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RESEARCH ARTICLE

Automatic Bone Marrow White Blood Cell Classification

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Abstract *- The proportion of counts of different types of white blood cells in the bone marrow, called differential counts, provides invaluable information to doctors for diagnosis. Due to the tedious nature of the differential white blood cell counting process, an automatic system is preferable. This is important because segmentation of nucleus is much easier than the segmentation of the entire cell, especially in the bone marrow where the white blood cell density is very high. We analyze a set of white-blood-cell-nucleus-based features using mathematical morphology. Fivefold cross validation is used in the experiments in which Bayes' classifiers and artificial neural networks are applied as classifiers. The classification performances are evaluated by two evaluation measures: traditional and class wise classification rates.*

Keywords- *Mathematical morphology, Fivefold cross validation, Bayes' classifiers*

I INTRODUCTION

Differential counts of white blood cells in bone marrow provide invaluable information to doctors, and aid in patients' diagnosis. Diseases such as leukemia, acquired Immunodeficiency syndrome (aids) or cancers can be diagnosed by analyzing the white blood cell differential counts, i.e., the counts of different cell classes. The traditional method for an expert is to use a microscope to select an area of interest. In a bone marrow slide, detect a white blood cell, classify the Cell based on his knowledge and experience, increase the count of the corresponding cell class, and repeat the cycle until all Cells in the area of interest are counted. To perform all these Processing manually is a very tedious process for a trained expert and, thus, an automated differential counting system that helps in saving time and money is highly desirable. Bone marrow cells are normally diagnosed by light microscopy.

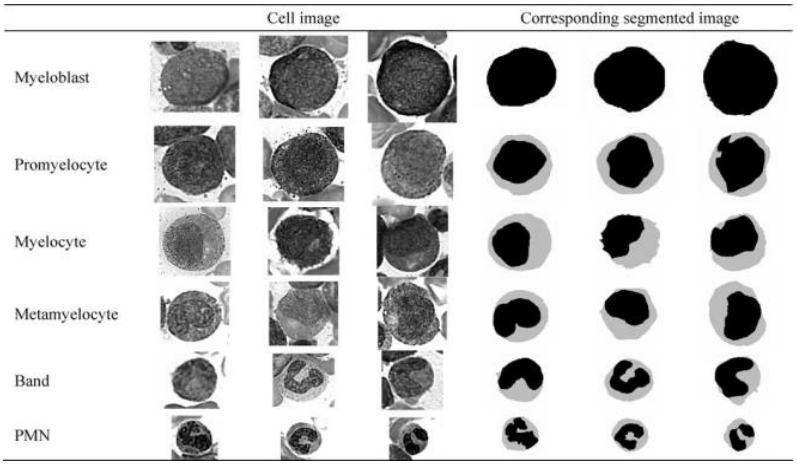

Fig.1. Cell samples and corresponding manually segmented images in the myelocytic or granulocytic series

White blood cells in bone marrow are classified according to their maturation stages. When a white blood cell becomes older, its size, the size and shape of the nucleus, and many other characteristics change. White blood cells in the myelocytic or granulocytic series can be classified into six classes, i.e., myeloblast, promyelocyte, myelocyte, metamyelocyte, band, and poly-morphonuclear (PMN) the proposed automatic techniques follow the traditional manual process of detecting a cell, extracting its features, classifying the cell.

We propose a method for the classification of white blood cells using only their nucleus information. This idea is very useful in practice because one of the difficulties in the differential counting in bone marrow is how to deal with the cells that touch each other. This problem occurs frequently in cells of the bone marrow because here the white blood cells are very dense. If the cell classification is based only on the information about the nucleus, then we do not need to segment the entire cell, and only nucleus segmentation is adequate. Although many techniques have been applied to cell segmentation, this problem is not solved, especially in touching cells. To decouple the effects of segmentation errors, we extract features from manually segmented nucleus of a white blood cell based on morphological granulometries. We apply Bayes classifiers and artificial neural networks to the problem of white blood cell classification of single-cell images and compare their results to those obtained.

II. METHODOLOGY

We use only four features, extracted from each blood cell's nucleus. Morphology-based information of an object called the pattern spectrum is the key here. The features are tested using Bayes classifiers and artificial neural networks.

A. Classifiers

We apply two classifiers, a Bayes classifier and an artificial neural network classifier. The Bayes classifier is a traditional statistics-based classifier that analyzes discriminant functions. A classifier assigns an input vector x to class Ck if $y_k(x) > y_j(x)$ for all $j = k$. By choosing $y_k(x) = P(C_k|x)$, this posterior probability is the probability of a pattern belonging to class Ck when we observe the input vector x.

Artificial neural networks have been widely applied to many areas of research such as military, medicine, business, etc., because they can be considered as universal approximations. Several approaches have previously been proposed in the literature to solve for the best set of weights, where the best being defined in terms of minimizing a total sum of

mean squared errors. However, in this research, because of the heavy computation load in the training process, we selected the Levenberg– Marquardt (LM) algorithm as it provides a faster convergence

B. Mathematical Morphology

Mathematical morphology is a branch of nonlinear image processing and analysis that was first introduced by Matheron in the context of random sets. Morphological methods are used in many aspects of image processing, e.g., enhancement, segmentation, restoration, edge detection, texture analysis, shapes analysis, etc. Here, we describe binary morphological operations only. We successively apply the opening operation to an image S and increase the size of structuring element E in order to diminish the image. This can be considered as a sieving process, where objects with larger sizes than the holes remain on the sieve. The shape of the holes is dictated by the shape of the structuring element. Let Ω(t) be area of SOtE where O denotes the opening operation, t is a real number, and Ω(0) is area of S. It should be noted that, in the continuous domain, tE is simply the scaled version of E by the factor t. In the discrete domain, however, tE is implemented by t successive dilations of E, with itself as the structuring element, and Ω(t) is called a size distribution. The normalized size distribution $\Phi(t) = 1 - \Omega(t)/\Omega(0)$ and d t)/dt are called granulometric size distribution or pattern spectrum of S.

III. DATA DESCRIPTION

We used the gray-scale bone marrow images collected at the University of Missouri Ellis Fischel Cancer Center. The images were taken from a slide of a patient's bone marrow smear, without any information about his/her health condition, by an Olympus BX50 microscope, a Sony B/W charge-coupled device (CCD) camera, and an 8-bit digitizer (PDI IMAXX.) Magnification of 600× was used without any special filters. Each white blood cell image was cropped manually to form a single-cell image. Then, a single-cell image was segmented manually into nucleus, cytoplasm, and background regions. The images were manually classified. The data set consists of six classes of white blood cells—myeloblast, promyelocyte, myelocyte, metamyelocyte, band, and PMN. There are respectively 20, 9, 139, 33, 45, and 185 manually segmented images for the six cell classes. Each manually segmented image is composed of three regions—nucleus, cytoplasm, and background—with gray levels equal to 0, 176, and 255, respectively. Samples of cell types in this data set and their corresponding segmented images are shown in Fig. 1.

IV. EXPERIMENTAL FRAMEWORK

Four features are extracted from each cell's nucleus. The features are used as the inputs to two types of classifiers, i.e., a Bayes classifier and an artificial neural network classifier. A fivefold cross validation is applied to let us perform the training and testing on the data set. The classification results are evaluated in terms of the traditional classification rate and the class wise classification rate. The nucleus feature extraction, the classification performance evaluation, and the experimental results and analysis.

A. Nucleus-Based Features

For a random set S, Ω(t) is a random function. The pattern spectrum $\Phi(t) = 1 - \Omega(t)/\Omega(0)$ of S is a probability distribution function. Its moments μ(1)(S), μ(2)(S), etc. are random variables called granulometric moments. In the discrete case, the scaling factor t is integer, therefore, the k th granulometric can be calculated by

$$\mu^{(k)}(s) = \frac{\sum_{t=1}^{\infty} tk\,\Phi(t)}{\sum_{t=1}^{\infty} \Phi(t)} \qquad \ldots\ldots (1)$$

Our objects of interest are the nuclei of the cells. We calculate a pattern spectrum of each nucleus and extract the first and second granulometric moments of the pattern spectrum as two of our features. We also extract two other features from each nucleus, i.e., the area of the nucleus and the location of its pattern spectrum's peak. We, therefore, determine four feature values for each cell image. In our experiments, we select a small digital disc as a structuring element, as shown in Fig. 2.

0	1	1	0
1	1	1	1
1	1	1	1
0	1	1	0

Fig. 2 Structuring element used in feature extraction.

B. Classwise Classification Rates

In a classification problem, we generally evaluate a classifier's performance using the traditional classification rate, which is the ratio of the total correct classifications to the total number of samples classified. In addition to the traditional classification rate calculation, we consider another rate called the classwise classification rate. Basically, the classwise classification rate is the average of the classification rates of all classes, i.e., classwise classification rate

$$\frac{1}{c}\sum_{i=1}^{c} \frac{number\ of correct\ classification\ in\ class\ i}{total number\ of\ samples\ in\ class\ i} \qquad \ldots\ldots(2)$$

where *C* is the number of classes

The basic idea of the classwise rate is to take out the effects of the number of samples in the training. While the traditional classification rate may be high if a large number of correct classifications occur in a class consisting of a large number of samples, the classwise rate is high only if all the classes have large numbers of correct classifications compared to their corresponding total number of samples. Therefore, we prefer to have a classifier that provides good classification performance in both the traditional and classwise senses.

C. Experimental Methods

Both the Bayes classifier and artificial neural network classifier require supervised learning, i.e., training and testing with known classified samples. From the data description, the available data set is not divided into training and test sets however, we need to have training and test sets to train and test our classifiers to evaluate their generalization properties. We, therefore, apply the cross validation method. The experiments are performed using the fivefold cross validation method. To save space, the confusion matrix of each experiment will not be shown in the experimental results section.

1. Bayes' Classifiers

We initially performed the cell classification using Bayes classifiers due to their simplicity. It is assumed that the conditional probability density is normal. There are two parts in the experiments of evaluating our features using Bayes' classifiers. First, the a priori

class probabilities P(Ck) are calculated from the proportion of the numbers of cells in the training set and second, all the six cell classes are assumed equally likely, i.e., P(Ck) = 1/6, k = 1, 2, . . .6.

$$\text{Posterior} = \frac{likelyhood \times prior}{normalizing\ constant}$$

2. Neural Networks

We chose a feedforward neural network consisting of one hidden layer of five hidden neurons. Various other numbers of hidden neurons were tried, but it was found that five was large enough to reasonably approximate a function with four inputs and six outputs. Also, we wanted to keep the number of neurons as small as possible for the sake of generalization and fast convergence. The desired output was set to 0.9 for the output neuron corresponding to the labeled class, and 0.1 for the other output neurons. The networks were trained using the LM algorithm. The training stops when the maximum number of epochs reaches 100 or the mean square error is less than 10−6. From the results obtained for the Bayes classifiers, same generalization problem would also happen for neural networks. we changed the desired output value such that it was smaller for a class that contains a larger number of samples. We achieved that by setting the desired output of the labeled class to

$$d = 1 - \frac{number\ of\ training\ sample\ in\ labled\ class}{total\ nu,ber\ of\ training\ samples} \quad \text{.....(3)}$$

and setting *d* equal to zero for all other classes. For each setting of the desired outputs, we performed a fivefold cross validation procedure 50 times in order to analyze the effects of randomness from the sample selection in the cross validation and the neural networks' initializations. Hence, we trained and tested (two settings) × (fivefolds) ×50 = 500 networks in total.

V. RESULTS AND ANALYSIS

A. Results for Bayes' Classifiers

Table I shows the classifier's performance. When *a priori* class probabilities are calculated from the numbers of cells in the training sets, we can see that the traditional classification rates of the classifiers on the training and test sets are 81% and 77%, respectively, and for the classwise classification, 73% and 63%, respectively. Most of the training and test cells are classified as myelocyte or PMN.

TABLE I

CLASSIFICATION RESULTS OF BAYES CLASSIFIERS

Training bias	Classification rates			
	Traditional		Classwise	
	Train	Test	Train	Test
$P(c_k)$ is proportion To no. of training Sample	81.1	77.49	73.25	63.39
$P(c_k) = 1/6$	73.90	69.37	82.17	68.08

B. Results for Neural Networks

We computed the sample average of the resulting classification rates of those 250 networks for each desired output setting. The average classification rates are show in Table II. The classwise classification rates were very low at 59% and 55%, respectively. The networks trained regularly achieved the traditional classification rates of 81% and 77% on the training and test sets, respectively.

TABLE II
CLASSIFICATION RESULTS OF NEURAL NETWORKS

Desired output	Classification rates(mean ± S.D			
	Traditional		Classwise	
	Train	Test	Train	Test
d=0.9 for the labeled class	80.36±	77.05±	59.34±	54.80±
d=0.1 for others	0.36	0.87	1.17	0.92
d is as in (3) for the labeled class	83.38±	76.55±	74.34±	61.03±
d=0 for others	0.72	1.15	2.17	2.02

VI. CONCLUSION

Thus the classification of white blood cell is done by using the information of the nucleus alone. This deals with the cells that are in touch with each other and solves the problem of the cells that are in touch. We applied Baye's classifiers and artificial neural network to the problem of white blood cell classification of single cell images and compare their results to those obtained by experts. Features based on morphological granulometries were extracted from each manually segmented blood cell classification. The disease in the blood cells is detected and the values are inserted into the table. To apply artificial neural network(ANN) for classification of white blood cells and a comparison will be made in deciding the efficacy of the classifiers namely Bayes' and Artificial Neural Network is accurately identifying the disease.

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