Biomedical Signal Processing and Control 44 (2018) 127–137

Contents lists available at ScienceDirect

Biomedical Signal Processing and Control

journal homepage: www.elsevier.com/locate/bspc

Classification of acute leukemia using medical-knowledge-based morphology and CD marker

Jakkrich Laosai, Kosin Chamnongthai*

Department of Electronic and Telecommunication Engineering Faculty of Engineering King Mongkut's University of Technology Thonburi, 126 Pracha- uthit Rd., Bangmod, Thungkhru, Bangkok, Thailand,

ARTICLE INFO

Article history:
Received 20 February 2017
Received in revised form 6 December 2017
Accepted 27 January 2018
Available online 24 April 2018

Keywords:
Acute lymphocytic leukemia (ALL)
Acute myelogenous leukemia (AML)
Cluster of differentiation (CD)
Immunophenotyping
Acute leukemia
Multiparameter flow cytometry
Support vector machine(SVM)
Morphologic immunologic cytogenetic(MIC)

ABSTRACT

Classification of subtypes in acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML) is a vital pre-process for selecting an appropriate treatment for acute-leukemia patients, and urgently requires an automatic expert system to assist medical experts. To develop the automatic system, a classification method of acute leukemia subtypes is required. Currently, the cluster of differentiation (CD) marker, proven by medical scientists as important genetic information, is clinically used to classify acute-leukemia subtypes by comparison with classification results using morphological features. In the medical field, blood cells are first classified into ALL, AML, and healthy groups by perceptron features such as number of nuclei, cytoplasmic ratio, and nucleus size, and the classified ALL and AML groups are then classified into subtypes such as L1, L2, M1, M2, and so on by using their nucleus features. We therefore propose a method of morphological cell-subtype classification based on the coarse-to-fine concept following current medical knowledge. This means ALL, AML, and healthy cell groups are first separated in the coarse step, and the cells already classified into ALL and AML groups are then categorized into their subtypes in the fine step. These subtypes, which represent morphological classification results, are finally used as candidates to confirm cell-subtypes with CD markers in the decision-making process. In performance evaluation of the proposed method, experiments with 200 and 300 acute-leukemia samples for training and testing respectively were performed, and the results indicate 99.67% accuracy, a 4.94% improvement compared with the conventional method.

1. Introduction

White blood cell or the leukocyte count plays a crucial role as an indicator in the diagnosis of leukemia, which is one of the most critical diseases. Leukemia is medically divided into four types, namely, acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). Among the four types of leukemia, AML and ALL affect young children, and there is an urgent need for diagnosis, especially in the early stages, to treat and cure the patient in time. For example, in the USA, an estimated 19,950 people of all ages (11,130 men and boys, and 8820 women and girls) were diagnosed with (AML) in 2016 [1]. Among those patients, 10,430 deaths (5950 men and boys, and 4480 women and girls) were estimated to occur in the same year. Moreover, the 5-year survival rate, which indicates the percent of people who live at least five years after the cancer is found, is only approximately 26% for AML patients. To diagnose AML and ALL, a patient's bone marrow is extracted for physical leukemia classification by a technician, and simultaneously, cluster of differentiation (CD) markers that represent a new way to identify specific molecules, are compared for diagnostic purposes. The two results are finally merged and considered by an expert physician to diagnose the leukemia and classify it into the various types of AML and ALL which are M0, M1, M2, M3, M4, M5, M6, and M7, and L1, L2, and L3, respectively. However, human errors sometimes can- not be avoided, and some images are unclear and difficult for human eyes to correctly analyze. An automatic expert system to identify AML and ALL is therefore urgently needed in order to diagnose patients in the disease's early stages, and finally to classify the leukemia types for proper treatment. An automatic expert system for ALL and AML detection and classification requires appropriate algorithms to physically classify eight sub-types of AML, and three sub-types of ALL which is regarded as a challenging task owing to low contrast between

* Corresponding author.
E-mail address: kosin.cha@kmutt.ac.th (K. Chamnongthai).

https://doi.org/10.1016/j.bspc.2018.01.020
1746-8094/

cytoplasm and nucleus, and to similar patterns of cytoplasm and nucleus among all sub-types [2]. Leukemia is currently classified using four morphology criteria limited to immunophenotype cytochemistry, and cytogenetics [3]. AML is a heterogeneous leukemia with 8 subtypes using the FAB classification (M0_M7) and 16 subtypes using the WHO classification [4]. Immunophenotyping is useful for assignment of myeloid lineage, but has had limited application in the subtyping and classification of myeloid leukemia [5]. There are three subtypes of myeloid leukemia with relatively specific immunophenotypes: AML-M0, AML-M6, and AML-M7 Image enhancement plays an important role in computer vision and image processing [6]. This method is relevant to the research problem on classification of ALL sub-types by evaluating a variety of features such as cell size, nucleus contour, nucleus shape, nucleus boundary, cytoplasm size, texture, color, and so on, which describe the nucleus and cytoplasm [7]. From expert hematologist knowledge, nucleoli, color, and shape of the nucleus are main points for classification of sub-type in not only ALL but also AML so they should be focused on and utilized as features to classify sub-types in ALL classification. Previous authors therefore set up sub-type classification of ALL and AML as the research problem, and attempted to determine appropriate algorithms for developers to implement an automatic system of acute leukemia classification for appropriate early treatment [8–11]. These previous methods involved trials of existing tools and objective measurements for the research problem, and should be combined and discussed in terms of merits and demerits. This paper hence evaluates the algorithms and proposes an approach based on the coarse-to-fine concept, which performs classifications among ALL, AML, and healthy cells in the first step, and then sub-types in each group of ALL and AML are morphologically categorized using features based on medical knowledge. The morphological classification results are then used to confirm the leukemia subtypes with comparisons to CD-markers in the decision-making process. As another approach, the deep-learning concept, which is a powerful classification tool using very large numbers of learning samples, is also studied in the experiments for reference purposes. Both approaches are finally discussed from the application viewpoint of a developer of automatic expects systems.

2. Analysis of acute leukemia classification

Classification of acute leukemia is required to be clinically relevant, and is vitally useful for clinical trials. The classification system may to influence the treatment regimens and leukemogenesis investigation. For example, discovery results of acute lymphoid and acute myeloid leukemias indicate that they differ in morphologic, clinical, immunologic, and molecular features, and in characteristic patterns of surface antigen expression (CD) [12], so each require appropriate diagnosis and treatment criteria. World-level organizations such as FAB (French-American British) Cooperative Group, WHO (World Health Organization) and Europe Group have set individual criterion standards [13,] and are always active in updating standards by organizing relevant international workshops and conferences for researchers in related fields.

An example of an analysis result by a classification tool (e.g., SVM) with samples involving color and size of blood-cell nuclei is shown in Fig. 1, where three types of ALL (L1_L3) and eight types of AML (M0_M7) are successfully identified separately from healthy cells. Although there is some overlap, it should be possible to categorize AML, ALL, and healthy cells into different groups. Additionally, sub-types of ALL and AML are also grouped by using some cell features. Based upon this concept, an image of blood cells is classified in the first step into three classes; AML, and ALL, and healthy, and another classifier then categorizes them into leukemia sub-type in the second step. This approach using selected important features is technically considered to perform with high accuracy and less complexity.

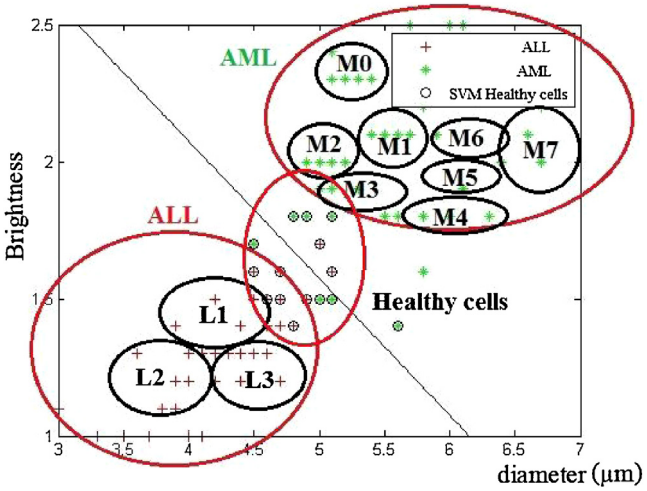

Fig. 1. ALL, AML, and Healthy Cells Detected by an SVM Classifier [30].

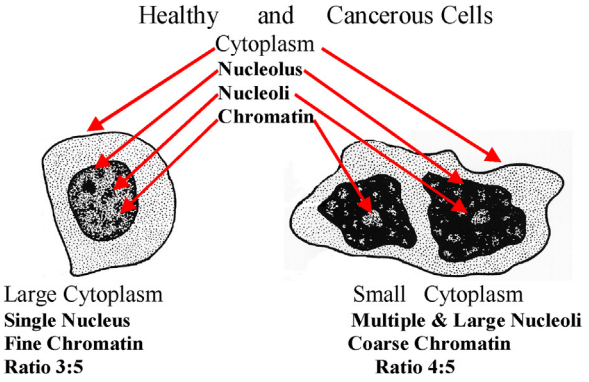

Fig. 2. Image of Healthy and Cancerous Cells [13].

Table 1
Features based on medical knowledge.

Features	ALL	AML	Healthy cells
No. of Nucleoli	1_3	4_11	1
Ratio of cytoplasm & nucleus size	1:5	2:5	3:5
Color	*Red*	*Red purple*	*Purple*
Texture			

In the analysis of the approach, the morphological differences among healthy, AML, and ALL cells are depicted in Fig. 2. A cell broadly comprises cytoplasm, nucleus, and chromatin. First, ratios between cytoplasm and nucleus size of those types of cells are obviously different. The ratios of healthy, ALL, AML cells are statistically approximately 1/5, 2/5, and 3/5, respectively. Second, textures of nuclei including chromatin may help to differentiate between healthy and cancerous cells. Third, the number of nucleoli is another obvious key to separate the groups [14]. These are summarized in Table 1.