, $\nu_{S=O}$ and $\nu_{S=N}$: 1062.78 cm^{-1} and 1076.28 cm^{-1}, $\nu_{C=O}$: 1253.73 cm^{-1}, ν_{C-NO2} : 1332.81 cm^{-1} [17].

In order to settle down the optimum reaction conditions which afford a maximum yield in N^1-[α-(2-chloro-4-sulphonamido-phenoxy)] propionyl-N^2-(2,4-dinitro benzylidene) hydrazone, a planned factorial experiment of first-degree order was followed, the limits of variation for the three parameters that influence the process [i.e. molar ration between the α-(2-chloro-4-sulphonamido-phenoxy) propionyl hidrazide and 2,4-dinitrobenzaldehyde, *M*, temperature, *t* and time, τ] being given in Table 1.

Table 1. Experimental data

Exp. no.	Molar ratio M	Temperature t, [°C]	Time τ, [min]	Yield η
1	0.75	35	35	46.8
2	1.25	35	35	48.93
3	0.75	45	45	48.93
4	1.25	45	35	53.19
5	1.25	35	45	23.40
6	0.75	35	45	21.27

Exp. no.	Molar ratio M	Temperature t, [°C]	Time τ, [min]	Yield η
7	0.75	45	35	44.68
8	1.25	45	45	40.42
9	1	40	40	46.80
10	1	40	40	46.38
11	1	40	40	46.80
12	1	40	40	46.30

Neural Network Modeling

In general, a neural network consists of processing neurons and information flow channels between neurons, usually called “interconnections”. Each processing neuron calculates the weighted sum of all interconnected signals from an output through its activation functions. The way in which neurons are connected to form a network represents the neural network topology (architecture).

Most papers on the use of neural networks apply a multilayered, feed-forward network (multilayer perceptron, MLP). The reasons for the use of this kind of neural network are the simplicity of its theory, the easiness of programming and good results and because this network is a universal function in the sense that if topology of the network is allowed to vary freely it can take the shape of any broken curve.

The success in obtaining a reliable and robust network depends strongly on the choice of process variables involved, as well as the available sets of data and the domain used for training purposes. The most important parameters considered to influence the reaction yield were molar ratio between the reagents (M), temperature (t), and time (τ). Consequently, the neural model to be design has three inputs (M, t, and τ) and one output (η) and allows the estimation of the reaction yield for different reaction conditions.

Firstly, the experimental data are split into training and validation data sets.

In the training phase, the neural network learns the behavior of the process. The training data set contains both input patterns and the corresponding output patterns (also called target patterns). Neural training leads to finding values of connection weights that minimize differences between the network outputs and the target values. The most extensively adopted algorithm for the learning phase is the back-propagation algorithm.

One major problem in the construction of a neural network is determining the network architecture, that is the number of hidden layers and the number of neurons in each hidden layer. In this work, the number of hidden layers and units was established by training a different range of networks and selecting the one that best balance generalization performance against network size. The best network topology was determined based upon the mean of squared errors (MSE) on the training data. We consider that training is terminated at the point where the network error (MSE) becomes sufficiently small. A topology with a single hidden layer with 5 neurons was obtained, having a good performance in the training phase: MSE = 0.000031, r = 0.9999 (the correlation between experimental data and the output of the neural network) and E_p = 0.1001 % (percent error). This feedforward neural network can be noted as MLP (3:5:1), referring to the number of neurons in the input, hidden and output layers, respectively.

The same algorithm is followed for the inverse neural network modeling, that is the identification of the working conditions (particularly, M) that lead to an imposed value for the yield. MLP (3:3:1) with three inputs (η, t, τ), one hidden layer with three neurons and one output (M) is designed with MSE = 0.000002, r = 1 and E_p = 0.0195 % to solve the following problem: *What is the molar ratio which lead to an imposed value for the reaction yield, working in pre-established conditions of time and temperature?*

An additional issue for inverse modeling consists of the identification of molar ratio and time needed to determine a pre-established yield, the parameter temperature being taken as an imposed value. In these conditions, a MLP (2:5:2) with two inputs (η, t), one intermediate layer with five neurons and two outputs (M, τ) is designed with MSE = 0.001, r = 1 and E_p = 0.19 % to solve the following problem: *What are the reaction*

conditions (molar ratio and time) which lead to an imposed value for the reaction yield, working with a pre-established temperature?

A special software application - *NeuroSolutions* - was used in this paper in order to project and obtain predictions of neural networks.

Results and discussion

The condensation between *α*-(2-chloro-4-sulphonamido-phenoxy) propionyl hidrazide and 2,4-dinitrobenzaldehyde takes place according to a bi-molecular nucleophylic substitution (nucleophylic addition followed by nucleophylic elimination). In spite of the easiness of this type of reaction, the yield of the process listed in Table 1 does not exceed about 53.2 % in the conditions employed for the classic planned experiment. The neural modeling provides supplementary information about the reaction conditions needed for an improved reaction yield.

When the condensation reaction is carried out at 45°C the *α*-(2-chloro-4-sulphonamido-phenoxy) propionyl hydrazide is solved much faster in acetone and the obtaining product precipitates easier. At a lower temperature the hydrazide can be more difficult solved in acetone.
The reaction product precipitates also easier at longer reaction time.

Table 2. Predictions of MLP (3:5:1) on training data in direct modeling.

Exp. no.	M	T [°C]	τ [min]	$\eta_{experim}$	$\eta_{network}$	error	correlation
1	0.75	35	35	46.8	46.8	2.137E-08	**0.999957**
2	1.25	35	35	48.93	48.93	0	
4	1.25	45	35	53.19	53.19	1.88E-08	
5	1.25	35	45	23.4	23.4	0	
6	0.75	35	45	21.27	21.27	0	
7	0.75	45	35	44.68	44.68	0	
8	1.25	45	45	40.42	40.42	4.948E-08	
10	1	40	40	46.38	46.59	0.0045278	
11	1	40	40	46.8	46.59	0.0044872	
				Average error		**0.0010017**	

Thus, the predictions of MLP (3:5:1) on training data presented in Table 2 show that the model learned well the behavior of the process. The correlation between the two sets of data, over 0.99 and a small average relative error (0.001), emphasize a good concordance between the model and the experimental results. This fact is also emphasized in Figures 1, which present the neural network predictions and the experimental yield obtained in different reaction conditions.

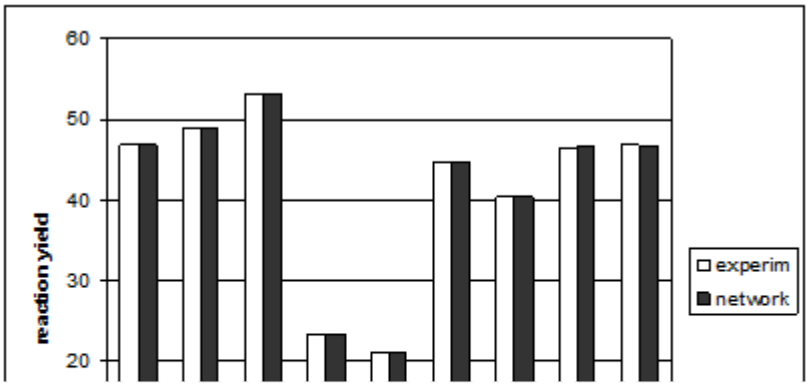


Figure 1. Predictions of MLP(3:5:1) on training data compared to the experimental data in direct modeling.

The errors in Table 2 were calculated using the following formula:

$$E = \frac{|\text{exp yield} - \text{network yield}|}{\text{exp yield}} \cdot 100 \quad (1)$$

The purpose of developing a neural model is to devise a network (set of formulae) that captures the essential relationships in the data. These formulae are then applied to new sets of inputs to produce corresponding outputs. This is called *generalization* and represents subsequent phase after training - *validation* or *testing phase*. A network is said to generalize well when the input-output relationship, found by the network, is correct for input/output patterns of validation data which were never used in training the network (*unseen data*).

Table 3 presents the prediction of MLP (3:5:1) in validation phase. Good results obtained in the validation phase allow to use the neural model to make predictions for different reaction conditions, not used experimentally. Some examples are given in Table 4.

Table 3. Predictions of MLP (3:5:1) on validation data in direct modeling

Exp. no.	M	T [°C]	τ [min]	$\eta_{experim}$	$\eta_{network}$
3	0.75	45	45	48.93	45.56
9	1	40	40	46.8	46.59
12	1	40	40	46.3	46.59

Table 4. Predictions of MLP (3:5:1) in direct modeling

M	t [°C]	τ [min]	$\eta_{network}$
0.75	40	35	46.20
0.75	40	30	47.75
0.75	40	45	27.94
1	35	35	49.94
1	45	30	51.63
1	45	45	38.40
1	45	35	50.29

M	t [°C]	τ [min]	$\eta_{network}$
1.25	40	35	52.97
1.25	40	45	25.73
1.25	40	30	53.59

The results from Table 4 show that is possible to obtain good reaction yield even for small value of M, for instance: M = 1, t = 45 °C and τ = 30 min.

Supplementary information is obtained by inverse neural modeling, that is an optimization problem representing the identification of reaction conditions, which lead to an imposed reaction yield.

For the first variant of inverse modeling, the network MLP(3:3:1) provides the molar ratio which gives an imposed reaction yield, working in pre-established conditions of time and temperature. Table 5 shows the training results for this model, Table 6 contains the validation data, and Table 7 presents some predictions made for a series of working hypothesis. Accurate results are obtained both in training and validation phases.

Table 5. Predictions of MLP (3:3:1) on training data in inverse modeling.

Exp. no.	$\eta_{imposed}$	t [°C]	τ [min]	$M_{experim}$	$M_{network}$	error	corr.
1	46.8	35	35	0.75	0.750005	6.66E-06	0.999998
2	48.93	35	35	1.25	1.249987	1.04E-05	
4	53.19	45	35	1.25	1.249978	1.76E-05	
5	23.4	35	45	1.25	1.250031	2.48E-05	
6	21.27	35	45	0.75	0.749984	2.13E-05	
7	44.68	45	35	0.75	0.750001	1.33E-06	
8	40.42	45	45	1.25	1.25	2.4E-06	
10	46.38	40	40	1	0.9992	0.000838	
11	46.8	40	40	1	1.0008	0.000836	
					Average error	**0.00019**	

Table 6. Predictions of MLP (3:3:1) on validation data in inverse modeling

Exp. no.	$\eta_{imposed}$	t [°C]	τ [min]	M	$M_{network}$
3	48.93	45	45	0.75	0.82
9	46.8	40	40	1	1.0008
12	46.3	40	40	1	0.9988

Table 7. Predictions of MLP(3:3:1) in inverse modeling

$\eta_{imposed}$	t [°C]	τ [min]	$M_{network}$
25	35	45	1.27
30	45	30	0.72
28	35	35	0.72
37	45	45	1.27
42	35	45	1.24
47	45	45	1.13
50	40	45	1.06
52	40	40	1.03

$\eta_{imposed}$	t [°C]	τ [min]	$M_{network}$
35	45	35	0.72
45	40	35	0.73

The highest value for η (η = 52 %) is obtained working in the following conditions: t=40°C, τ = 40 min, M = 1.03.

In the second variant of optimization, the reaction yield and the temperature are imposed at the beginning of the process and, by inverse neural network modeling, the molar ration and reaction time are determined.

Table 8 shows the training results for the model MLP(2:5:2), Table 9 contains the validation data, and Table 10 is the result of some predictions made with un-used test data.

Table 8. Predictions of MLP (2:5:2) on training data in inverse modeling.

Exp. no.	$\eta_{imposed}$	$t_{imposed}$ [°C]	τ [min]	$\tau_{network}$ [min]	error for τ	corr. for τ	M	$M_{network}$	error for M	corr. for M
1	46.8	35	35	34.97	0.00075	0.99926	0.75	0.75	0.00015	0.99999
2	48.93	35	35	35.03	0.00083		1.25	1.25	5.8E-05	
4	53.19	45	35	34.98	0.00048		1.25	1.25	7.8E-05	
5	23.4	35	45	45.55	0.01226		1.25	1.25	4.7E-05	
6	21.27	35	45	45.55	0.01231		0.75	0.75	0.00018	
7	44.68	45	35	35.03	0.0009		0.75	0.75	0.00025	
8	40.42	45	45	44.99	0.00026		1.25	1.25	3.7E-05	
10	46.38	40	40	40.04	0.00106		1	1.00	0.00212	
11	46.8	40	40	39.95	0.00113		1	1.00	0.00212	
average errors					**0.00333**				**0.00056**	

Table 9. Predictions of MLP (2:5:2) on validation data in inverse modeling

Exp. no.	η	t [°C]	τ [min]	$\tau_{network}$ [min]	M	$M_{network}$
3	48.93	45	45	37.25	0.75	0.75
9	46.8	40	40	39.95	1	1.00
12	46.3	40	40	40.06	1	1.00

A complete description of the synthesis of N^1-[α-(2-chloro-4-sulphonamido-phenoxy)]propionyl-N^2-(2,4-dinitro-benzylidene) hydrazone is realized using direct and inverse modeling based on artificial neural networks. The predictions of these models represent useful information for experimental practice.

Table 10. Additional predictions of MLP(2:5:2) in inverse modelling

η	t [°C]	$\tau_{network}$ [min]	$M_{network}$
45	45	34.98	0.75
47	40	39.91	1.01
55	40	37.36	1.28
60	35	35.08	1.28
35	45	45.39	1.26
38	35	45.27	1.20
50	35	35.06	1.28

η	t [°C]	$\tau_{network}$ [min]	$M_{network}$
48	45	34.88	0.74
42	35	35.35	0.73
49	40	39.48	1.15

Conclusions

The last step in the synthesis of N^1-[α-(2-chloro-4-sulphonamido-phenoxy)]propionyl-N^2-(2,4-dinitro-benzylidene) hydrazone consists of the condensation between α-(2-chloro-4-amidosulphonyl-phenoxy) propionyl hidrazide and 2,4-dinitro-benzaldehyde. The main parameters influencing the process are molar ratio between the reagents, temperature and time. In order to find out the optimum conditions affording the maximum yield in the reaction product, a planned factorial experiment of first-degree order was accomplished, in which the real values of the process variables and their limits of variation were chosen arbitrarily.

Simple feedforward neural networks were used for direct and inverse modeling of the process. MLP (3:5:1), with molar ratio, temperature and time as input variables and 5 hidden neurons into an intermediate layer accurately predicted the yield of the reaction in a direct modeling. An inverse neural modeling is performed with MLP (3:3:1) and MLP (2:5:2) and represents the identification of reaction conditions (temperature, time and molar ratio), which leads to an imposed reaction yield. The main conclusion of this procedure is that the optimum values of the parameters which afford a maximum yield N^1-[α-(2-chloro-4-sulphonamido-phenoxy)] propionyl-N^2-(2,4-dinitro-benzylidene) hydrazone are the following: ethyl α-(2-chloro-4-amidosulphonyl-phenoxy) propionate/2,4-dinitro-benzaldehyde molar ratio = 1.25, temperature = 40 °C and time = 35 minutes.

We can conclude that direct and inverse neural network modeling technique describes well the behavior of the real condensation process. Consequently, the accurate predictions obtained by simulations on neural model are useful information for the chemical synthesis.

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