Classification of the Images of Gene Expression Patterns Using Neural Network Based on Multi-Valued Neurons with the Minimal Number of Inputs

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ABSTRACT

Multi-valued neurons (MVN) are the neural processing elements with complex-valued weights and high functionality. It is possible to implement an arbitrary mapping described by partial-defined multiple-valued function on the single MVN.

The MVN-based neural networks are applied to temporal classification of images of gene expression patterns, obtained by confocal scanning microscopy. The classification results confirmed the efficiency of this method for image recognition. It was shown that frequency domain of the representation of gene expression images is highly effective for their description.

Keywords: neural network, multi-valued neuron, image recognition

1. INTRODUCTION

The ability of neural networks to accumulate knowledge about objects and processes using learning algorithms makes their application in pattern recognition very promising and attractive[1]. In particular, different kinds of neural networks are successfully used for solving the image recognition problem[2].

Neural networks based on multi-valued neurons have been introduced[3] and further developed[4,5,6,7]. A comprehensive observation of multi-valued neurons theory, their learning and applications are given in[8]. Multi-valued neural element (MVN) is based on the ideas of multiple-valued threshold logic[8]. Its main properties are ability to implement arbitrary mapping between inputs and output described by partially defined multiple-valued function, quickly converging learning algorithms based on simple linear learning rules and complex-valued internal arithmetic. Several kinds of MVN-based neural networks have been proposed for solving the image recognition problems. Different models of associative memory have been considered in[4, 5, 8, 9, 10]. An approach to image recognition, which will be used here, has been introduced in[6] and further developed in[7, 8, 11, 12]. This approach is based on the following consideration. Since it is always difficult to formalize the image description so that it can be adapted for learning, a good solution to this challenge is an objectification of image presentation. Transformation of the image presentation from spatial to the frequency domain is an appropriate way to realize this objectification. Of course, in itself this approach is not new. Frequency domain representation of data for pattern recognition was proposed and successfully used in 70[ths], e.g., in[13]. The nature of this data presentation is clear: since in frequency domain the signal energy is concentrated in a small number of the low frequency part spectral coefficients, it is possible to use exactly these coefficients as an objective description of the signal.

In our study MVN-based neural network is applied to classification of images of gene expression patterns, obtained by confocal scanning microscopy[14]. This is a new promising approach for acquisition of quantitative data on gene expression at

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the resolution of a single cell. Gene expression data are of crucial importance for elucidation of mechanisms of cell functioning, as well as for the early diagnosis of many diseases.

The data are described in detail in Section 2. MVN, their learning and MVN-based neural network for image recognition are considered in Section 3. The preliminary results based on the gene expression images classification using three-layered MVN-based neural network are presented in Section 4. The main goal of the work presented here was a significant reduction of the features (Fourier spectrum phases) used for the classification. This reduction leads to the decreasing of the number of inputs for each neuron of the network without loss of the classification quality. Moreover, sometimes the classification is even more stable. This reduction allows also improvement of the network performance. The results of classification obtained using MVN-based neural network with the reduced number of inputs are given in Section 5.

2. DESCRIPTION OF THE DATA

We perform temporal classification of images of expression patterns of genes controlling segmentation in the fruit fly *Drosophila*, which is a model organism for molecular biology studies. Like all other insects, the body of the *Drosophila* is made up of repeated units called segments. During the process of segment determination a fly embryo consists of a roughly prolate spheroid of about 5000 nuclei. Genes that act to determine segments are expressed in patterns that become more spatially refined over time. One can view each gene's expression pattern as a collection of “domains” (stripes), each of which is a region of expression containing one maximum (Fig 1, 2). In our experiments gene expression was recorded by confocal scanning of embryos stained with fluorescence tagged antibodies. The obtained images were subjected to image segmentation procedure to obtain the data in terms of nuclear location[15] and then rescaled to remove a nonspecific background signal. In the processed image the nuclei are presented by single pixels with fluorescence intensity proportional to the average value of gene expression in the respective nucleus.

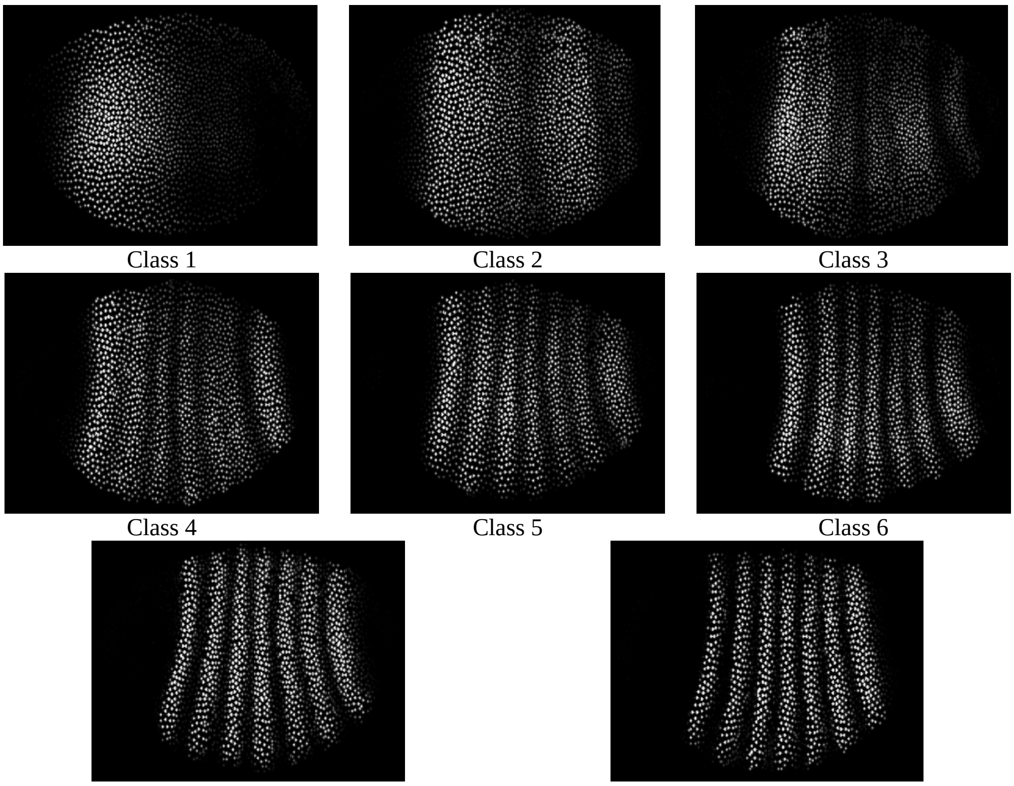

Fig. 1. Representative images of segmented and rescaled expression patterns belonging to the 8 temporal classes.

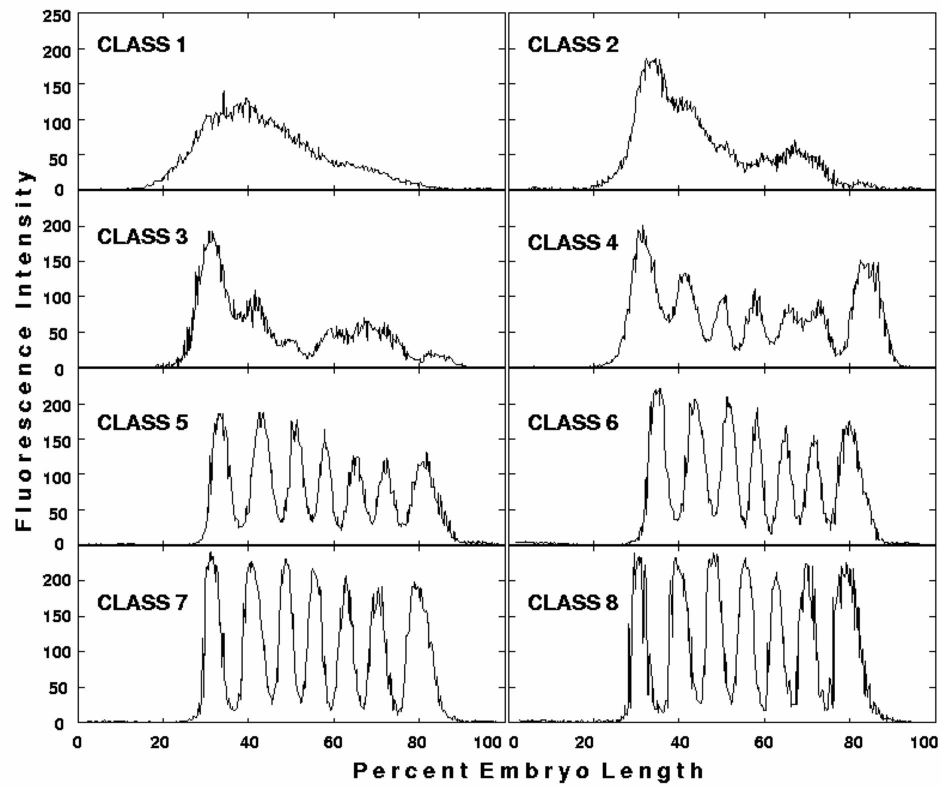

Fig. 2. Representative 1D expression patterns belonging to each of 8 temporal classes

Human observers classify the developmental stage of an embryo by careful study of its pattern, since each stripe possesses its own features at any stage of an embryo development. In such a way 809 embryos were subdivided into 8 temporal classes[16] (their representatives are shown in Fig.1). Each embryo was allocated to one of the temporal classes on the basis of thorough and extensive visual inspection of the expression pattern of the *eve* gene, which is highly dynamic. We selected embryos for scanning without regard for age, so we expect our dataset to be uniformly distributed in time. The 8 classes were approximately equally populated.

The evolution of the *eve* expression patterns during the segment determination shows the following tendency (see Fig. 1). Time classes 1, 2, and 3 do not have seven well-defined stripes and the number and location of stripes changes rapidly. The remaining groups (classes 4 to 8) do have seven well-defined stripes. After all the stripes are clearly visible their intensities increase in the posterior portion of the embryo. By the end of the period, all stripes have reached maximum and equal intensity and maximum sharpness. Time classes 1 to 3 could be grouped according to the number of individual stripes, which have formed. The remaining groups (classes 4, 5, 6, 7 and 8) all have 7 well-defined stripes and were classified by features of the overall pattern.

3. MULTI-VALUED NEURONS: LEARNING, NETWORKS, APPLICATION IN IMAGE RECOGNITION

3.1. Multi-Valued neuron and its learning

The concept of the multi-valued neuron (MVN) was introduced in[3]. The learning algorithms for MVN have been presented elsewhere[3, 5, 7]. The most comprehensive observation of MVN, its theoretical aspects, learning and properties are presented in[8]. Here we briefly review key mathematical properties of MVN and their learning algorithms.

An MVN[3, 8] performs a mapping between n inputs and single output. The mapping is described by multiple-valued (k-valued) function of n variables $f(x_1, ..., x_n)$ characterized by n+1 complex-valued weights w_0 ,w_1 , ...,w_n , so that

$$f(x_1,...,x_n) = P(w_0 + w_1 x_1 + ... + w_n x_n), \tag{1}$$

where $x_1, \ldots, x_n$ are neuron's inputs or in other words variables, on which the performed function depends. Values of the function and variables are also coded by complex numbers which are k^{th} roots of unity: $\varepsilon^j = \exp(i2\pi j/k)$, $j \in \{0, k\text{-}1\}$, i is an imaginary unity. In other words, values of the k-valued logic are represented as k^{th} roots of unity: $j \to \varepsilon^j$. P is the activation function of the neuron:

$$P(z) = \exp(i2\pi j/k), \quad \text{if } 2\pi j/k \le \arg(z) < 2\pi(j+1)/k, \tag{2}$$

where j=0, 1, ..., k-1 are the values of the k-valued logic, $z = w_0 + w_1 x_1 + \ldots + w_n x_n$ is the weighted sum , arg(z) is the argument of the complex number z. Thus the complex plane is divided into k sectors by (2), and if z belongs to the jth sector, neuron's output is equal to ε^j (Fig. 3).

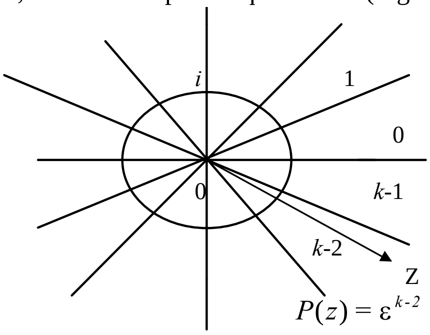

Fig. 3. Definition of the MVN activation function

MVN has some wonderful properties, which make them much more powerful than traditional artificial neurons. The representation (1) – (2) makes possible an implementation of the input/output mappings described by arbitrary partially defined multiple-valued functions. This makes it possible to develop more simple networks adapted for solving complicated applied problems. Another important property of the MVN is the simplicity of its learning algorithms. Theoretical aspects of the learning, which are based on the motion within the unit circle, have been considered in[8]. Considering MVN learning as a generalization of perceptron learning, we obtain the following. If a perceptron output is incorrect for some element of the learning set (1 instead of -1, or -1 instead of 1) then the weights have to be corrected according to some rule to ensure an inversion of the weighted sum sign. Therefore, it is necessary to move the weighted sum to the opposite subdomain (respectively, from "positive" to "negative", or from "negative" to "positive"). For the MVN, which performs a mapping described by a k-valued function we have exactly k domains. Geometrically they are sectors on the complex plane (see Fig. 3). If the desired output of the MVN on some element from the learning set is equal to, ε^q then the weighted sum has to be placed into the q^{th} sector. But if the actual output is equal to ε^s then the weighted sum belongs to the sector number s (see Fig.4). The learning rule must correct the weights to move the weighted sum from sector s to sector q.

We use here a previously proposed correction rule for MVN learning[8]:

$$W_{m+1} = W_m + \frac{C_m}{(n+1)} (\varepsilon^q - \varepsilon^s)\, \overline{X}, \tag{3}$$

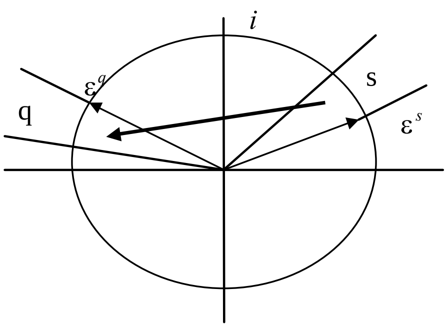

Fig. 4. Problem of the MVN learning

where W_m and W_{m+1} are the current and next weighting vectors, $\overline{X}$ is the complex conjugate of the vector of the neuron's input signals, ε is a primitive kth root of unity (k is chosen from (2)), C_m is a scale coefficient, q is a number of the desired sector on the complex plane, s is the sector into which the actual value of the weighted sum has fallen, n is the number of inputs to the neuron.

The learning rule (3) is a generalization of the perceptron error-correction rule, which has been considered earlier[1]. Since the learning rule (3) is linear, its computing implementation is very simple. The learning algorithm based on the rule (3) is very quickly converging. It is always possible to find such a value of k in the representation (2) that (1) will hold for a given function f describing the mapping between neuron's inputs and output[8].

3.2. MVN-based neural network for image recognition

Let us consider N classes of objects, which are presented by images of $n \times m$ pixels. The problem is formulated in the following way: we have to create a recognition system based on a neural network, which affords successful classification of the objects by fast learning on the minimal number of representatives from all the classes.

An MVN-based single-layer neural network, which contains the same number of neurons as the number of classes to be classified (Fig. 5), has been proposed in a form of such a system in[6].

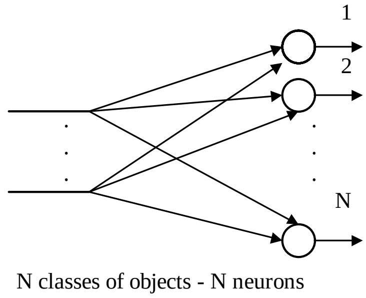

Fig. 5. MVN based neural network for image recognition

This model has been further developed[7, 8, 11, 12]. All 2D images are replaced by their Fourier spectra. Moreover, taking into account that a spectrum phase contains more information about an object presented by a signal than the amplitude[10, 13], only the phase is used for an object representation. Each neuron has to recognize pattern belonging only to its class and to reject any pattern from any other class. To classify an object in terms of neural networks we have to train a neural network on a learning set containing the spectral phase of representatives of the classes. Then the weights obtained in the learning process will be used for the classification of unknown objects.

Representation of the recognized objects by phases of Fourier spectral coefficients is appropriate for an MVN-based neural network. Since the inputs and outputs of an MVN are the complex numbers, moreover roots of unity, it is natural to use phases as the inputs. The nature of the MVN suggests how to make use of phase while neglecting amplitude: rather than normalize, we apply the transformation based on (2) to the inputs:

$$P(phase) = \exp(i2\pi j/k), \quad if \;\; 2\pi j/k \le phaze < 2\pi\,(j+1)/k \,. \qquad \textbf{(4)}$$

For classification of the pattern as belonging to the given class, the first l=k/2 sectors on the complex plane (see (2)) should be reserved. The other k/2 sectors correspond to the rejected patterns (Fig. 6).

Extraction of the phases from Fourier spectral coefficients is organized according to frequency ordering. We start from the lowest ones and then we proceed according to the so-called “zigzag” rule (Fig. 7).

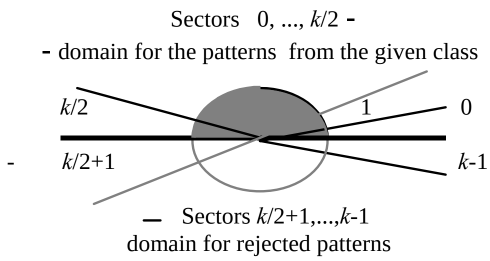

Fig. 6. Reservation of the domains for the recognition

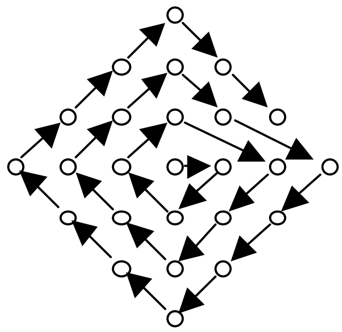

Fig. 7. Extraction of the phases

4. RECOGNITION AND CLASSIFICATION. PRELIMINARY RESULTS

The preliminary results, which we want to present in this Section, were obtained on the base of the considerations discussed in[11, 12]. At the same time they are different in comparison to the results presented in[11, 12], because the scaling of the input images after a segmentation[15] procedure was done in a different way.

To solve the classification problem we used the MVN-based neural network described above. Since the images from neighboring classes are often similar to each other, the architecture of the network has been modified in the following dichotomous way. A three-layered network was used. Two neurons of the first layer classify patterns into those belonging to classes 1-4 and 5-8, respectively. Four neurons of the second layer classify patterns into one of the classes 1-2, 3-4, 5-6 and 7-8, respectively. Finally, 8 neurons of the third layer classify a pattern into a particular class (Fig. 8), and the single neuron of output layer analyses the results coming from the neurons of the third layer.

To create representative learning sets for all the neurons, we used images that have been *a priori* correctly classified as representative for each particular class. This classification is based on the objective biological view described in section 2. Since it is natural to teach the neural network using maximally distinguished data, the definitely representative images were included in the learning set (from 28 to 35 images per class) and the other images were used for testing. All the neurons were taught using a learning algorithm based on the rule (3).

It is clear from Fig. 2 that the images are of low contrast and many of important details remain invisible. Moreover, the small level of brightness jumps between important details of the images negatively affects the informational capacity of the Fourier representation of the image. Phases of the image spectrum corresponding to neighboring classes are sometimes very close to each other. As a result, the number of misclassified images still remains relatively high, especially for the neurons of the third layer[11].

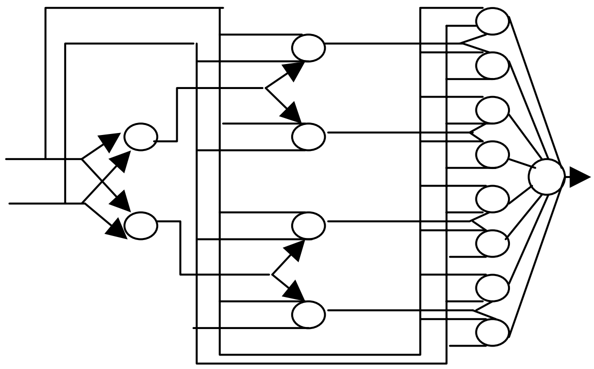

Fig. 8. The dichotomous neural network architecture used for classification

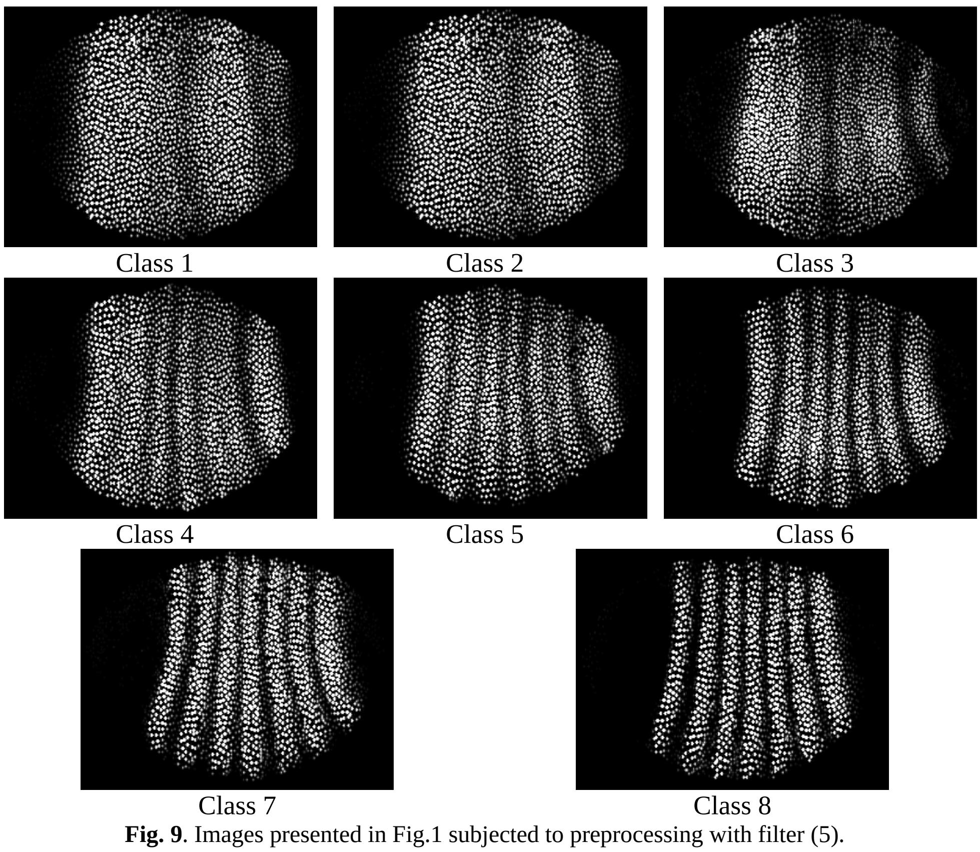

Fig. 9. Images presented in Fig.1 subjected to preprocessing with filter (5).

To fix this problem it is natural to use a filter, which can amplify high spatial frequencies while preserving at the same time low and medium spatial frequencies[12]. High frequency amplification makes it possible to enhance a contrast of the smallest objects against a residual image background. The application of spatial domain filter with the mentioned features significantly changes the spectrum modulo in the high frequency domain. At the same time such a filter changes the spectral phase in whole domain. The last property could be applied for the classification with the same parameters as those used before the proposed preprocessing procedure. We apply the following frequency correction spatial domain filter for the preprocessing:

$$\hat{B}_{ij} = (G_1 + G_2)B_{ij} - G_2 B_m + c\ , \tag{5}$$

where B_m is the local mean value in a 3 × 3 window surrounding the pixel B_{ij}; B_{ij}, and $\widehat{B}_{ij}$ are the signal values in ij^{th} pixel before and after processing; respectively, G_1 defines the correction of the low spatial frequencies, G_2 defines the correction of the high spatial frequencies, c is the mean value of the background after processing. The significant improvement of image quality after applying the filter (5) is shown in Fig.9, which shows the same images, which are presented in Fig.1 processed with the filter (5).

We present here the classification results obtained for all three layers of the network. These results are given in Table 2. Each neuron has been taught using the most representative features (Fourier spectrum phases) corresponding to each particular case. All the parameters are chosen experimentally for each neuron. A choice of *k* is determined by ensuring the best precision for the representation of phases. In all cases a value of *k*, which is used, provides the better results than those obtained with smaller values of *k*. A chosen number of frequencies and the chosen frequencies themselves are sufficient to achieve good results, which could not be obtained in case of a smaller number of frequencies or different frequency range. On the other hand the further increasing of the frequencies number does not lead to the recognition improvement in each case.

Table 1. Classification results

Class #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
The results of testing for the 1st layer of neurons								
Classes	**Classes 1-4**				**Classes 5-8**			
Number of frequencies/ inputs/*k*	1-6/ 84/ 4096				1-6/ 84/ 4096			
Number of Images	48	43	68	55	78	89	66	46
Recognized	36	42	68	43	52	83	63	40
Unrecognized	2	0	0	0	0	1	3	0
Misclassified	10	1	0	12	26	5	0	6
The results of testing for the 2d layer of neurons								
Classes	**1-2**		**3-4**		**5-6**		**7-8**	
Number of frequencies/ inputs/*k*	1-5/ 60/ 2048		1-5/ 60/ 2048		1-6/ 84/ 4096		1-6/ 84/ 4096	
Number of Images	48	43	68	55	78	89	66	46
Recognized	34	33	51	55	74	69	45	39
Unrecognized	0	1	0	0	1	0	1	0
Misclassified	14	9	17	0	3	20	20	7
The results of testing for the 3d layer of neurons (final classification results)								
Classes	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Number of frequencies/ inputs/*k*	1-8/ 144/ 4096	1-8/ 144/ 4096	1-5/ 60/ 2048	1-5/ 60/ 2048	1-8/ 144/ 4096	1-8/ 144/ 4096	1-5/ 60/ 2048	1-5/ 60/ 2048
Number of Images	48	43	68	55	78	89	66	46
Recognized	46 (95%)	33 (76%)	53 (77%)	47 (85%)	56 (71%)	65 (73%)	48 (72%)	32 (69%)
Unrecognized	0	1	1	1	0	0	0	0
Misclassified	2	9	14	7	22	24	18	14

5. RECOGNITION AND CLASSIFICATION. FINAL RESULTS

The classification results presented in Table 3 are good. They confirm the efficiency of the proposed solution. At the same time these results can be improved.

There are several ways to improve the results. We would like to consider here one of them. As it was described above, the Fourier spectrum phases, which are used as the features of the images and inputs of the neural network, are taken regularly: all phases from someone to some another one are used as inputs of the neural network. At the same time the importance of the particular inputs is not taken into account. This is a disadvantage because the informational capacity of the phases is not uniformly distributed. Some of them are very important, some other ones are less important. So a good idea is the analysis of the phases that are used as the features for the classification and the estimation of their importance. Then the features, which are not important, may be excluded from the consideration.

There are several different methods to estimate the importance of the features. The method, which we would like to propose here, is based on the estimation of informational capacity of the features.

Let us consider the equation for the weighted sum of the neuron's inputs:

$$z = w_0 + w_1 x_1 + \ldots + w_n x_n , \tag{6}$$

where $x_1, \ldots, x_n$ are neuron's inputs, $w_0, w_1, \ldots, w_n$ are the weights. Let us suppose that the learning process is finished. It means that the weights $w_0, w_1, \ldots, w_n$ are already obtained. It is clear that the addends in (6) corresponding to the small values of the weights do not contribute a lot to the value of the weighted sum. Indeed, it is clear from the sectors reservation for the classification (Fig. 6) that small addends in (6) can not have a principal influence on the neuron's output.

At the same tome a philosophy of the learning says that the smallest weights correspond to the features, which are the less important. Really, since the corresponding addends in (6) do have a very small influence on the result, the informational capacity of the corresponding features is very small. This consideration leads us to the following conclusion: the features (phases) corresponding to the weights, for which

$$|w_i| < \delta , \tag{7}$$

where δ is some number satisfying a criterion $|w_i|_{\substack{\min \\ i=1,\ldots,n}} < \delta < |w_i|_{\substack{mean \\ i=1,\ldots,n}}$ ($|w|$ is an absolute value of the complex number *w*), can be removed from the feature vectors.

After this removal the network might be relearned using the reduced number of inputs. A choice of δ in (7) has to be such that the classification rate after re-learning would be at least on the same level.

The main advantage of the reduction of inputs, which is proposed, is the performance improvement both for the learning and the classification.

The proposed method of the features (network's inputs) reduction has been tested using the same data that have been used in the previous Section. The weighting vectors of each neuron obtained after the learning were analyzed according to (7), and some amount of inputs has been removed. Then all the neurons were re-taught using the reduced number of inputs. The classification results are shown in Table 2. Comparison of these results to the results presented in Table 1 shows that the proposed approach of the estimation the informational capacity of the features is effective. The removal of the less important features does not lead to the reduction of the classification rate.

6. CONCLUSIONS AND FUTURE WORK

We have performed a temporal classification of *Drosophila* embryos on the basis of the knowledge about their gene expression patterns. These patterns have been presented by the images obtained using confocal scanning microscopy. To ensure the better description of the data we used their frequency domain representation.

The MVN-based neural network has been used for solving the classification problem. A limited number of the Fourier spectrum phases have been used as the features for the classification. A method for the estimation of the importance of the features has been proposed. Using this method a number of features that are important for the classification has been reduced. This reduction is important for improvement of the network performance both on the stages of learning and classification. The obtained results are promising.

A future work will be directed to deeper analysis of the feature importance and further reduction of the features' number, which ensures good classification results. The prime tests and factor analysis methods will be used for this purpose.

Table 2. Classification results after the reduction of the features (inputs) nember

Class #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
The results of testing for the 1st layer of neurons								
Classes	**Classes 1-4**				**Classes 5-8**			
Number of frequencies/ inputs/*k*	1-6/ 84/ 4096				1-6/ 84/ 4096			
Number of Images	48	43	68	55	78	89	66	46
Recognized	36	42	68	43	52	83	63	40
Unrecognized	2	0	0	0	0	1	3	0
Misclassified	10	1	0	12	26	5	0	6
The results of testing for the 2d layer of neurons								
Classes	**1-2**		**3-4**		**5-6**		**7-8**	
Number of frequencies/ inputs/*k*	1-5/ 18/ 2048		1-5/ 18/ 2048		1-6/ 48/ 4096		1-6/ 48/ 4096	
Number of Images	48	43	68	55	78	89	66	46
Recognized	32	34	53	55	75	68	44	37
Unrecognized	7	1	4	0	0	1	3	1
Misclassified	9	8	11	0	3	20	19	8
The results of testing for the 3d layer of neurons (final classification results)								
Classes	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Number of frequencies/ inputs/*k*	1-8/ 43/ 4096	1-8/ 43/ 4096	1-5/ 50/ 2048	1-5/ 54/ 2048	1-8/ 76/ 4096	1-8/ 74/ 4096	1-5/ 43/ 2048	1-5/ 43/ 2048
Number of Images	48	43	68	55	78	89	66	46
Recognized	46 (95%)	33 (76%)	52 (76%)	48 (87%)	55 (70%)	64 (71%)	48 (72%)	32 (69%)
Unrecognized	0	1	1	0	0	2	0	0
Misclassified	2	9	15	7	23	23	18	14

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