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APPLICATION OF THE VOLUME LEARNING ALGORITHM ARTIFICIAL NEURAL NETWORKS FOR RECOGNITION OF THE TYPE OF INTERACTION BETWEEN NEURONS FROM THEIR CROSS-CORRELATION HISTOGRAMS

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An algorithm based on two types artificial neural networks (ANNs) is proposed. The first network is an associative ANN while the second network is a Self-Organizing Map of Kohonen. The results for a test set are similar to the performance of our previous expert system algorithm developed with Group Method of Data Handling (GMDH). However, while GMDH uses indices derived using the expert knowledge (and thus require considerable time and resources) the VLA process initial raw data.

INTRODUCTION

The problem of the neuron interaction type recognition is of great practical importance in neurophysiology. Many investigations show the presence of a close relation between various types of neurological diseases and functional disorders in neuron interaction in comparison with a reference pattern. For example, a study of Parkinson disease model in macaques showed a high oscillatory activity and a high degree of correlation of the neurons in *globus pallidus* [1]. At the same time, the cross-correlograms of healthy monkeys usually showed the absence of any interaction between neurons. Note that the type of interaction between particular neurons is determined not only by their physiology (e.g., by synaptic relations between neurons) but also by the functional condition of the entire brain. So for this reason, it may change depending on the state of the animal (such as sleep and wakefulness, or accomplishment a certain task by the animal [2, 3]); sometimes, it may change in a fraction of a second [4]. Examination of the interaction between neurons helps us to better understand the functioning of the brain and get new methods of treatment of the nervous system diseases. Thereby an analysis of a cross-correlation histogram is one of the most applied methods to classify the functional types of neuron interaction. Other more complex methods for estimating functional relations in pairs [5], triples [6], and arbitrary sets [7] of neurons were also developed. However, the method based on analyzing cross-correlograms remains one of the most frequently used methods all over the world because the interpretation of the results obtained by this method is most evident and simple.

The cross-correlation histogram is the empirical distributions of the impulses time delay of one neuron comparatively to the impulses of another neuron plotted in the time range of 0 to 500 ms at 1 ms interval. The cross-correlograms are plotted for pairs of neurons and used to classify several basic types of neuron interaction according to the shape and arrangement of the histogram peak [8]. The basic interaction types include (a) the absence of interaction between neurons; (b) the

presence of a common input; and (c) the presence of direct activating/inhibiting connections between neurons. The strength and duration of a neuron interaction can be estimated based on the shape of a peak.

In order to recognize type of neuron interaction, in our previous work we used various parameters that characterize the shape of cross-correlograms [9]. The choice of these parameters was done in collaboration with experts who analyzed the data. Thus the experience of the experts was *a priory* incorporated in the classification system in form of these parameters. The interesting question was if a similar in performance classification system could be constructed without using any *a priory* knowledge of an expert.

Recently a Volume Learning Algorithm (VLA) was proposed to study quantitative structure-activity relationships (QSAR) in medicinal chemistry [10]. This algorithm was successfully applied to correlate tens of thousands of input molecular parameters representing electrostatic and steric interactions of molecules with biological activities of series of cannabimimetic aminoalkyindoles, *N*-benzylpiperidine analogs, etc [10, 11, 12]. The VLA is a combination of supervised and unsupervised neural networks. The algorithm defines clusters in input parameter space using the Self-Organizing Map of Kohonen (SOM) [14] and then uses the mean values of these clusters for the training of the ensemble of the feed-forward back-propagation neural networks. This approach decreases the number of input parameters required for neural network training and calculates neural network models with high generalization ability.

In the current study we extend application of this algorithm for classification of types of neuron interaction and demonstrate that its performance is comparable with the expert system developed in our previous studies.

DATA

The data used in this study were previously described in [13]. Each interaction type was presented as three-symbol code. The first symbol of the code described the kind of neuronal interaction, while the second and third symbols denoted the strength and duration of the interaction, respectively.

The first symbol of the code of a histogram was a letter; depending on the kind of the interaction, it could be:

C — a common input,

E — an exciting input,

I — inhibition (suppression),

L — a «large» input, or

Z — a non typical code (i.e., the classification of the cross-correlogram was not performed).

The second symbol of the code was a number showing the interaction strength measured on the four-grade scale according to the ratio of the maximum histogram value to the first and second confidence levels.

The second number could be

0 — the interaction was present, but the maximum histogram value was below the first confidence level («a very weakly manifested type»),

1 — the maximum histogram value was at the first confidence level («a weakly manifested type»),

2 — the maximum histogram value was at the second confidence level («a moderate type»), or

3 — the maximum histogram value was above the second confidence level («a distinct type»).

The third symbol of the code was a letter showing the duration of the interaction:

$A - T = 1$ ms (a rare type);

$B - T = 2$ ms (a rare type);

$C - 2 < \widetilde{T}\, 20$ ms;

$D - 20 < \widetilde{T}\, 50$ ms;

$E - 50 < \widetilde{T}\, 150$ ms;

$F - 150 < \widetilde{T}\, 200$ ms;

$G - 200 < \widetilde{T}\, 400$ ms (only for the L type);

$H - T > 400$ ms (only for L).

If there was no interaction between neurons (this was the most frequent type) the code was marked the value 0.

The initial training data set included 3444 histograms recorded in the auditory cortex of wild and mutated mice. There was also another set of 2666 histograms recorded in a different set of experiments. This set was used to further test performance of the developed method.

METHOD

The VLA method combines unsupervised and supervised neural network methods. Here we only give a brief description of this algorithm and more details can be found elsewhere [10, 11].

Artificial neural networks can be subdivided into two main categories. The first category, unsupervised neural networks, such as Kohonen neural network [14], realize training without the teacher [14, 15]. This means that the target values are considered to be not known or absent and neural network learning consists of the detection and clustering of input samples according to some internal relationships among them. However, in practice, the user explicitly or implicitly is interested in some particular clustering that is relevant to some target activity, i.e. the clustering is always «target»-based. Such clustering is usually achieved by pre-selection input parameters that are considered to be relevant to this target activity. Basically, this pre-selection corresponds to introducing some weighting scheme of input parameters, e.g. some parameters receive unit weight and are selected for clustering and other receive zero weight and are not selected. Thus, pre-selection introduces some metric in the space of input parameters and the performance of unsupervised method to a great degree depends on the correct choice of this metric.

The VLA uses the supervised algorithm to explicitly determine the relevant clustering metric and importance of input parameters and to improve the clustering of unsupervised methods as shown below.

The supervised neural networks are used to calculate dependencies between input and output variables. One of the most well known neural networks belong-

ing to the second class are the feed forward neural networks (FFNNs) trained with the back propagation algorithm [16, 17]. The application of FFNNs to a data set with a large number of input parameters, e.g. the data points of cross-correlograms, is complicated. Firstly, the speed of a neural network is low when dealing with a large number of input parameters. Secondly, FFNN can have low generalization ability due to the overfitting/overtraining problem, which becomes more critical if the number of inputs increases. Presence of correlation effects between input variables could further impair the FFNNs generalization. This algorithm could provide better performance if one would cluster the input parameters, and provide a limited number of inputs for the neural network training. Of course, such clustering should be performed using similarity measure corresponding to the target activity of the supervised approach. The question is how to determine measure of similarity for such clustering. The VLA clusters the input parameters that have similar input-to-hidden layer weights of neural networks following their training.

Thus, in VLA the supervised method is used to determine a metric for unsupervised method (this improves «target»-based clustering) while the unsupervised method is used to decrease the number of inputs for the supervised algorithm (Fig. 1).

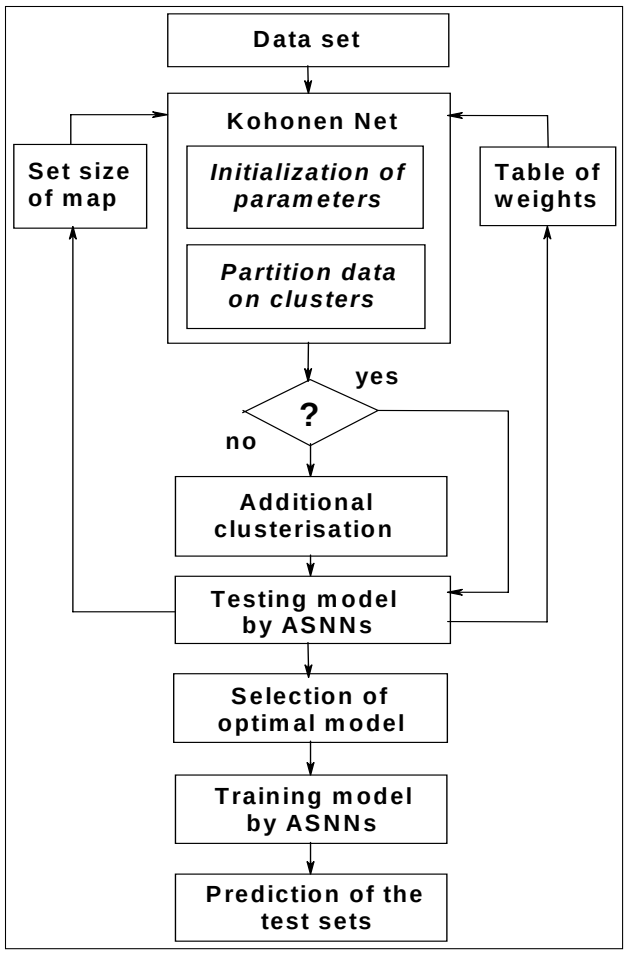

Fig. 1. Block scheme of the volume learning algorithm

The clustering decreases dimension of input space of parameters, increases signal-to-noise ration and improves performance of supervised algorithms. Thus both supervised and unsupervised algorithms «collaborate», help one another and mutually profit from such «collaboration». In practice the work of algorithm consists of several iterations that consistently improves quality of clustering and supervised learning of both algorithms (Fig. 1).

On the first iteration of algorithm, in the absent of supervised learning results, the clustering of inputs is performed using initial values. The unsupervised learning was done using Kohonen neural networks. The SOM of Kohonen

is a «self-organizing» system capable to solve the unsupervised problems. The SOM represents a lattice of neurons with dimension of each neuron (weights of SOM neuron) corresponding to the dimension of input cases. Staring with initial random initialization of neurons the SOM automatically adapts itself in such way that the similar input objects are associated with the topologically close neurons in the map, i.e. physically located close to each other on the map.

The supervised learning was performed using our implementation of FFFN, so-called Associative Neural Network (ASNN) [18]. This type of networks improves prediction ability of FFNN by explicit correction of the bias of this method. The architecture of the ASNN was consisted of three-layers with five neurons in the hidden layer. The number of output neurons corresponded to the number of classes of neuronal interactions. For each interaction all output values were zero except one that indicated the class of the sample. The bias neuron was presented on the input and on the hidden layer. $M = 200$ independent ASNNs were trained and used to cluster input parameters.

RESULTS AND DISCUSSION

The statistics of the type frequencies is present in Tabl. 1. Since the types *C0C*, *C0D* and *C0E* are very rare, the histograms of these types are united in one conventional type *C0*. The conventional type *E* is formed similarly. Tabl. 2 shows the formation and enumeration of the $M_{\text{type}} = 12$ types used to solve the recognition problem.

Table 1. The frequency of histogram types for $N = 3444$ histograms

Kind of interaction	Interaction strength	Interaction duration		
		C 2–20ms	*D* 20–50ms	*E* <150ms
Common input (*C*) 1588	0	4	10	20
	1	212	128	206
	2	223	138	302
	3	97	61	159
Exciting input (*E*) 56	0	–	–	–
	1	10	20	1
	2	4	13	–
	3	–	1	–
«Large» input (*L*) 8	0	–	–	–
	1	–	–	5
	2	–	–	3
	3	–	–	–
The «no interaction» type – 1774 histograms				

The initial data set of 3444 histograms was used to train the VLA while the second set of 2666 histograms was used to test the received model.

The input and target values were scaled between 0.1 and 0.9 for network training. As since all parameters of data were dependent among themselves, the data were normalized on maximal and minimal values founded for all samples of the data.

Table 2. The neighboring table of 12 histogram types

Type 10 (1774)			
Type	*C*	*D*	*E*
C0		Type 0 (48)	
C1	Type 1 *C1C* (169)	Type 2 *C1D* (269)	Type 3 *C1E* (109)
C2	Type 4 *C2C* (127)	Type 5 *C2D* (395)	Type 6 *C3E* (141)
C3	Type 7 *C3C* (22)	Type 8 *C3D* (188)	Type 9 *C3E* (107)
E		Type 11E^{**} (52)	

The input parameters, $n = 500$, were divided by VLA into 22 clusters. Most of clusters were relatively small (size of clusters were varied from 4 to 50 parameters), whereas one cluster consisted of 115 parameters.

In order to evaluate the stability of neural network recognition we used scheme with decision rejection for various threshold values P_0 (see Tabl. 3) proposed in [9].

Table 3. The recognition LOO results for the training set according to the scheme with rejection of making a decision for various threshold value P_0

Num.	P_0	S_{rej}	S_{100}	S_{50}	S_{00}	NS_{rej}	$M(\%)$	$S(\%)$	$S_{\text{rej}}(\%)$
GMDH									
1	0.00	0	2535	489	420	3444	81	74	0.00
2	0.25	167	2472	438	336	3277	82	75	4.85
3	0.45	354	2391	376	306	3090	83	77	10.28
4	0.50	499	2322	349	259	2945	85	79	14.49
5	0.55	574	2272	329	253	2870	85	79	16.67
6	0.75	841	2117	255	218	2603	86	81	23.95
7	1.00	1129	1960	165	180	2315	88	85	32.78
VLA									
1	0.00	0	2263	598	583	3444	74	66	0.00
2	0.46	167	2213	552	512	3277	76	68	4.84
3	0.57	355	2154	498	437	3089	78	70	10.31
4	0.65	498	2107	439	400	2946	79	72	14.45
5	0.67	575	2071	413	385	2869	79	72	16.69
6	0.75	844	1978	306	316	2081	82	76	24.50
7	0.83	1153	1849	204	238	2291	85	81	33.47

VLA — volume learning algorithm; GMDH-algorithm of the group method of data handling; LOO — line-one-out. Here N is the total number of histograms.

In Tabl. 3, the following notation is used:

N is the total number of histograms;

S_{rej} is the number of rejections to make a decision;

S_{00} is the number of gross classification errors;

S_{50} is the number of minor classification errors;

S_{100} is the number of histograms classified correctly;

$N - S_{\text{rej}}$ is the number of observations that are classified;

$M(\%)$ is the «soft» estimate of recognition accuracy (in percent):

$$M = \frac{100\left(S_{100} + 0.5\,S_{50}\right)}{N - S_{\text{rej}}};$$

$S(\%)$ is the «rigid» estimate of the recognition accuracy (in percent):

$$S = \frac{100\,S_{100}}{N - S_{\text{rej}}};$$

$O_{\text{rej}}(\%)$ is the percentage of rejections:

$$O_{\text{rej}} = \frac{100\,S_{\text{rej}}}{N}.$$

We used two recognition accuracy types (soft and rigid) to differentiate gross prediction errors from minor ones (an incorrect prediction of «neighboring» type), which affect on the general pattern of the empirical distribution of neural links over interaction types only insignificantly (the approximate symmetry of errors for the pair of types under consideration is taken into account) [9]. As neighboring types we mean interaction types of kind *C* (a common input) under the condition that they differ by only one grade on the strength or duration scale. For example, for the type *C1C* the neighboring types are *C1D*, *C2C* (Table 2) whereas for the type *C2D* the neighboring types are *C1D*, *C2C*, *C2E* and *C3D*. It will be observed that the type E^{**} has no neighboring types.

Interesting results can be provided by an analysis of distribution of recognition accuracy for various threshold values P_0 (Table 3). The condition for a decision rejection can be written in the following form:

$$V_1 - V_2 < P_0.$$

Here V_1 and V_2 are the two highest predictions of the neural network outputs. The threshold value $P_0 = 0$ in Table 3 corresponded to the results received according to the scheme without rejections of decisions.

In order to estimates the prediction quality of the VLA algorithm let us compare it with results received GMDH algorithm. The analysis of results received by GMDH showed that the percentage of rejections for threshold value P_0 between 0.45 and 0.55 are slightly increased therefore $P_0 = 0.5$ could be taken as an optimal one.

For the training data set (for the threshold value $P_0 = 0.5$) the soft estimate of recognition accuracy of GMDH was 85% and the rigid estimate of recognition quality was 79% (the number of rejection of decisions was 499). For the very

close number of rejected decision (499) VLA results were 79% soft and 72% the rigid estimate of recognition quality. Also VLA results were similar to those calculated by the GMDH for the threshold value $P_0 = 0.75$ (see Table 3). A smaller performance of ASNN compared to the GMDH method can be to some extent explained by more severe validation procedure used in this algorithm. Indeed, for the training of ASNN only 50% of initial samples from the training set (i.e., $N = 1722$ samples) where used to adjust neural network weights. The remaining samples were used to determine stopping conditions for ASNN training and to calculate LOO results (see for details refs 19, 20). At the same time the GMDH results were calculated using $N = 3443$ samples. Thus a difference in the implementation details of both methods could account for the apparent difference in their performance for the training set.

In order to independently estimates the prediction quality of the algorithm, VLA also was applied to test set of 2666 histograms. The performance of the method for the test set was comparable to that for the training set: the soft evaluation of prediction accuracy (for threshold value $P_0 = 0.61$) was 79% and the rigid estimate of recognition quality was 75% (the number of rejection of decisions was 298). For the very similar number of rejected decisions (295) GMDH results were 81% soft and 76% rigid classification performance.

These results demonstrate that VLA can be applied for recognizing the type of interaction between two neurons. However, compared to the previous method, the VLA uses raw parameters of cross-correlation histograms and it does not require calculation of additional indexes or expert knowledge while providing a comparable accuracy.

CONCLUSION

We have introduced a fast, automatic system based on Volume Learning Algorithm for recognizing of the interaction type between two neurons. The self-organizing map clustered input parameters and ASNNs used their mean values to correlate the type of analyzed activity with their cross-correlograms. This significantly decreased the number of input parameters and made it possible to calculate models with prediction ability similar to the GMDH – based approach developed using expert knowledge.

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