Classification of bone marrow cells in the diagnosis of acute lymphoblastic leukemia

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Abstract. The paper presents approaches to automated classification of bone marrow cells in the diagnosis of acute lymphoblastic leukemia and minimal residual disease using image recognition procedures. The classification methods that show the best accuracy in the recognition of eight types of bone marrow cells were experimentally determined. Recommendations for their use are given.

1. Introduction

In information and measurement systems for recognizing bone marrow cells, classification is associated with the final stage of belonging to one of the classes of cells. The correct classification of different types (classes) of cells is crucial in the diagnosis of dangerous oncological diseases - acute leukemia.

Classification of bone marrow cells is important in the diagnosis of blood diseases. Correctly classifying and counting the different classes of bone marrow cells is crucial in the diagnosis of acute lymphoblastic leukemia (ALL) and minimal residual disease (MRD).

The results of differential analysis of bone marrow and blood cells reveal a wide range of different pathologies [1, 2]. For example, an increase in the level of lymphocytes in the human blood occurs because of to infectious, autoimmune, and allergic diseases [3], and may also indicate the presence of a lymphoproliferative disease.

Microscopic examination of bone marrow and blood smears provides significant diagnostic information about the health status of patients. The traditional method of differential analysis of bone marrow smears is performed by experienced specialists. Using a microscope, they determine the percentage of different cells in the smears. Obviously, the manual process of counting cells is very time-consuming, tedious, and as a result can lead to errors. The accuracy of the calculation depends
significantly on the experience of the doctor and the quality of the preparation of smears. Therefore, the application and improvement of automated differential counting systems is an actual task [1].

Mathematical models of blood cell classification methods used in practice are presented in [4]. The experiment used a data set of 668 images for four types of blood cells. The LogitBoost method proved to be the best, the implementation of which made it possible to achieve high accuracy - at least 98.1 %.

The article [5] analyzes the Generative adversarial network (GAN). The experimental data set contained 242 images of cells (neutrophils-50, eosinophils-39, lymphocytes-52, monocytes-48, and basophils-53). White blood cells were classified into five types (classes). The classification accuracy was at least 98%.

Machine learning methods in modern research are becoming an important decision-making tool in many areas of science and technology.

One of the determining factors for the accuracy of a machine learning algorithm is the quality of the data set. For this reason, a high-quality data set is formed by expert doctors. This data set is used in training classifiers to ensure their high accuracy [4].

It should be noted that there are the following unsolved problems in the classification of cells in the images of bone marrow preparations:
- majority of works in the field of computer image analysis in oncohematology are devoted to blood cells, not bone marrow;
- the presented papers are characterized by a different sample size and lack of description of the conditions under which the results of cell classification were obtained;
- the analyzed sets of cell images include four to five classes of blood cells, so it is necessary to expand them for bone marrow cells with an increase in the number of cell types.

The aim of the work is to determine the best methods of computer classification of bone marrow cells in information and measurement systems for the diagnosis of acute lymphoblastic leukemias.

2. Materials and methods

The object of the study is the nuclei of bone marrow cells. As the initial data, a set of quantitative texture characteristics of the object of study was used, in different color models (RGB, HSV, HSI, HSL, XYZ, LAB, CMY, YIQ, YUV). This set was formed using an original computer program for processing images of bone marrow cells, developed by specialists of the Department of Computer Medical Systems of the National Research Nuclear University MEPhI [6, 7].

The texture analysis program includes the calculation of the following texture features (provided that the brightness of the color components is encoded with an eight-bit code – brightness values from 0 to 255):
- energy \( E = \sum_i \sum_j g_{ij}^2 \);
- moment of inertia \(CON = \sum_i \sum_j (i - j)^2 g_{ij} \);
- maximum probability \(MPR = \max_i \max_j g_{ij} \);
- local uniformity \(LUN = \sum_i \sum_j \frac{g_{ij}}{1 + (i - j)^2} \);
- entropy \(ENT = \sum_i \sum_j g_{ij} \log g_{ij} \);
- trace of a normalized spatial adjacency matrix: \(TR = \sum_{i=0}^{255} g_{ii} \);
- average brightness value \(AV = \frac{\sum_{i=0}^{255} g_{ij}}{\sum_{j=0}^{255} g_{ij}}\);
- correlation \(CORR = \frac{\sum_{i=0}^{255}(i-\text{AV}) \cdot \sum_{j=0}^{255}(j-\text{AV}) g_{ij}}{\sum_{i=0}^{255}(i-\text{AV})^2 \sum_{j=0}^{255} g_{ij}}\).

The following standard methods were used to classify bone marrow cells [8]:
- Support Vector Machines (SVC);
- LinearSVC (LVC);
- gradient boosting of decision trees (GBC);
- logistic regression (LR);
- Extra Trees Classifier (ETC);
– bayesian classifier (GNB);
– decision tree classifier (DTC);
– random forest (RFT);
– bagging classifier (BG)

3. Experimental research
The aim of the experiment is to determine the best classifier for the recognition of bone marrow cells among the considered classification methods.

Input data: total number of bone marrow cell nuclei images - 2240: blasts (280), lymphocytes (280), metamyelocytes (280), monocytes (280), myelocytes (280), normoblasts (280), rod-shaped neutrophils (280), segmented neutrophils (280). Examples of different cell types are shown in Figure 1.

![Figure 1. Examples of images of the nuclei of bone marrow cells.](image)

3.1. Preparing for the experiment
To train the classifier, a reference set of images of bone marrow cells was used. Unique bone marrow preparations are manufactured and described in the Laboratory of Hematopoietic Immunology of the National Medical Research Center of Oncology named after N.N. Blokhin. The formation and calculation of texture characteristics were carried out using an original computer program developed by the Department of Computer Medical Systems of the National Research Nuclear University MEPhI [6,7].

Eight cell types were selected for the study (blasts, lymphocytes, metamyelocytes, monocytes, myelocytes, normoblasts, rod-shaped neutrophils, segmental neutrophils). The training sample consisted of 1792 cells (sum up the cells of each of the studied bone marrow cell types, Fig.1). The cells that were not included in the training sample were used for testing.

A computer program for the classification of bone marrow cells was developed for the experiment. The algorithm of the program is shown in Fig. 2.

![Figure 2. The algorithm of the program of classification of bone marrow cells.](image)
3.2. Conducting the experiment
The experiment was processed (carried out) by performing a program for classifying bone marrow cells according to the algorithm shown in Figure 2.

The classification accuracy was determined by the formula:

\[ \text{Accuracy} = \frac{n_+}{N} \]

where \( n_+ \) is the number of correctly recognized images of the bone marrow cells of the type under study, \( N \) is the total number of images of this type.

The results of the experiment are presented in Table 1.

3.3. Analysis of the results of the experiment
As a result of the conducted experimental studies, classifiers were identified that showed the best accuracy of classification of bone marrow cells, not less than 95% (ETC, DTC, RFT). The classifiers LVC, SVC, LR, BC, showed unsatisfactory classification accuracy.

| Bone marrow cell type | Accuracy of classification of bone marrow types for the considered classifiers (%) |
|-----------------------|---------------------------------------------------------------------------------|
|                       | GBC | ETC | BC | DTC | RFT |
| Blasts                | 95  | >99 | 98 | 98  | >99 |
| Lymphocytes           | 96  | 96  | 80 | >99 | 96  |
| Metamyelocytes        | >99 | >99 | 91 | 93  | >99 |
| Monocytes             | 98  | 98  | 89 | 95  | 96  |
| Myelocytes            | >99 | 96  | 96 | 96  | 96  |
| Normoblasts           | 98  | 96  | 92 | 98  | 96  |
| Rod neutrophil        | 96  | 93  | 92 | 95  | 95  |
| Segmented neutrophil  | 95  | 95  | 96 | 98  | 93  |

4. Conclusion
This work is devoted to the study of eight typical methods of classification of bone marrow cells in the diagnosis of acute lymphoblastic leukemia and minimal residual disease: the support vector method, the linear support vector method, gradient boosting of decision trees, logistic regression, the classifier of extremely randomized trees, the Bayesian classifier, the classifier of the decision tree, random forest. The formation of the feature space was carried out on the basis of models of color texture features.

In the course of the experiment, a data set of 2240 images from bone marrow cell preparations were used. Unique bone marrow preparations are manufactured and described in the Laboratory of Hematopoietic Immunology of the National Medical Research Center of Oncology named after N. N. Blokhin. At the Department of Computer Medical Systems of the National Research Nuclear University MEPhI, feature spaces were formed and textural features were calculated using an original computer program. The number of images by class of bone marrow cells was 280. The results of the experiment revealed the three best classification methods considered: the classifier of extremely randomized trees, the decision tree, and the random forest, which showed an accuracy of 99 % or higher. The conducted studies are preliminary, their development is associated with an increase in the sample size for each of the types of bone marrow cells.

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