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Tracking and Preventing Diseases with Artificial Intelligence

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Chapter 6
Microscopic Analysis of Blood Cells for Disease Detection: A Review

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Abstract Any contamination in the human body can prompt changes in blood cell morphology and various parameters of cells. The minuscule images of blood cells are examined for recognizing the contamination inside the body with an expectation of maladies and variations from the norm. Appropriate segmentation of these cells makes the detection of a disease progressively exact and vigorous. Microscopic blood cell analysis is a critical activity in the pathological analysis. It highlights the investigation of appropriate malady after exact location followed by an order of abnormalities, which assumes an essential job in the analysis of various disorders, treatment arranging, and assessment of results of treatment. A survey on different areas where microscopic imaging of blood cells is used for disease detection is presented in this paper. A small note on Blood composition is presented, which is followed by a generalized methodology for microscopic blood image analysis for certain application of medical imaging. Comparison of existing methodologies proposed by researchers for disease detection using microscopic blood cell image analysis is discussed in this paper.

Keywords Blood cells · Microscopic images · Disease detection · Image processing · Red blood cells · White blood cells · Leukemia detection · Sickle cell

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6.1 Introduction

6.1.1 Background

Normally health of any person is judged by the analysis of different features of blood cells and their counts. Previously manual methods of blood cells analysis were used by pathologists. This might cause error in disease prediction since manual methods are dependent on experience and skills of pathologists. Hence, it is proposed that an automated system of image processing be developed using different algorithms. Thus microscopic blood images could be analyzed for prediction and detection of particular diseases. A simplified, automated and cost effective method is required for detection of diseases. Thus the above components explained are analyzed for knowing health indication of human being and thereby detecting abnormalities related to health.

6.1.1.1 Blood and Its Composition

Blood, the most integral part of body is constituted of white blood cells (WBC), red blood cells (RBC), platelets and plasma. This can be further categorized as; cells and platelets are about 45% of human blood, whereas remaining 55% is filled by plasma (the yellow fluid in blood) [1, 2]. These components and their physical properties like size, shape, color and count in the whole blood, changes due to ingress of any foreign object or micro-organism that can lead to any sort of infections. There are different pathological procedures for detection of diseases [3]. In many cases, microscopic imaging plays a vital role in prediction and detection of abnormalities and occurrence of diseases within body.

Figure 6.1 shows the details of different blood components. Blood is made up of following elements- erythrocytes, known as red blood cells (RBC), leukocytes,

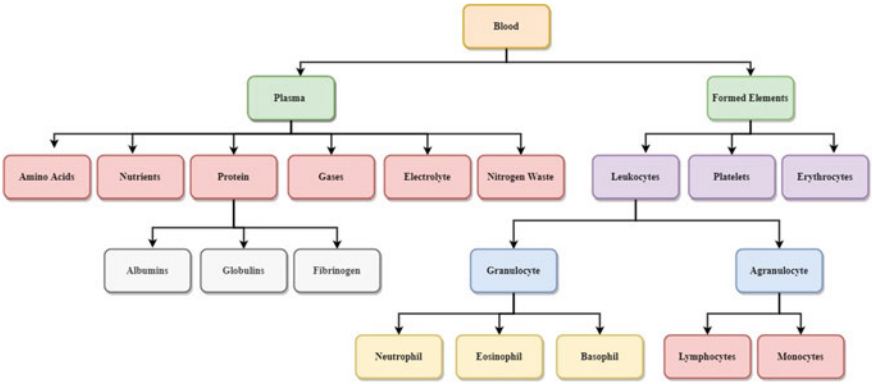

Fig. 6.1 Composition of blood. *Source* https://healthengine.com.au/info/blood-function-and-composition, assessed on 25th Sept. 2020 [4]

known as white blood cells (WBC) and platelets. These are combinedly present within the plasma membrane.

Leukocytes are further classified into two subcategories called granulocytes which consist of neutrophils, eosinophil and basophils and agranulocytes which consist of lymphocytes and monocytes. Blood plasma is a mixture of proteins, enzymes, nutrients, wastes, hormones and gases. Platelets are small fragments of bone marrow cells. The main function of red blood cells is to carry oxygen from lungs to different body organs. Carbon dioxide is carried back to the lungs, which will be exhaled afterwards. RBC count is the measure of different diseases in the human body. A low RBC count means anemia and high means polycythemia. White blood cells protect the body against infection. The different components of blood are identified to know about the health of a human being. Microscopic images of blood smear are analyzed for different disease detection.

6.1.1.2 Traditional Methods of Disease Detection

Disease detection is generally by two different ways traditionally. First is the detection through symptoms and second is through different tests. Routine symptoms of any disease include cough, fever, headache etc. Depending upon the prolonged symptoms, there is need to go for some tests those detect presence of some malady in the body. Different types of tests are shown below.

Imaging tests: Different imaging tests include X ray, computed tomography (CT) imaging, nuclear medicine, ultrasound, and microscopic imaging.

Chemical tests: Blood test and urine test.

In case of many diseases, microscopic analysis is preferred, that utilizes the blood cells.

6.1.1.3 Procedure of Microscopic Analysis of Blood

Trained pathologist collects the blood sample of a patient. The sample is to be collected carefully and the proper hygiene is to be taken in this process (Fig. 6.2).

For analysis of microscopic blood images, the blood film needs to be prepared. Glass slide is used for making of the blood film. For examination and analysis of this film under microscope, staining is required. Preparation of blood film requires a slide, a tube and a blood spreader. Generally weldge method is used for this purpose.

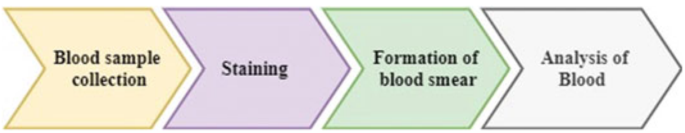

Fig. 6.2 Blood analysis procedure

On a base slide, a drop of blood is placed. A spreader slide is moved over this blood drop backwards to touch the blood to get the blood spread over the slide uniformly. To get perfection and accuracy in the smear, spreader slide should be inclined at an angle of 30°–45° to the blood base slide. Prepared blood smear is dried using air dryer and then staining is performed. Dried smear is fixed by absolute methanol or ethyl alcohol. Afterwards, it is stained using any of the staining methods—rewmanosky stain, leishmon stain, may-grawald giema or wright-giemsa stain, which differs with the liquid used for staining purpose. These stained slides are then used for analysis under microscope [1, 2, 5].

6.1.1.4 Open Source Datasets Available for Work

For the analysis of blood cells for detection and diagnosis of diseases there are different databases available. These databases include images of blood cells with blood cells of healthy subjects, infected cells, blast cells (in case of blood cancer), cells containing parasites and so on. Table 6.1 shows these different databases available for the work (Table 6.2).

6.2 Literature Review

6.2.1 Collection and Exclusion of Articles for Review

Google scholar platform is used for collection of different articles in the microscopic imaging area. Popular keywords such as white blood cell, red blood cell, machine learning, disease, deep learning, and image processing are used for the database searching. Large numbers of articles are obtained as a result of the search. Out of these, the articles those signify the unique contribution are shortlisted for writing the review. Generally articles utilizing the images processing and machine learning are considered. Articles from purely medical background are omitted from the review. Although for basic concepts related to blood and staining, the medical field articles are reviewed those added the correct conceptual interpretation of the basic terminologies related to the blood and different diseases.

6.2.2 Generalized Methodology of Disease Detection

A generalized methodology for microscopic blood cell analysis is shown in Fig. 6.3. It consists of different stages like image acquisition, image segmentation, feature extraction, and disease detection [56]. Blood sample is taken from the patient by a trained pathologist. After that, a slide is prepared to form a blood smear. The same

Table 6.1 Different open source databases of microscopic blood cells

Name		Image formats	Number of images	Color depth	Remark
BCCD database [6]		JPEG, xml, metadata	12,500	Not mentioned	Different sub-types of blood cells
ALL-IDB (acute lymphoblastic Leukemia Database [7–9])	ALL-IDB-1	JPEG	109 (510 lymphoblast)	24-bit, 2592 × 1944	Cancerous
	ALL-IDB-2	JPEG	260 (130 lymphoblast)	24-bit 257 × 257	Cancerous
Atlas of hematology by Mediros [10]		JPEG	300	Not mentioned	Visceral leishmaniasis, cellular similarity, morphologic similarities
ASH Image Bank [11]		JPEG	5084	Not mentioned	Cancerous and other different types of images
Leukocyte images for segmentation and classification (LISC)			400 (720 × 576)	Not mentioned	Healthy subjects with different sub-types of blood cells
C-NMC Dataset [12, 13]		BMP	15,135	Not mentioned	Normal and cancerous images of blood cells

slide is observed under the good quality microscope that will give an image. This image is taken either by camera directly or from an adaptor connected to a microscope. This image is considered for further analysis. Acquired images may have some unwanted regions and overlapping of different components of blood. This image is enhanced by applying a suitable image enhancement technique. So that, good quality image is now available for analysis. After pre-processing, separation of different components of blood is done which include separation of RBC, WBC, plasma, and platelets. Considering the generalized characteristics of blood components, segmentation is done. This will separate the region of interest for further classification. RBC, WBC and, other components are further classified into their respective subclasses. This will help to specify a particular sub-class image for extracting features of blood cells and depending upon the analysis in further stages such as classifier, detection of disease is done. After the segmentation, different features are extracted by considering different components of blood. Features include size, shape, color,

Table 6.2 Analysis of different applications of blood cells analysis

Application	WBC/RBC segmentation
References	[14–27]
Author opinion/potential of further research	In blood cell analysis, WBC and RBC segmentation is the major thrust. For diagnosis of different diseases, the morphology of these cells plays an important role. The segmentation is still progressing and there is a good potential of work in the segmentation of blood cells
Application	RBC/WBC counting
References	[14, 28–30]
Author opinion/potential of further research	Counting of RBC and WBC is the indication of different infections within the body. This process is generally less costly and is routinely done by equipment based analysis. Although for microscopic analysis computer aided framework is also been developed by many researchers. There is still potential in this area, as segmentation of different parts of the blood (RBC, WBC, and platelet) is still in the pipeline of improvement
Application	Anemia or Sickle Cell Detection
References	[31–35]
Author opinion/potential of further research	Anemia detection is primarily done with RBC counting. There are some shape changes in RBC also detects the anemia. In major cases.
Application	Malaria/dengue and other viral diseases detection
References	[36–39]
Author opinion/potential of further research	In viral diseases like malaria and dengue, the platelet count in blood comes into picture. Also there might be presence of the parasites due to these malady infections. Parasites detection is done by morphological analysis that is done with microscopic imaging. This work also has potential, as the amount of parasites and types of parasites can lead to severity of disease and will provide a distinct treatment guideline further
Application	Thalassemia detection
References	[40–42]
Author opinion/potential of further research	There are 12 different types of thalassemia depending upon the size and shapes of the RBC. In major cases, thalassemia is detected as infected cells and non-infected cell. There is still the potential in detection of this disease
Application	Leukemia detection
References	[7, 8, 10, 15, 26, 43–55]

(continued)

Table 6.2 (continued)

Application	WBC/RBC segmentation
Author opinion/potential of further research	In Leukemia, the white blood cells created by bone marrow are anomalous. It has two significant subtypes, acute Leukemia, and chronic Leukemia. Leukemia can further be classified into other following types namely, acute lymphocytic (ALL), acute myelogenous (AML), chronic lymphocytic (CLL), and chronic myelogenous (CML). Detection of Leukemia is done primarily by morphological analysis. This has different sub-types which led to different treatment guidelines. Many researchers worked on detection and diagnosis of Leukemia. Still many hybrid, optimized algorithms of machine learning and artificial intelligence are to be worked out for the improvement and trust of these existing frameworks

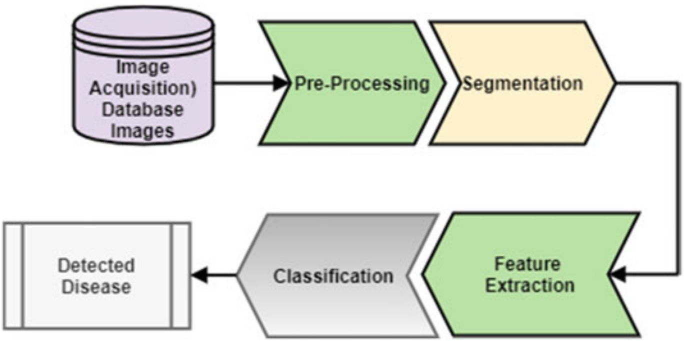

Fig. 6.3 Generalized methodology for blood cell analysis

count [21–25, 31, 32, 37, 50, 52, 54, 57–59] of different blood components like WBC, RBC. Analysis of these features will further detect the disease or count the cells. Depending upon different features extracted, the decision about the disease could be taken. To take decisions different classifiers could be designed.

6.2.3 State-of-the-Art Methods for Different Stages of Microscopic Analysis for Disease Detection

6.2.3.1 Image Pre-processing

The different methods used for pre-processing are, Self dual multi-scale morphological toggle (SMTT) block [60], Wiener filter [33], median filtering Gaussian filtering [6], gray scale transformation [32, 61–67] which has 3 types viz, linear, logarithmic and power-law, histogram stretching [32, 62–64], green color component from RGM image [44], morphological operations [32], edge detection [67].

6.2.3.2 Image Segmentation

The following are the different segmentation methods employed by the researchers. Watershed transform [31, 60] granulometric analysis and mathematical morphology (MM) operation, fuzzy logic approach [66], zack algorithm [43], k-means clustering [44], marker controlled watershed segmentation [45], stimulating discriminant measures (SDM) based clustering [45], Hough transform [57], iterative thresholding followed by watershed transform [67], edge thresholding [51, 64], Otsu's algorithm [18, 37, 65], a conventional neural network chen prepared laplacian of Gaussian (LOG) and coupled edge profile active contours(C- EPAC) algorithm [37], triangular thresholding DOST algorithm [51], SMACC, Iterative ISODATA clustering algorithm along with rotation and invariant LBP [52].

6.2.3.3 Feature Extraction

There are number of features that could be considered for feature extraction purpose. Some of them are given below.

Color Features: Color of the cell can be one of the features which can separate a cell from other types. For example: color of plasma is very different (yellow) than other blood components. In many cases, the color of the cell talks much about the abnormalities.

Geometric Features: These are the features based on the geometry or shape of the cell. These include following,

$$Elongation = 1 - \frac{Majoraxis}{Minoraxis} \tag{6.1}$$

$$Eccentricity = \frac{\sqrt{majoraxis^2 - monoraxis^2}}{minoraxis} \tag{6.2}$$

$$Rectangularity = \frac{area}{majoraxis \times minoraxis} \tag{6.3}$$

$$convexity = \frac{perimeterconvex}{perimeter} \tag{6.4}$$

$$Compactness = \frac{4 \times \pi \times area}{perimeter} \tag{6.5}$$

Statistical Features: Statistical moments such as, mean and standard deviation gives information about the appearance of distribution. Skewness and kurtosis shape the distribution along with the area and perimeter of the shape. The following are the different statistical features.

$$Mean, \overline{x} = \frac{1}{N}\sum_{i=1}^{N} x_i \tag{6.6}$$

Standard Deviation,

$$\sigma = \sqrt{\frac{1}{N-1}\sum_{i=1}^{n}(X_i - \overline{X})^2} \tag{6.7}$$

$$Skewness, SK = \frac{1}{N}\sum_{i=1}^{N}\frac{(x_i - \overline{x})^3}{\sigma^3} \tag{6.8}$$

$$Kurtosis, K = \frac{1}{N}\sum_{i=1}^{N}\frac{(x_i - \overline{x})^4}{\sigma^4} \tag{6.9}$$

Texture Features: There are different texture features that are defined such as entropy, correlation, energy, contrast, homogeneity, and so on.

Entropy generally defines randomness in the characterization of texture of an image. When co-occurrence elements are same, entropy leads to its maximum value. The equation of entropy as follows.

$$Entropy, Ent = \sum_{i=0}^{N-1}\sum_{j=0}^{N-1} M(i, j)(-\ln(M(i, j))) \tag{6.10}$$

Contrast is the intensity variations in the neighboring pixels in an image.

$$Contrast = \sum_{i=0}^{N-1}\sum_{j=0}^{N-1}(i - j)^2(M(i, j) \tag{6.11}$$

Energy (E) is the measure of the extent of repetitions of pixel pairs. It gives an uniformity of the image. It gives a larger value for similar pixels.

$$Energy, E = \sqrt{\sum_{i=0}^{N-1}\sum_{j=0}^{N-1} M^2(i, j)} \tag{6.12}$$

Correlation Features: The repetitive nature of the texture elements position in the image is an important. An auto-correlation function gives the coarseness in an image.

Auto-correlation,

$$P(x, y) = \frac{\sum_{u=0}^{N}\sum_{v=0}^{N} I(u, v)I(u + x, v + y)}{\sum_{u=0}^{N}\sum_{v=0}^{N} I^2(u, v)} \tag{6.13}$$

Inverse Difference Moment or Homogeneity gauges the local homogeneity of a picture. IDM features acquire the proportions of the closeness of the distribution of the GLCM components to the diagonal of GLCM. IDM has a scope of determining the image and classify it as textured or non-textured.

$$IDM = \sum_{i=0}^{N-1}\sum_{j=0}^{N-1} \frac{1}{1 + (i - j)^2} M(i, j) \tag{6.14}$$

Directional Moment: In this, the image alignment is considered with respect to the angle.

$$DM = \sum_{i=0}^{N-1}\sum_{j=0}^{N-1} M(i, j)|i = j| \tag{6.15}$$

6.2.3.4 Classifier for Disease Detection

There are different classifiers for the classification of images which are employed for microscopic imaging of blood cells. These include machine learning algorithms as below. Different classifiers include, Decision Tree Classifier, Random Forest, K-Nearest Neighbors (KNN) [57], Logistic Regression, Binary Logistic Regression model, Multinomial logistic regression, and Ordinal regression, Naïve Bayes Algorithms including Gaussian Naive Bayes, Multinomial Naive Bayes, and Bernoulli Naive Bayes, Support Vector Machine (SVM) [43, 45, 47, 68], Convolutional Neural Networks [54, 58].

These classifiers are utilized by different researchers for disease detection purpose during the microscopic analysis of blood. Depending upon the disease to be identified, the classifier is employed by researchers. Literature does not found any hard rule about using a particular classifier for a particular disease. Generally, SVM, decision tree, Naïve Bayes are the classifier those are well explained in their performances.

Also these classifiers need a comparatively less size of database for training purposes. The advanced machine learning classifiers such as NN and its other types, require larger database size for its training purpose. So this can increase the time required for taking the decisions. Moreover, NN is found to be efficient in major cases in terms of accuracy of classification and detection of diseases (Tables 6.3 and 6.4).

6.3 Research Gaps

After having reviewed the related literature, the following research gaps are obtained. Overlapping cells are not considered at the segmentation stage by many researchers. As many practical cases have the overlapping of cells, during the staining procedure. For segmentation, different bio-inspired algorithms could be employed, which may prove efficient. Different optimization techniques are yet to be applied for improvement in the classifier performance. Leukemia is the disease that proves very dangerous in its later stages. It has different types such as Acute Lymphoblastic Leukemia (ALL), Acute Mylogeneous Leukemia (AML), Chronic Lymphoblastic Leukemia (CLL), and Chronic Mylogeneous Leukemia (ACL) [69]. For detection of these types, is a big challenge for the pathologists, as only morphology speaks in this cases.

ALL is further sub-classified in to its sub-types such as L1, L2, and L3. This classification is based upon the morphological features of the blasts cells and WBC in the blood. These different sub-types of ALL are indicative of different infections and are suggestive of the different line of treatment in the patients. The identification of these sub-types is not considered by most of the researchers in this area. Similarly, AML has different subtypes such as M0 to M7. These sub-types also differ in regard to the treatment guidelines. Moreover, types T1, T2, and T3 are so similar that, the distinctness is still a challenge for the researchers. The diagnosis of these different sub-types is not considered in most of the cases. Performance measures are limited to accuracy in most of the cases. There is a scope of improvement in accuracy. Accuracy of different stages of blood cell analysis is tested on a limited database.

6.4 Conclusion

Blood cell analysis assumes a crucial job in location and expectation of various issue and maladies identified with person. There are distinctive neurotic strategies for the equivalent, which ends up being exorbitant and furthermore requires long understanding for location. Image processing and computer vision strategies are produced for investigation of blood cells and discovery of maladies. Microscopic blood cell analysis framework has various stages to be specific, pre-processing, segmentation, feature extraction, classifier and illness identification. Pre-processing comprises of improving the gained picture quality and commotion expulsion. This incorporates

Table 6.3 Comparison of different techniques for Leukemia detection

Author	Year	Methodology	Performance measure	Database	No. of images
Patel and Mishra [43]	2015	K-means clustering for detection of WBC. Histogram and Zack algorithm for grouping WBCs, SVM for classification	Efficiency: 93.57%	ALL-IDB	7
Neoh et al. [45]	2015	Multilayer perceptron, support vector machine (SVM) and Dempster Shafer	Accuracy: Dempster-Shafer method: 96.72%, SVM model: 96.67%	ALL-IDB2	180
Negm et al. [44]	2018	Panel selection for segmentation, K-means clustering for features extraction, and image refinement. Classification by morphological features of Leukemia cells detection	Accuracy: 99.517%, Sensitivity: 99.348%, Specificity: 99.529%	Private datasets	757
Shafique et al. [47]	2019	Histogram equalization, Zack algorithm, watershed segmentation, support vector machine (SVM) classification	Accuracy: 93.70%, Sensitivity: 92%, Specificity: 91%	ALL-IDB	108
Abbasi et al. [68]	2019	K-means and watershed algorithm, SVM, PCA	Accuracy, specificity, sensitivity, FNR, precision all are above 97%	Private	Not mentioned
Mishra et al. [51]	2019	Triangle thresholding, discrete orthogonal	Accuracy: 99.66%	ALL-IDB1	108
Kumar et al. [33]	2019	SMI based model, local directional pattern (LDP)chronological sine cosine algorithm (SCA)	Accuracy: 98.7%, TPR:987%, TNR:98%	AA-IDB2	Not mentioned

(continued)

Table 6.3 (continued)

Author	Year	Methodology	Performance measure	Database	No. of images
Iltaf et al. [53]	2019	Expectation maximization algorithm, PCA, sparse representation	Accuracy, specificity, sensitivity all more than 92%	ALL-IDB2	260
Ahmed et al. [58]	2019	CNN	Accuracy: 88% Leukemia cells and 81% for subtypes classification	ALL-IDB, ASH Image Bank	Not mentioned
Matek et al. [54]	2019	ResNeXt CNN	Accuracy, sensitivity and precision above 90%	Private	18,365
Sahlol et al. [59]	2020	VGGNet, statistically enhanced Salp Swarm Algorithm (SESSA)	Accuracy: 96% dataset 1 and 87.9% for dataset 2	ALL-IDB, C-NMC	Not mentioned

gray-scale conversion, thersholding, filtering, and histogram stretching, morphological operations. Pre-processed image is portioned to get the locale of interest for further processing. Here WBC, RBC and platelets are isolated. Distinctive computer vision techniques utilized for segmentation are edge detection, watershed transformation, mathematical morphology, zack algorithm, k-means clustering, SDM, HSV thresholding, otsu's algorithm. There are overlapping cells at the time of staining of blood smear. Expulsion of these overlapping cells at the time of segmentation is a difficult undertaking. Hough transform evacuates certain overlapping however it makes the framework slower. Segmented images are classified by algorithms like SVM, ANN classifier, ELM classifier, circular Hough transform. There are various databases accessible for experimentation and investigation of microscopic blood cell such as BCCD (Kaggle) Database, ALL-IDB1, ALL-IDB2, Atlas of Hematology by Nivaldo Meridos, Leukocyte pictures for division and characterization (LISC), Ash image bank, and C-NMC dataset. There are different application territories where microscopic blood cell examination assumes a crucial job. RBC, WBC count, blood group identification, leukemia detection, sickle cells detection, partition of various WBC sub-classes, malaria parasite detection could be performed utilizing complex image processing and computer vision techniques.

Table 6.4 Analysis of articles adding significant research contribution in the area

1	Application	Blood cancer diagnosis
	Background	Need of an automated technique for blood cancer detection
	Objective	Hybrid CNN model for ALL detection
	Data source	(2019) Journal of Digital Imaging, https://doi.org/10.1007/s10278-019-00288-y
	Interventions/participants	Anuj Sharma, Bala Buksh
	Methods	K-means clustering, Fuzzy based CNN with firefly optimization algorithm
	Results	97.01%
	Limitation	Accuracy needs to be increased
	Key findings	Hybridization of FOA as optimization technique is used here with the basis used is k means clustering and CNN classifier Histogram of Oriented Gradients (HOG) descriptor with FOA is used as feature extraction and selection mechanism from the Region of Blood Cell (ROBC)
	Authors opinion	Proposed method given good result in terms of accuracy. But the commonly used validation technique for classifiers such as Cross fold etc. is not mentioned
2	Application	Detection of Leukemia
	Background	Need of an automated technique for blood cancer detection
	Objective	Segmentation of WBCs, classification of normal and blasts cells
	Data source	(2019), International Journal of Engineering and Advanced Technology (IJEAT) ISSN: 2249-8958
	Interventions/participants	Roopa B. Hegde, Keerthana Prasad, Harishchandra Hebbar, Brij Mohan Kumar Singh, Sandhya
	Methods	Thresholding, morphology, SVM and NN classifier
	Results	98% for segmentation of WBC, 92.8% for Leukemia detection
	limitation	Blasts detection needs improvement
	Key findings	Segmentation is done by using traditional techniques such as thresholding, morphology and filtering. Classification is done with the combination of two classifiers SVM and NN
	Authors opinion	Validation of SVM classifier is done using hold-out validation but for NN classifier the validation technique is not mentioned. Also the combination of NN and SVM might need a proper exploration of a particular suitable validation technique
3	Application	Acute lymphoblastic Leukemia detection
	Background	Need to detect Leukemia with its subtypes L1, L2 and L3
	Objective	Detection of Leukemia, classification into its sub-types
	Data source	(2018), Technology in cancer research and treatment 17 1,533,033,818,802,789
	Interventions/participants	Shafique, Sarmad, and Samabia Tehsin

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Table 6.4 (continued)

	Methods	Deep CNN AlexNet architecture
	Results	Average accuracy of 98% for detection and 95–96% for sub-types classification
	limitation	Database images used are limited. Also pre-processing and feature extraction is not performed
	Key findings	Transfer learning approach is used with the Alexnet architecture that improve the performance of classification
	Authors opinion	Pre-processing and other enhancement techniques can improve the performance of system. Other DCNN architectures could also be explored and could be tested to find the best suitable architecture for this application
4	Application	ALL detection and diagnosis
	Background	Need for a computer assisted framework for ALL diagnosis
	objective	Segmentation of WBC, RBC, and platelets, feature extraction, classification into normal and blasts cells
	Data source	(2019), 2nd International Conference on Communication, Computing and Digital systems (C-CODE) (pp. 184–189). IEEE
	Interventions/participants	Shafique, S., Tehsin, S., Anas, S., & Masud, F.
	methods	Zack algorithm, SVM classifier
	Results	Accuracy of 93.7%
	Limitation	Dataset images are limited to 108 only
	Key findings	Color and shape features are used, compared with KNN SVM found improved performance slightly
	Authors opinion	Deep classifier can be applied further for improvement of framework but dataset is to be increased in that case. Different types of ALL such as L1, L2, and L3 could be detected in the future study
5	Application	WBC identification
	Background	Under-segmentation and over segmentation, complexity in feature extraction methods
	objective	Pre-processing, feature extraction and selection, classification, applying TLA approach, WBCs Net architecture
	Data source	(2019), White blood cells identification system based on convolutional deep neural learning networks. Computer methods and programs in biomedicine, 168, 69–80
	Interventions/participants	Shahin, A. I., Guo, Y., Amin, K. M., & Sharawi, A. A.
	methods	CNN, SVM, WBCsNet
	Results	Accuracy up to 96%
	Limitation	For higher dataset s accuracy is reduced to 92.6%
	Key findings	CNN and SVM are used in combination, WBCsNet improves accuracy

(continued)

Table 6.4 (continued)

	Authors opinion	As the deep learning is applied, data size to be increased to improve the performance of system
6	Application	ALL detection
	Background	Need of automated CAD framework for ALL detection
	Objective	Pre-processing, feature extraction, dimensionality reduction, classifier
	Data source	(2019), Texture feature based classification on microscopic blood smear for acute lymphoblastic Leukemia detection. Biomedical Signal Processing and Control, 47, 303–311
	Interventions/participants	Mishra, S., Majhi, B., & Sa, P. K.
	Methods	Triangle thresholding, discrete orthogonal S-transform, Adaboost algorithm with RF(ADBRF) classifier
	Results	Accuracy of about 99%
	Limitation	Only one dataset IDB1 is used with less number of cells of 799. ALL sub-types, L1, L2, and L3 are not detected
	Key findings	ADABOOST RF classifier found superior compared with SVM and NN classifier
	Authors opinion	The framework can be extended for acute myloid Leukemia detection with its sub-types. Also ALL subtypes can be detected with some improved and optimized version further
7	Application	ALL detection in single cell
	Background	Need to develop image processing framework for diagnosis with deep learning for improvement in accuracies of popular system
	Objective	Pre-processing, segmentation, feature extraction, classification
	Data source	(2019), Mutual Information based hybrid model and deep learning for Acute Lymphocytic Leukemia detection in single cell blood smear images. Computer Methods and Programs in Biomedicine, 179: 104987, 2019. ISSN 18727565. https://doi.org/10.1016/j.cmpb.2019.104987. URL https://doi.org/10.1016/j.cmpb.2019.104987
	Interventions/participants	Krishna Kumar Jha and Himadri Sekhar Dutta
	methods	MI based hybrid model, Deep CNN classifier with chronological Sine Cosine Algorithm (SCA), k fold validation
	Results	Accuracy of 98.7%
	Limitation	Only single cell is considered for analysis
	Conclusion	DCN N with SCA gives good results compared to current state of the art using NN with hybridized work
	Key findings	Hybrid segmentation with fuzzy means and active contour
	Authors opinion	Single cells identification is done in this work. The work can be extended to multiple cells. Also hybrid optimization algorithms can be employed for performance improvement further

(continued)

Table 6.4 (continued)

8	Application	ALL diagnosis
	Background	Leukocyte segmentation under uneven imaging conditions
	Objective	Leukocyte segmentation, feature extraction and classification
	Data source	(2018), An automatic and robust decision support system for accurate acute Leukemia diagnosis from blood microscopic images. Journal of digital imaging, 31(5), 702–717
	Interventions/participants	Moshavash, Z., Danyali, H., & Helfroush, M. S.
	Methods	Zack algorithm, SVM, KNN, Naïve Bayes, and decision tree
	Results	Accuracy of 97.6%
	Limitation	Overlapping cells can be detected by this framework. The system could not be assured for further classification of Leukemia in to its sub-classes
	Key findings	Two ensemble classifiers are combinedly used for classification purpose. Classifier 1 with 4 different classifier combinations and classifier 2 using SVM with different kernel functions Two types of features extractions are compared, GLCM and LBP. LBP achieved higher accuracy
	Authors opinion	The system is much complex as it utilizes two different ensemble classifiers with different combinations and also feature extraction with two methods
9	Application	ALL detection
	Background	Time consuming manual methods based on morphology of cells
	Objective	Segmentation of WBC, feature extraction, and classification as normal, and blast cell
	Data source	(2019), Computer-assisted Acute Lymphoblastic Leukemia detection and diagnosis." In 2019 2nd International Conference on Communication, Computing and Digital systems (C-CODE), pp. 184–189. IEEE
	Interventions/participants	Shafique, Sarmad, Samabia Tehsin, Syed Anas, and Farrukh Masud
	Methods	Histogram equalization, zack algorithm, watershed algorithm, SVM classifier
	Results	Accuracy of 93.7%
	Limitation	Database images used are lesser, 108 images
	Key findings	As shape features can be affected during segmentation and pre-processing stages, here color features are used along with shape features
	Authors opinion	There is scope to use different features, other than specified here for performance improvement. In order to apply deep learning algorithm further, the dataset images are to be increased. The classification done here is in terms of normal cell and blast cells only. The framework could not be justified for detection of other different subtypes of leukemia

(continued)

Table 6.4 (continued)

10	Application	ALL detection and classification
	Background	Manual detection of Leukemia is critical and challenging task
	Objective	Pre-processing, processing, post processing, data normalization, feature extraction, and classification
	Data source	(2018), A decision support system for Acute Leukaemia classification based on digital microscopic images. Alexandria engineering journal, 57(4), 2319–2332
	Interventions/participants	Negm, A. S., Hassan, O. A., & Kandil, A. H.
	Methods	Histogram equalization, k means algorithm, watershed algorithm, decision tree, and NN classifier
	Results	Overall accuracy of decision tree is 96.6%, and NN is 96.76%
	Limitation	Dataset size is limited to 115 images for public dataset
	Key findings	NN is performed better than decision tree, but decision tree proves to be faster than NN approach
	Authors opinion	There are different sub-types of both ALL and AML. Further expansion of this algorithm can explore these sub-types
11	Application	ALL detection
	Background	Need of improvement of diagnosis system of Leukemia
	Objective	Segmentation, feature extraction, classification
	Data source	(2019), Automatic detection of acute lymphoblastic leukaemia based on extending the multifractal features, IET Image Processing 14, no. 1 (2019): 132–137
	Interventions/participants	Abbasi, Mohamadreza, Saeed Kermani, Ardeshir Tajebib, Morteza Moradi Amin, and Manije Abbasi
	Methods	k-means algorithm, watershed transform, SVM classifier
	Results	Accuracy up to 99%
	Limitation	Dataset images are limited to 600. Popular datasets for this study such as ALL-IDB1, ALL-IDB2 etc. are not used in this work
	Key findings	Fractal features are used. Feature reduction is taken care by using PCA algorithm. Use of chaotic features at feature extraction stage increases the accuracy of classification
	Authors opinion	The similar framework could be extended for AML detection along with its sub-types. Exact selection of features is not explored in depth here. There can be the exploration related to complexity and processing time with regard to the use of PCA algorithm
12	Application	ALL detection
	Background	Need of an automatic and novel approach for ALL detection
	Objective	Pre-processing, feature extraction and selection, classification

(continued)

Table 6.4 (continued)

	Data source	"Automated acute lymphoblastic leukaemia detection system using microscopic images." IET Image Processing 13, no. 13 (2019): 2548–2553
	Interventions/participants	Sukhia, Komal Nain, Abdul Ghafoor, Muhammad Mohsin Riaz, and Naima Iltaf
	Methods	Diffused expectation maximization (DEM) algorithm, thresholding, sparse classifier
	Results	Accuracy of 94%
	Limitation	Database has limited dataset images, 260. Out of these, 160 used for training and 100 for validation purpose
	Key findings	Accuracy of local binary pattern (LBP), HD, and SFTA is more as compared with the color and shape features
	Authors opinion	The paper has given more stress upon the feature extraction and selection stage. Also sparse classifier is introduced for this work that proves to be good in terms of accuracy. Further the similar framework could be extended for diagnosis of other types of leukemia
13	Application	Anemia detection
	Background	Image processing techniques can prove more reliable and cost effective in analysis of anemia
	Objective	For Sickle Cell Detection: Ellipse detection, sickle cell detection for Thalassemia: image acquisition, pre-processing, segmentation, feature extraction, classification
	Data source	Detection of Sickle Cell Anemia and Thalassemia using Image Processing Techniques
	Interventions/participants	Lavanya, T. H., Tumkur Gubbi, and S. Sushritha
	Methods	Edge detection, midpoint ellipse algorithm(MEA), histogram thersholding, diffused expectation maximization (DEM), Otsu's thresholding, KNN classifier
	Results	Not evaluated in percentage of accuracy
	Limitation	Datasets are not mentioned
	Key findings	Ellipse detection and DE (diffused expectation) algorithm is used for anemia detection. Thalassemia different types are not considered here
	Authors opinion	Mentioned framework could not be justified as, accuracy and datasets are not clearly explored in system evaluation
14	Application	Detection of healthy and unhealthy RBC
	Background	Anemia detection by hemoglobin percentage and microscopic examination
	Objective	Detection of RBC, separation of overlapped cells, classification
	Data source	(2016), "Healthy and unhealthy red blood cell detection in human blood smears using neural networks." Micron 83: 32–41
	Interventions/participants	Elsalamony, Hany A

(continued)

Table 6.4 (continued)

	Methods	Morphological operations, circular hough transform, watershed transform, NN
	Results	Accuracy of detection of different cell types is greater than 97.8%
	Limitation	Dataset contains fewer images, limited to 160
	Key findings	Different anemia type including sickle cell, elliptocytosis, microsites and unknown shapes are detected. Green color is considered as a detection parameter for healthy cells
	Authors opinion	Different parameters of cells, area, convex area, perimeter, eccentricity, solidity, and ratio are considered for differentiating healthy and unhealthy cells
15	Application	Thalassemia detection
	Background	Requirement of accurate diagnosis system for the disease
	Objective	Image acquisition, enhancement, segmentation, and filtering
	Data source	(2015), "Unsupervised color image segmentation of red blood cell for thalassemia disease." In 2015 2nd International Conference on Biomedical Engineering (ICoBE), pp. 1–6. IEEE
	Interventions/participants	Rashid, Nurul Zhafikha Noor, Mohd Yusoff Mashor, and Rosline Hassan
	Methods	Global contrast technique, image color conversion, k-means clustering, median filtering, seed region growing area extraction (SRGAE) algorithm
	Results	Average segmentation accuracy is of 94.57%
	Limitation	Database has limited size, containing only 60 images
	Key findings	Alpha, beta, and thalassemia trait images are used and analyzed in the study. These two types are distinguished significantly. SRGAE algorithm is effectively used for getting region of interest
	Authors opinion	Contrast technique is used for image enhancement which is comparatively simple. Color conversion has given a good importance in the detection. Use of SRGAE added the novelty in this study. This algorithm could be further utilized for other applications of microscopic analysis
16	Application	Thalassemia identification
	Background	Need of an automated framework for detection
	Objective	Image acquisition, feature extraction, information processing, classification
	Data source	(2016), "Automated Thalassemia Identifier Using Image Processing."
	Interventions/participants	Sandanayake, T. C., A. T. P. M. N. Thalewela, H. P. Thilakesooriya, R. M. A. U. Rathnayake, and S. A. Y. A. Wimalasooriya

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Table 6.4 (continued)

	Methods	Gray scaling, thresholding, edge detection, ANN, and SVM classifier
	Results	Accuracy of 89% for female and 97% for male patients
	Limitation	Thalassemia has many types depending upon the shapes of RBC. All these types are not detected in this work
	Key findings	Six different parameters are considered for thalassemia analysis including RBC, hemoglobin (HB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and RBC distribution width (RDW)
	Authors opinion	Research can be extended to detect and diagnose all the types of thalassemia. Also severity of the disease can also be diagnosed by exploring the research in that direction
17	Application	Minor thalassemia detection
	Background	Need of an automated framework for thalassemia detection
	Objective	Preprocessing, segmentation, feature extraction, and classification
	Data source	(2017), "The classification of abnormal red blood cell on the minor thalassemia case using artificial neural network and convolutional neural network." In Proceedings of the International Conference on Video and Image Processing, pp. 228–233
	Interventions/participants	Tyas, Dyah Aruming, Tri Ratnaningsih, Agus Harjoko, and Sri Hartati
	Methods	Histogram equalization, morphological operations, back propagation NN
	Results	Accuracy reached to 92.55%
	Limitation	Number of images are limited in the database to 256 only
	Key findings	Texture features, color features, and shape features are used for feature extraction purpose
	Authors opinion	A total of 43 values of features are used for one cell. This shows the feature extraction is more precise. But this may increase the processing time
18	Application	Malaria detection and cell counting
	Background	Requirement of faster and trustable method for malaria diagnosis
	Objective	RBC detection, feature computation, cell classification
	Data source	(2018), Malaria parasite detection and cell counting for human and mouse using thin blood smear microscopy. Journal of Medical Imaging 5, no. 4: 044,506
	Interventions/participants	Poostchi, Mahdieh, Ilker Ersoy, Katie McMenamin, Emile Gordon, Nila Palaniappan, Susan Pierce, Richard J. Maude et al.

(continued)

Table 6.4 (continued)

	Methods	Microscopic imaging with thin blood smear, multiscale Laplacian of Gaussian (LOG) along with coupled edge profile active contours(C-EPAC), SVM, ANN
	Results	Accuracy of 98% and 99% for SVM and ANN respectively
	Limitation	Dataset has less number of images, 70 in this case
	Key findings	Multiscale LOG and C-EPAC are combined. ANN achieves higher accuracy compared to SVM
	Authors opinion	The work could be explored further for more types of parasites. The counts of parasites and there life stages could be detected to explore the severity of the disease
19	Application	WBC classification
	Background	WBC classification is important for different disease detections
	Objective	Pre-processing, classification
	Data source	(2019), "Classification of White Blood Cells by Deep Learning Methods for Diagnosing Disease." Revue d' Intelligence Artificielle 33, no. 5: 335–340
	Interventions/participants	Yildirim, Muhammed, and Ahmet Çinar
	methods	Median and Gaussian filtering, CNN classifier
	Results	Accuracy is in between 62 and 83% for different deep learning architectures
	Limitation	Accuracy is less as compared to other popular frameworks
	Key findings	Different architecutres of Deep learning are applied to the problem. Alexnet, RessNet, DenseNet201, GoogleNet are used for analysis. Original data as well as pre-processed data is analyzed for segmentation. Pre-processed data with Gaussian and median filtering gives an improvement in the accuracy
	Authors opinion	Pre-processing improves accuracy. Deep learning architecture could improve the performance by increasing the dataset size
20	Application	Detection of dengue
	Background	Requirement of a framework for viral disease detection
	Objective	Blood cell classification, dengue virus detection
	Data source	(2015), "Image processing for detection of dengue virus based on WBC classification and decision tree." In 2015 13th International Conference on ICT and Knowledge Engineering (ICT & Knowledge Engineering 2015), pp. 84–89. IEEE
	Interventions/participants	Tantikitti, Sarach, Sompong Tumswadi, and Wichian Premchaiswadi
	methods	Color transformation, multi-level thersholding, decision tree classification
	Results	Accuracy of 72% for dengue detection and 92% for WBC classification

(continued)

Table 6.4 (continued)

	Limitation	Database images are limited. Sub-types of dengue virus are not detected
	Key findings	Different types of parameters are considered such as number of Lymphocytes, number of Phagocyte, number of WBC, percentage of Lymphocytes, percentage of Phagocyte and percentage of Hct
	Authors opinion	Decision tree algorithm is used for classification. It spends more time but is more trusted compared with NN

6.5 Future Scope

A powerful division of white and red cells in minuscule blood smear pictures to meet better precision could be actualized. To conquer overlapping cells issue at the hour of division will likewise end up being a significant extension. A viable feature extraction by utilizing distinctive image transforms will like- wise demonstrate to a significant degree. There are different optimization algorithms which could be utilized efficiently for classification of blood cells. Different deep learning algorithms, that may demonstrate productive and might give high accuracy to various phases of examination of blood cells. The designed algorithms must be tasted with various publicly accessible databases for precision. Precision of the calculation should be similar enough with all the databases. Another parameter like vigor can be presented for this reason. Relative accuracy of various databases can be determined. To gauge the exhibition of framework with various measures such as true positive, true negative, faults, sensitivity, specificity, precision, FI score, J-score in addition with accuracy.

Contribution is still needed for various ailments location, such as diabetes, viral diseases such as chickungunya and dengue, anemia diseases such as pancytopenia, thalassemia and leukemia.

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