Wpływ technik rozpoznawania wzorców na ocene złośliwości nowotworów piersi

Influence of Pattern Recognition Techniques on Breast Cytology Grading

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Treść. W ninieszym artykule prezentujemy zastosowania technik rozpoznawania wzorców oraz analizy obrazu do automatycznej obróbki i analizy obrazów cytologicznych. W celu wskazania nowych wyzwań w tej dziedzinie przegląd literatury zwiazanej z tym zagadnieniem został zaprezentowany. Ocena złośliwości nowotworów piersi jest skomplikowanym problemem gdzie doświadczenie jest bardzo istotne i może mieć wpływ na końcową diagnozę. Zastosowanie komputerowego systemu oceny pozwoli na zobiektywizowanie tego procesu. Artykuł prezentuje liczne zastosowania technik rozpozanwania wzorców w odniesieniu do zdjęć cytologicznych nowowtworów piersi w celu lepszej separowalności nietylko między komórkami nowtworowymi i zdrowymi, ale także między stpniami złośliwości. Wyznaczenie stopnia złośliwości jest bardzo istotne w diagnostyc, ponieważ ma wpływ na wybór sposobu leczenia. W niniejszym artykule prezentujemy także porównanie trzech sieci neuronowych wykorzystanych do oceny zdjęć cytologicznych piersi oraz porównujemy ich działanie z perceptronem wielowarstwowym opisanym w literaturze.

Słowa kluczowe: aspiracyjna biopsja cienkoigłowa, ocena złośliwości nowotworów piersi, rozpoznawanie wzorców

Abstract. In this paper we discuss applications of pattern recognition and image processing to automatic processing and analysis of cytological images. The literature survey of the problem is presented to point out new chalenges. The brest cancer malignancy grading is a difficult procedure that involves a lot of experiance which can have an impact on the diagnosis. A role of the computerized system is to help to make the diagnosis process more objective. The paper presents numerous applications of the patteren recognition techniques to breast cancer cytology to produce better discriminations not only between cancerous and helthy cells but also malignancy grades. Determination of the maligancy grade is crutial during the diagnosis because it will have an impact on the patient treatment. In the paper we also present a comparison of three neural networks applied to the breast cytology and compare them to the multilayer approach from the literature.

Keywords: fine needle aspirates, breast cancer malignancy grading, pattern recognition

1. Introduction

Automatic detection of pathologies from histopathological and cytological images is currently a very active and important area of research. In the present paper we will survey application and influence of pattern recognition techniques on automatic grading of breast cancer fine needle biopsy slides. We will focus on automatic cancer grading because it a very challenging task due to large variation in cancer imaging and analysis. Section 2 consists of the review of pattern recognition applied to breast cancer diagnosis as this is the main reasearch interest but in the remainder of the paper we shall focus on automatic malignancy grading of breast cancer fine needle aspiration biopsies.

2. Breast Cancer Diagnosis

According to statistics breast cancer is one of the most deadly cancers among middle-aged women. Based on the data provided by the Breast Cancer Society of Canada about 415 women will be diagnosed with breast cancer each week in Canada. Most of the diagnosed cases can be fully recovered when diagnosed at an early stage. Cancers in their early stages are vulnerable to treatment while cancers in their most advanced stages are usually almost impossible to treat. During the diagnosis process, the cancer is assigned a grade that is used to determine the appropriate treatment. Successful treatment is a key to reduce the high death rate. The most common diagnostic tools are a mammography and a fine needle aspiration biopsy (FNA). Mammography, which is a non-invasive method, is most often used for screening purposes rather than for precise diagnosis. It allows a physician to find possible locations of microcalcifications and other indicators in the breast tis-

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sue. When a suspicious region is found, the patient is sent to a pathologist for a more precise diagnosis. This is when the FNA is taken. A fine needle aspiration biopsy is an invasive method to extract a small sample of the questionable breast tissue that allows the pathologist to describe the type of the cancer in detail. Using this method pathologists can very adequately describe not only the type of the cancer but also its genealogy and malignancy. The determination of the malignancy is essential when predicting the progression of cancer.

2.1. Computer-aided Breast Cancer Diagnosis

Breast cancer diagnosis is a very wide field of research studying not only medical issues but also computer science issues. Breast cancer diagnosis is a multi-stage process that involves different diagnostic examinations.

Pattern classification is a well-known problem in the field of Artificial Intelligence concerned with the discrimination between classes of different objects [1]. We can use the same techniques in cancer diagnosis to assist doctors with their decisions. Cheng et al. [2] provided an extensive survey on automated approaches in mammograms classification and importance of computer assisted diagnosis. Since mammography is one of the preliminary tests performed to locate abnormalities in the breast tissue, it is used for screening purposes and has raised a lot of interest within the scientific community [2–8].

To the best of our knowledge, the computerized breast cytology classification problem was first investigated by Wolberg et al. in 1990 [9]. The authors described an application of a multi-surface pattern separation method to cancer diagnosis. The proposed algorithm was able to distinguish between a 169 malignant and 201 benign cases with 6.5% and 4.1% error rates, respectively depending on the size of the training set. When 50% of samples were used for training, the method returned a larger error. Using 67% of sample images reduced the error to 4.1%. The same authors introduced a widely used data-base of pre-extracted features of breast cancer nuclei obtained from fine needle aspiration biopsy images [10]. Later, in 1993, Street et al. [11] used an active contour algorithm, called ‘snake’ for precise nuclei shape representation. The authors also described 10 features of a nucleus used for classification. They achieved a 97.3% classification rate using multi-surface method for classification. The features described by the authors are mainly geometrical features of the nucleus. Based on these features, Street [12], in his PhD Thesis introduced a system called XCyt. In 1999, Lee and Street [13] described an iterative approach for automated nuclei segmentation as an addition to the previously described framework. In 2003, they introduced flexible templates to their iterative Generalized Hough Transform approach for segmentation. They created a set of predefined templates of a nuclei and each iteration shuffles the templates in such a way that those that were used the most often during the previous iteration are visited first to save time. The authors were able to segment nuclei with 78.19% accuracy [14]. They also introduced a neural network approach for classification stage, achieving 96% accuracy. Classification was based on the features previously described by Street et al. [11].

All work presented above was based on the Wisconsin Breast Cancer Database (WBCD) introduced by Mangasarian et al. [10]. This data-base consists of pre-extracted nuclear features and is widely used among researchers. Features included in the data-base are the features proposed by Street et al. [11]. WBCD [10] and its variations [15, 16] are the only data sets publicly available. Therefore, the majority of work in this field is performed on this data-base and involves research on different classification algorithms. In 1998, Walker et al. [17, 18] introduced Evolved Neural Networks for breast cancer classification and tested their algorithm on WBCD data-base achieving 96% correctness. Nezafat et al. [19] used WBCD to compare several classification algorithms such as k-nearest neighbor classifier, radial-basis function, neural networks, multilayer perceptron and probabilistic neural networks. The authors showed that among these classifiers, multilayer perceptron with one hidden layer performed the most efficiently giving 2.1% error rate. Additionally they also compared and reported which of the features extracted by Wolberg et al. [9] were most significant for classification. In 2002, Estevez et al. [20] introduced a different approach for classification based on the Fuzzy Finite State Machine, but their system performed rather poorly giving 19.4% error for the testing set of images. To extract features, the authors first manually segment nuclei from the image and then apply a low-pass filter and in the following step topological map of a nuclei is created. The extracted features are texture based. Motivation for them was that benign cell textures have bigger homogenous gray areas and more concentric contours than malignant cell textures. Bagui et al. [21] recently introduced a classification algorithm applied to WBCD. The authors described a generalization of the rank nearest neighbor rule and obtained results that show a 97% recognition rate, which, according the authors, is better than that previously reported in the literature. From the above discussion we can deduct that majority of work in the field of breast cancer detection and classification was performed by Street et al. and Wolberg et al. We can find other approaches such as wavelet based approach of Weyn et al. [22]. Here the authors introduce a textural approach for chromatin description and claim that it has a 100% recognition rate.

Another approach is one introduced by Schnorrenberg et al. [23] that uses receptive fields for nuclei localization as an integral part of a bigger system, called ‘BASS.‘ In 1996, they introduced a content-based approach [24] and provided an extensive survey on existing histopathological systems [25]. The authors presented two types of color-based features, luminance-based local features and global features. Luminance features were obtained from image RGB values. Global features are the variance and average of luminance in the image. They also introduce

one texture measure that is calculated according to the luminance variance and current nucleus luminance. Approaches presented by Schnorrenberg et al. are mostly based on histological samples rather than cytological. In 2000, they presented a description of features used in their research [26] on classification of cryostat samples during intra-operative examination based on feed-forward neural networks achieving the highest accuracy of 76% on their own database.

In the literature we can also find some other approaches that involve segmentation of a breast cancer nuclei rather than classification. In 1996, Belhomme *et al.* [27] proposed a watershed based algorithm for segmentation of breast cancer cytological and histological images.Their algorithm is a more general version of the method described by Adams and Bischof [28]. The generalization involves the usage of numerous merging criteria. Authors use the segmentation principles described by Beucher in his PhD thesis [29]. This involves the decomposition of the segmentation procedure into two steps. In the first step, the image is simplified based on a set of markers. The second stage involves region decomposition by the construction of the watershed lines [27]. The algorithm proposed by Belhomme *et al.* is the extension of the Beucher and Meyer [30] method by introduction of a general segmentation operator.

In 1998, Olivier *et al.* [31] introduced another extension to the watershed algorithm in addition to that of Belhomme *et al.* Their extension incorporates the color information in the image regardless of the color space. The authors compared their segmentation results against the segmentation performed by three experts and they reported the correctness of their method to be between 89.2% and 98.3% for the nuclei.

Another approach to nuclear segmentation is based on fuzzy c-means clustering and multiple active contours models described by Schüpp *et al.* [32]. The authors describe a level set active contours method, where the initial level set is obtained by the fuzzy c-means algorithm.

2.2. Computer-aided Breast Cancer Grading

In the previous section we described different approaches for breast cancer diagnosis. Most of those systems discriminate only benign and malignant cases. For good diagnosis it is crucial to evaluate the malignancy grade. In cytology, the malignancy is graded according to the Bloom-Richardson scheme [33]. This system is based on grading of cells' polymorphy, the ability to reform histoformative structures, and mitotic index. All of these features are described by the Bloom-Richardson scheme as three factors that use a point based scale for assessing each feature. The malignancy of the tumor is assigned a grade that depends on the quantitative values of the above factors and is determined by the summation of all awarded points for each factor. Depending on the value, the tumor is assigned with low, intermediate or high malignancy grade. In [34] we can see attempts at prognostication along with nuclear classification. For their grading approach, the authors used only nuclear features of a cell, which correspond to the second factor in Bloom-Richardson grading scheme. They were estimating the prognosis of the breast cancer according to these features. Further attempts for malignancy grading include VLSI approach introduced by Cheng et al. [35] in 1991 and applied in 1998 to breast cancer diagnosis [36]. In this method, the authors propose a parallel approach to tubule grading for histological slides. The authors divided their algorithm into four stages. The first stage consists of image enhancement for which purpose they use median filtering to remove artifacts. In stage two, the authors locate possible tubule formations by image thresholding with a threshold level known *a priori*. The next stage is a classification stage, where regions are classified as tubular formations. The features used in this study consists of brightness, bright homogeneity, circularity, size, and boundary colors. In the fourth stage, the authors count the number of tubular formations. The work presented by the authors not only deals with histology but also only mentions grading using only one factor on the Bloom-Richardson scale. The authors showed time improvement of the parallel algorithm that grades tubules to $O(n)$ time while previously reported run time complexities were $O(n^2)$, where n is the size of the input data. In 1991, MacAulay *et al.* [37] introduced a graphics package for Bloom-Richardson grading of histological tissue. Their application acts as a typical graphics program that allows user to pick the nuclei from the image and perform some basic calculations. This process is almost completely user dependent. The authors provide an extensive description of the interface of the package but no further information on computation grading was found. Another approach found in literature is an algorithm based on wavelet texture description of chromatin [22]. This work was also performed on histological slides. The features calculated by the authors are calculated according to wavelet parameters and are divided into three groups. The first group are co-occurrence parameters that describe the color intensity in the image. The second set of parameters are densitometric parameters that are based on intensity values of the nucleus. The third group consists morphometric parameters that describe the geometry of the nucleus. Authors performed tests on their data-base of 83 histological slides and claim to have 100% classification rate. Such a high rate suggests a good separation between the classes.

In 2004, Gurevich and Murashov [38] proposed a method for chromatin structure analysis based on scale-space approach of Florack and Kuijper [39]. The authors claim that chromatin distribution corresponds to the grade of malignancy. This statement is supported by additional studies of Rodenacker [40, 41, 42] and Weyn *et al.* [43]. The authors also mention another approach to chromatin description. This method uses heterogeneity, clumpiness, margination and radius of particles and was introduced by Young *et al.* [44]. The algorithm of Guverich and Murashov uses topological properties of iso-intensity manifolds

in the spatial extrema neighborhoods [38]. Their algorithm is able to measure the number of chromatin particles in the input image. For testing purposes the authors trained several classifiers achieving a classification rate between 72% and 85.4%. In 2006, Gurevich *et al.* [45] described a system for automatic analysis of cytological slides for the lymphatic system tumors. The authors used a Gaussian filter for segmentation of a nuclei from the previously extracted blue channel of the image. The feature extraction part of the proposed system is the same as in [38] plus an additional 47 features described by Churakova *et al.* [46]. These features include a well known and widely used morphological features such as the area of a nuclei, histogram features and features based on a Fourier spectrum of a nucleus [45]. In this paper, the same choice of classifiers was used as in [38] but the accuracy increased and is claimed by the authors to be above 90%. The authors did not provide an accurate error rate of their experiments and therefore it is difficult to assess the accuracy of the proposed system.

To the best of our knowledge, currently there is no publicly available database and most of the approaches presented in the literature are tested on the databases created by the authors, which makes the comparison of the obtained classification results with those reported in the literature difficult. The only commonly used database that we came across during this study is the Wisconsin Breast Cancer Database, which was described earlier in this thesis. This database is freely available from the authors web page [9]. In this study, some of the proposed features are the same as in WBCD but the testing of the presented system on that database would be limited only to the classification stage due to the fact that WBCD is a database of pre-extracted features.

In 2005 a commercial system for automated histopathological tissue grading was released by QinetiQ [47]. According to the specifications and discussion with a pathologist, the results obtained by this system seem to be difficult to confirm. According to the authors, their system showed performance similar to the pathologists during clinical evaluation that was performed on 100 patients.

The most recent development in the field of automated breast cancer grading was described by Jeleń in his PhD thesis [48]. There are also other recent approaches by Naik *et al.* [49] and Jeleń *et al.* [50–54].

In [49] describe various segmentation methods such as level sets for classification of prostate and breast cancer histological slides. The described system was able to distinguish between low and high malignancy grades with 80.52% accuracy when automatic classification was used. The accuracy described by Jeleń in [48] was as high as 86.75% for cytological slides. The author in his thesis did an extensive study of the features and classification methods to determine a set of features and the classification method that will be able to classify the breast cancer malignancy into intermediate and high malignancy grades. Author also introduced a set of three new features that are used for the determination of the first factor of Bloom-Richardson scheme. These features where described in [50] and their discriminatory power were described in [52]. Features that were introduced by Jeleń include the area of grouped cells in the FNA slide (see Fig. 1), the number of groups that are visible on the slide and the third feature is a dispersion that describes if the cells in the image are grouped or dispersed. Beside a set of so called low magnification features author proposed the usage of 31 features that represented the nuclear structures of the cell. These features related to the second and third factor of the Bloom-Richardson grading scheme. In the thesis, the author performed a set of classification tests performed the calculations of the discriminatory power of the features to propose a set of features that are not correlated and provide the best classification results. From all of the tests, the author showed that the multilayer perceptron was the best performing classifier. The 34 element feature vector was reduced to 15 features. Fig. 2 shows graphically the correlation between the original set of 34 features. The features with the best discriminatory power were the three low magnification features described earlier and 12 nuclear features such as perimeter of a nucleus, convexity, x-centroid of the cell, nuclei orientation, its vertical projection, the φ_3 momentum feature, histogram mean, energy, textural homogeneity, red channel histogram mean, skew and width.

In [51] the authors did a comparative study of the discriminatory power of the low magnification features against

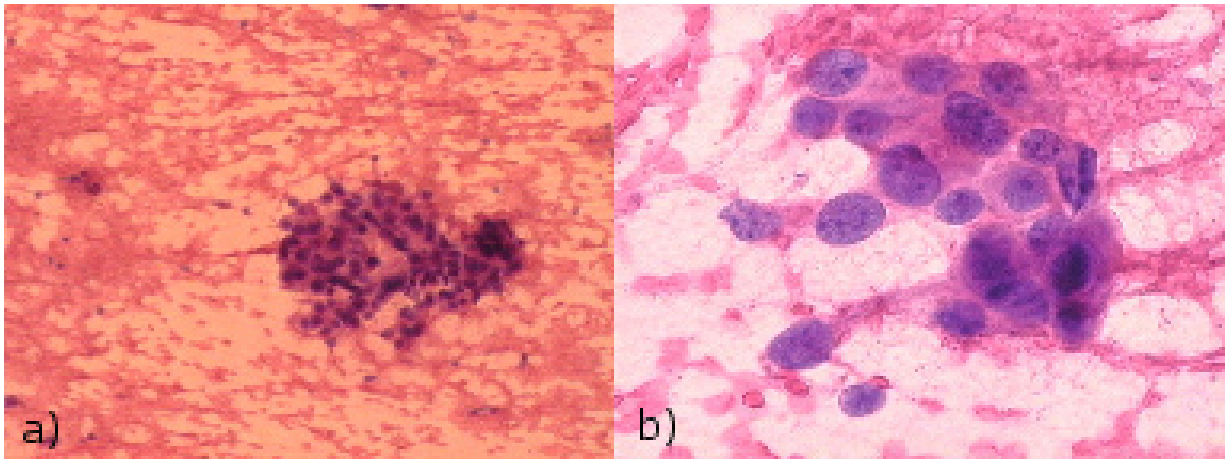

Figure 1: FNA images: a) 100 x resolution; b) 400 x resolution.

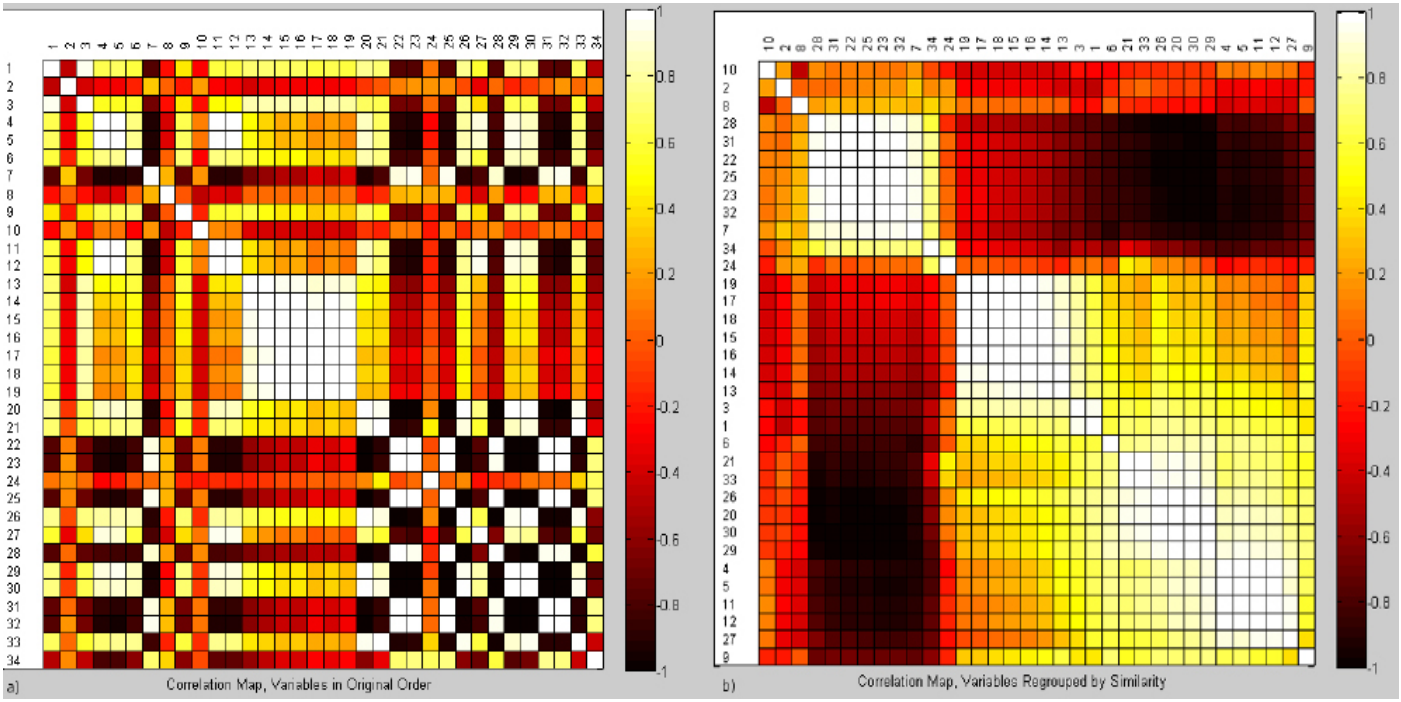

Figure 2: Correlation between extracted features: a) with variables in original order; b) with variables regrouped by similarity.

the features based on the cell nucleus. From their study, one can notice that on average low magnification features perform better but the best classification was recorded for a feature vector that consisted of both types of features. In [53] the authors showed that the best classification was achieved for the multilayer perceptron when the fuzzy c-means segmentation was used. On average, for most tested classifiers, the best classifications where obtained when the level set segmentation was used.

The described work done by Jeleń *et al.* was applied to a classification system built and currently being tested in the pathological laboratory. In [54] the authors show that preliminary medical tests provide promising results and the automated breast cancer grading system performs with a high accuracy when applied to the real and unseen data. The achieved accuracy was 81.96%.

3. Comparision of the Breast Cancer Malignancy Classification

In this paper we present a comarative study of the classification performance of the multilayer perceptron, as described by Jeleń, and three other types of neural networks. The tested networks include modular neural networks [55], radial basis function networks [56] and recurrent neural networks [57]. Modular networks make use of several multilayer perceptrons in parallel to process the input signals. The results obtained by all of the MLPs is then recombined to provide the final answer of the network. Because not all of the layers are interconnected and therefore less weights needs to be recalculated, the training process of these networks is reduced. The radial basis function (RBF) networks are, in fact, nonlinear hybrid networks. They are built with one hidden layer that uses the gaussian transfer function. The recurrent neural networks are constructed in such a way that each hidden layer consists of the feedback loop to itself. This feedback allows for the determination of the relationships in time as well as through the input space [57].

For the purpose of this study, four neural networks described above were used and their classification accuracy was compared. The classification results are summarized in the Tab. 1. For test purposes a reduced set of features was used, as proposed by Jeleń in [48]. The described classifiers were applied to Jeleń's database to maitain the significance of the results. Additionally, a 10-fold cross-validation method was used to partition the data into ten subsets. One of these subsets was retained for testing and the remaining 9 were used for training. The overall error is calculated as an average error of all 10 tests.

Table 1: Classification error rates obtained with cross-vallidation.

Test No.	MLP	Modular NN	RBF NN	
1	17.01	20.35	22.30	11.62
2	41.65	31.30	15.14	33.71
3	4.78	11.20	12.14	17.29
4	13.11	24.88	14.35	23.20
5	6.32	9.32	18.79	23.83
6	5.84	18.85	32.27	11.06
7	2.44	1.36	2.42	15.72
8	3.33	2.58	23.80	33.32
9	20.37	12.40	25.93	23.17
10	19.97	17.84	27.95	25.28
Avg.	13.48	15.01	19.51	21.82

Classification results summarized in Tab. 1 show the performance of the tested classifiers. It can easily be noticed that the multilayer perceptorn provides the best classification accuracy. The best performance from the newely proposed neural networks was noticed for modular networks which consits of several MLPs in parallel. It can also be noticed that the addition fo of the recurrent loop did not provide us with better results and overall achieved the highest error rate of all tested neural networks.

4. Conclusions

The objective of this study was to compare the performance of other than multilayer perceoptron neural networks. From the results presented in sec. 5 one can notice that the proposed neural networks did not achieve better accuracy than MLP. This brings the conclusion that for breast cancer grading the more complicated structure of the network does not improve the classification. In sec. 4 it was mentioned that the system based on the multilayer perceptron is currently tested and so far its accuracy is 81.96 %. Looking at the Tab. 1 it can be noticed that the accuracy of modular networks was 84.99 %. Comparing this two accuracy rates allows to draw the conclusion that it is worth to test the performans of these network on the real data and see how the accuracy of the classifiaction will change.

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