Integrated information and measurement system for the diagnosis of acute leukemia and minimal residual disease based on computer microscopy, flow laser cytofluorimetry and artificial intelligence

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Abstract. The article considers a new integrated information and measurement system for the diagnosis of acute leukemia and minimal residual disease based on computer microscopy and flow laser cytofluorimetry. The system is based on combining the results of computer microscopy in the analysis of bone marrow preparations and the results of flow laser cytofluorimetry. A special feature of the system is the use of artificial intelligence technologies in the recognition of images of bone marrow cells in the computer microscopy subsystem. The work was the result of joint work of the Department of Computer Medical Systems of the National Research Nuclear University "MEPhI" and the Laboratory of Hematopoietic Immunology of the National Medical Research Center of Oncology named after N. N. Blokhin.

1. Introduction
Acute leukemia is an oncological disease of the blood system, that results in producing big number of immature (blast) cells that suppress the growth of normal bone marrow cells, disrupting the balance of blood cells in the human body. In the absence of treatment, acute leukemia leads to death. Modern medical technologies usage result into successful treatment in most cases of acute leukemia. The use of modern medical means leads to the transition of acute leukemia to the remission phase in 60-80% of patients; of these, 20-30% manage to achieve complete recovery. The earlier the disease is detected, the more successful the result of treatment. Therefore, timely diagnosis of acute leukemia is an urgent task. During treatment, when it is possible to achieve the disappearance of the manifestations of the disease, it is possible to preserve residual tumor cells in the bone marrow, which can subsequently lead to the resumption of the disease. Therefore, it is necessary to monitor the state of the patient's blood system and identify residual tumor cells-minimal residual disease.
Minimal residual disease (MDS), or minimal residual disease (MRD, Minimal residual diseases) is the small number of tumor cells remaining in the body after achieving clinical and hematological remission (the number of blast cells in the myelogram is less than 5%). MOB is the main cause of relapses of the disease, and further therapy is aimed precisely at destroying the remnants of tumor cells [1, 2].

MOB monitoring serves several purposes: to evaluate the effectiveness of therapy, to compare different treatment protocols, to monitor the preservation of remission, and to detect relapses as early as possible for timely correction of treatment tactics.

The most important thing is the assessment of MOB at the end of the first stage of therapy, and the quantitative diagnosis of MOB is important at almost all stages of treatment of hemoblastoses [3].

Overall, the conclusion is that monitoring of the MOT is important not only for monitoring the course and prognosis of the disease, but also for choosing the most effective and less risky treatment strategy [4].

The basis for the diagnosis of acute leukemia is the assessment of the morphology of peripheral blood and bone marrow cells. This study is performed by light microscopy of stained blood and bone marrow smears. In the study of blood products, the percentage of different types of white blood cells among 100 white blood cells is calculated (white blood cell formula). The analysis of bone marrow preparations is based on the calculation of the percentage of various types of nucleated bone marrow cells - myelogram (as a rule, 200-500 cells are examined) [5, 6].

In light microscopy, an important role is played by an accurate assessment of a number of parameters of blasts, which include: the shape and size of the cells, the outlines of the nuclei, the features of the structure of chromatin (thin-leaved, lumpy and dense structure).

The use of light microscopy in combination with computer data processing makes it possible to objectify the obtained data in the form of numerical indices and improve the differential diagnosis of acute leukemia [7].

The development and application of new methods that clarify the morphological characteristics of lymphoid elements is currently an urgent scientific and technical task. Recently, numerous attempts have been made to automate microscopic studies to improve the accuracy of detecting "young" cell forms.

In order to confirm and identify the type of acute leukemia, a bone marrow analysis with cytochemical and immunophenotypic studies is performed. Cytochemical marker reactions and immunophenotyping of blast cells allow us to accurately determine the form of acute leukemia. If necessary, additional cytogenetic, molecular genetic analysis of tumor cells and other research methods are performed.

The cytochemical study includes the analysis of markers of granulocyte and monocyte series of hematopoiesis. They allow to differentiate acute lymphoblastic leukemias from myeloid leukemias. However, this method is not sufficient in most cases.

The immunophenotypic study is based on the study of the antigenic structure of blasts using flow laser cytofluorometry. This method is based on the passage of cells through a cuvette with antibodies and further exposure to the cells of the laser beam. As a result, the object glows, and its radiation is automatically registered. Based on this glow, the cells are classified by type.

The use of a wide range of diagnostic antibodies allows us to determine the direction of cell differentiation and establish the stage of maturation of blasts. Analysis of the results of immunophenotyping, taking into account morphological and cytochemical parameters, makes it possible to determine the degree of differentiation of blasts. Currently, the method of flow laser cytofluorimetry is considered to be the fastest and easiest way to detect MOBS. The method is most valuable in T-and B-linear acute lymphoblastic leukemia (ALL).

Thus, the main research methods for the diagnosis of acute leukemia and minimally residual disease are cytological and cytochemical studies of bone marrow and peripheral blood smears (using a light microscope) and immunophenotyping of bone marrow cells (using a multiparametric flow laser cytofluorimeter). In addition, cytogenetic, molecular-genetic studies, etc. can be carried out [8].
Let’s have a look at problems in the diagnosis of acute leukemia and minimal residual disease. To improve the accuracy of the diagnosis, we should store/record the results of the performed studies in the knowledge base, to use the accumulated knowledge and experience of highly qualified medical experts effectively in complex diagnostic cases. The creation of an integrated system that would include the results of various types of studies (morphometry, cytochemistry, flow laser cytofluorimetry, as well as, if necessary, additional cytogenetic and molecular genetic studies) will allow you to quickly compare these data and, in complex cases, find similar cases, previously conducted studies that have been verified by the results of a retrospective analysis of clinical cases. In addition, to develop a system for recognizing blood cells and bone marrow, a reference database of microscopic images is needed. Along with the use of this database for research, it can be used both for medical students training, doctors skill improvement, clinical practice, increasing the accuracy of diagnostics when doctors can use reference database to determine type of a blood cell in a complex situations.

A brief review of the work shows that one of the unresolved key problems is the creation of an integrated system for the diagnosis of acute leukemia and minimal residual disease based on computer microscopy and flow laser cytofluorimetry to improve the accuracy of the diagnosis of acute leukemia and minimal residual disease.

The aim of the work is to develop a model of an integrated information and measurement system for the diagnosis of acute leukemia and minimally residual disease based on computer microscopy, cytochemistry, flow laser cytometry and additional cytogenetic and molecular genetic studies. This model is an important stage in the design of the diagnostic system.

2. Materials and methods.
The initial data for the work are bone marrow preparations, myelograms obtained as a result of morphological research, and the results of immunophenotyping of bone marrow cells provided by the Laboratory of Hematopoietic Immunology of the National Medical Research Center of Oncology named after N. N. Blokhin (Head of the laboratory, Doctor of Medical Sciences, Professor N. N. Tupitsyn). To obtain the images, a computer microscopy system was used: an Olympus BX-43 robotic biological microscope with an Imperx IPX-4M1ST-GCFB digital camera, a personal computer. The volume of one image of a bone marrow preparation (Fig. 1) in RGB – 24bit format, 2048 x 2048 pixels is 12 MB.

![Figure 1](image.png)

**Figure 1.** Example of an image of a bone marrow preparation. Coloring by the May-Grunwald-Romanovsky method. x 100 microscope lens for oil immersion (image scale 1000:1).
The final sample set contains the results of studies of 48 patients with a confirmed diagnosis of acute leukemia [9]. The objects of the recognition system are white blood cells in the images of peripheral blood and bone marrow smear preparations.

The images of blood and bone marrow preparations can contain the following types of objects (Fig. 2): red blood cells (Fig. 2, a); platelets; artifacts that are not related to blood elements, but were introduced from the outside or formed during the work with the preparation (Fig. 2, b). The most diverse in shape and texture are white blood cells, based on the characteristics of the nuclei of which the diagnosis of acute leukemia is carried out.

The knowledge base developed by specialists of the Department of Computer Medical Systems of the National Research Nuclear University "MEPhI" (Head of the Department, Doctor of Technical Sciences, Professor, laureate of the prize of the Government of the Russian Federation in the field of education Nikitaev V. G.) contains a description of 12960 cells [9]. The sample includes the following cell types: blasts (lymphoblast), promyelocyte (neutrophil), myelocyte (neutrophil), metamyelocyte, rod-shaped neutrophil, segmental neutrophil, eosinophil, basophil, monocyte, lymphocyte, plasma cell, normoblast, megakaryocyte. The volume of images of bone marrow preparations in the knowledge base from 48 patients is 28.5 GB.

Figure 2. Examples of images: a) red blood cells and platelets (in the center of the image), b) artifacts – a scratch on the image of the cell nucleus, c) defocused images of cells, d) white blood cells.

Figure 3 shows the developed conceptual model of an integrated system for the diagnosis of acute leukemia and minimal residual disease based on computer microscopy and flow laser cytofluorimetry using artificial intelligence technologies. It combines two knowledge bases - a knowledge base of clinical cases and a knowledge base of reference images of bone marrow cells. The first database contains data on patients (medical history), including the results of morphological (microscopic analysis of peripheral blood and bone marrow smears), cytochemical, and immunophenotypic methods widely used in the diagnosis of acute leukemia. When constructing a myelogram, a knowledge base is used that contains reference images of the bone marrow and a module for recognizing cells in images of bone marrow preparations (based on the use of artificial intelligence technologies). Figure 4 illustrates an example of normal bone marrow cell composition (myelogram).

The current level of development of high-tech medical diagnostics systems with the use of artificial intelligence includes the construction of clinical, research, educational, telemedicine and information systems on a single software and hardware platform [10-12]. This fully applies to the system described in the article.
Recognition of cell types (morphological analysis) for the diagnosis of acute leukemias and minimal residual disease is implemented according to the following scheme: registration of images from the sensor, pre-processing of microscopic images, isolation of white blood cells (segmentation), detection of the cell nucleus area, measurement on images of blood cell nuclei (description), classification of cells.

**Figure 3.** A conceptual model of an integrated system for the diagnosis of acute leukemia and minimal residual disease based on computer microscopy and flow laser cytofluorimetry using artificial intelligence technologies.

3. Discussion and analysis of the results.
A model of an integrated information and measurement system for the diagnosis of acute leukemia and minimal residual disease based on computer microscopy and flow laser cytofluorimetry is proposed, which combines the data of clinical cases and the knowledge base "Reference images of bone marrow cells" with a cell recognition module into a single system. The recognition module is used when constructing a myelogram. The integration of the clinical case knowledge base and the reference image knowledge base in a single system improves the accuracy and efficiency of diagnostic decision-making.
Figure 4. An example of the cellular composition of the bone marrow (myelogram) is normal.

The use of the cell recognition module is designed to increase the objectivity of the classification of blood cells, and the use of a database of reference images-to increase the accuracy of diagnosis. In addition, the proposed architecture of an integrated information and measurement system for the diagnosis of acute leukemia and minimal residual disease based on computer microscopy and flow laser cytofluorimetry can be used in the training of medical students and in the professional development of doctors.

The model proposed by the authors is based on their successful experience in the development and implementation of clinical systems of oncohematology using artificial intelligence technologies.

4. Conclusion
The article is devoted to the development of a conceptual model of a new integrated information and measurement system for the diagnosis of acute leukemia and minimal residual disease based on computer microscopy and flow laser cytofluorimetry using artificial intelligence technologies. The model is based on combining the data of reference images of bone marrow cells obtained in the computer microscopy subsystem and the results of flow laser cytofluorimetry during the diagnostic procedures for acute leukemia and minimal residual disease. As a result, all the necessary data about the patient is concentrated in the hands of the doctor on a single hardware and software platform. A distinctive feature of the computer microscopy subsystem is the use of automatic classification of images of bone marrow cells. This architecture makes it possible to increase the objectivity of the diagnosis of acute leukemia and minimal residual disease. The model is based on the positive experience of practical cooperation between the Department of Computer Medical Systems of the National Research Nuclear University.
"MEPhI" and the Laboratory of Hematopoietic Immunology of the National Medical Research Center of Oncology named after N. N. Blokhin in the field of application of artificial intelligence technologies in oncohematology. The system can be used for training students of medical universities and advanced training of doctors.

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