CHAPTER 2

REVIEW OF LITERATURE

Automatic detection and classification systems to identify ALL have gained extensive attention in research community concentrating on healthcare industry. These systems are designed as a pipe-line-based system centered on various tasks like enhancement, WBC identification and classification. Several researchers and academicians have implemented several different solutions to perform each of these tasks and this chapter reports some of them that are related to this research work. Literature survey reports related to ALL-C is very limited (Das *et al.,* 2022a). Bagasjvara *et al.,* (2016) reviewed ALL detection based on the image processing and machine learning algorithms used. On the other hand, Al-Dulaimi *et al.,* (2021) reviewed the various segmentation algorithm used during ALL classification. A similar review was also conducted by Anilkumar *et al.,* (2020). Parthvi *et al.,* (2020) also presented description on the various machine learning algorithms that have been used during ALL-C. Traveling in the same line, this chapter also presents the result of the literature study conducted to understand the current status of the researches related with ALL-C.

2.1. PREPROCESSING

The preprocessing step of ALL-C system performs various operations that enhance the quality of the input microscopic images and identify the white blood cells. The quality of the microscopic images are often degraded by the variations in contrast, weak edges and noise. In this research work, the quality is improved through contrast enhancement, edge enhancement and noise removal. The following section presents the review of the various algorithms proposed to perform these three tasks.

2.1.1. Contrast Enhancement

Contrast enhancement is used to enhance the global and local contrast variations in an image. A simple and most frequently used solution to tackle this issue is histogram equalization or any other enhanced version of it like adaptive histogram equalization or Contrast Limited Adaptive Histogram Equalization (CLAHE). Several researchers have also attempted to propose other methods to handle contrast variations in an image.

A global shifting of the intensity values in the approximation-coefficients of wavelets was used by Chen *et al.,* (1997) enhance the contrast in an image. However, this method did not propose a method to shifting step size determination, which was user-defined and hence was not efficient. The work also used zero-crossing tree to reduce noise and maintain edge details.

Fu *et al.,* (2000) handled the issues in histogram equalization using wavelet decomposition. This method applied histogram equalization in spatial domain and the result was transformed into a wavelet domain, where all approximate coefficients were squared. This method overcame the issue of loss of information in histogram equalization.

Ritika and Kaur *et al.,* (2013) presented a comparative work histogram equalization with CLAHE and morphological operator-based methods. Later, Abdoli *et al.,* (2015) used Gaussian mixture model based algorithm. This algorithm used Gaussian to represent dominant intensity level in low contrast images and enhanced them using sub-histograms separated by the mean value of Gaussians of the global contrast of the image. Lidong *et al.,* (2015) used CLAHE and DWT (Discrete Wavelet Transformation) enhance contrast of an image. This method decomposed the input image into low and high frequency coefficients. The low frequency coefficients were then enhanced using CLAHE. The application of inverse DWT produced the enhanced image.

Shin and Park *et al.,* (2015) also improved histogram equalization using an optimization procedure that preserved the localities of the histograms constructed. This algorithm could preserve shape details efficiently and could work with images having different statistical properties. Tiwari *et al.,* (2015) proposed a fast quantile-based histogram equalization, which omitted the recursive segmentation process of histogram. Wei *et al.,* (2015) also modified histogram equalization which performed global histogram equalization using pixel population mergence first that used entropy maximization rule and gray-level distribution.

In the next year, Eunkin *et al.,* (2016) used wavelets based on entropy to adjust contrast variations. The method scaled the image in wavelet domain using local entropy and then used a HSI color model-based color enhancement method to further improve the quality of the image. The algorithm modified the wavelet low frequencies and scaled them in HSI color space to enhance the intensities. Thus, this method improved contrast without losing color information. Alternatively, Parihar and Verma *et al.,* (2016) implemented an entropy-based dynamic sub-histogram equalization method for adjusting contrast variations over the whole dynamic range. The main advantage of this method was that it was parameterless.

Usage of local histogram equalization for contrast enhancement was proposed by Shakeri *et al.,* (2017). This method started with clustering the image according to the brightness levels and then used histogram equalization on each cluster. The method claimed to preserve image and edge details effectively. In the same year, a social spider algorithm that resulted with a contrast enhanced image and an entropy increased image was proposed by Maurya *et al.,* (2017). These two images were fused to obtain the final contrast enhanced image.

Yadav *et al.,* (2020) presented an overview of contrast enhancement algorithms along with its variants. The algorithms were described using medical images. The methods analyzed were Histogram equalization, Linear contrast enhancement, Non-linear contrast enhancement (Gamma correction), Inverted-Gauss based contrast enhancement, Adaptive histogram equalization and CLAHE.

Jaiswal *et al.,* (2022) proposed a contrast enhancement method using a combination of morphological transformations. This algorithm applied top hat transformation to make its brighter regions brighter. The black hat transformation is then used to make the dark regions darker. The enhanced image is obtained by adding top hat transform result to the input image and then subtract the black hat transform result. A similar work was previously proposed by Kushol *et al.*, (2019).

Marimuthu *et al.*, (2022) described the working of CLAHE algorithm to perform contrast enhancement in images. Joshi *et al.,* (2023) presented a comparative study on three different contrast enhancement algorithms, namely, histogram equalization, CLAHE and min-max contrast stretching algorithms.

From the various studies, it is clear that histogram equalization is the most popularly used method. This method has the disadvantage of over enhancing white regions of the image. On the other hand, adaptive histogram equalization method, CLAHE, can produce better results, but it lacks local contrast. However, the advantage obtained makes CLAHE as an optimal choice for contrast enhancement.

2.1.2. Edge Enhancement

Edge enhancement is defined as an image processing filter that improves the contrast of the edges in an image, so that they appear sharper. According to Li *et al.*, (2007), edge enhancement is an important operation which helps in detecting organ boundaries, in subsequent diagnosis and treatment of the disease. It helps in differentiating the features by improving the visual quality perception of the image and provides insight into the shape and outline of objects and offers vital information to the Human Visual System (HVS).

Enhancing edges is an important step in ALL classification, as it can help to detect WBC accurately. Edge enhancement has been used as early as 1970s (Yonezawa *et al.*, 1978), who used the anti-aliasing wherein the algorithm detects two neighbouring pixels in the oblique direction and inserts a corrective pixels to smoothen the line. Following this work, several other researchers have also proposed the manipulation of image content to produce quality edges (Gupta, 1981; Ort, 1981, Shirasaka, 1998). These methods while producing quality edges, failed with complex contours.

Alternatively, template matching method was proposed to improve edge quality. In these methods, the image is first divided into regions, which are then scanned window-wise and compared against a set of pre-defined patterns that are to be rectified (Yao *et al.*, 2006; Lund, 1997; Tung, 1989). However, these methods required pre-defined regions and had high time complexity.

Clayton *et al,*. (2006) who proposed a method, was the first to convert the image into black and white (binary form), enhanced edges and reconstructed to its original color form. In the same year, Braica *et al.*, (2006) proposed a method that increased the contrast of the image regions at the edges. After this, several researchers have investigated methods that can enhance image edge detection and enhancement tasks.

Tsai and Yeh *et al.*, (2021) proposed an enhancement method to work with microscopic images obtained by scanning electron microscope images. The algorithm starts with the training phase where calibrate scale and orientation were used to extract profiles, which are then used to train a neural network. During testing, the centerlines of boundaries are found, whose profiles are extracted and used for prediction to produce the final enhanced image.

Pang *et al.,* (2021) found that the edges were often degraded by blooming and noise during scanning electron microscope images. To solve this an improvement method was proposed, which was based on inpainting and anisotropic diffucion method for scanned electron microscopic images.

A distributed edge-enhancement using fractional spiral phase filter using random light was proposed by Wang *et al.,* (2022). A gradual edge-enhanced ghost imaging method with pseudo-thermal light was also proposed in both the theory and experiment.

Nur *et al,.* (2022) presented an edge enhancement and detection method to work with cervical cytology images, in order to enhance the detection of nucleus. The algorithm was enhanced through the use of contrast enhancement based on CLAHE algorithm.

Zhao and Zhu *et al.,* (2022) developed an edge detail enhancement algorithm for high dynamic range images. The proposed method used Fourier transformation and then applied Gaussian filtering to obtain low and high frequency images. The low frequency image contrast was enhanced using CLAHE, while the high frequency image was enhanced by the application of non-sharpening masking and grey transformation. The enhanced low and high frequency images were then fused to obtain the edge enhanced image. Finally an inverse Fourier transformation was used to obtain the final enhanced image.

2.1.2. Denoising Algorithms

As described earlier, noise are undesirable electronic variations or fluctuations in microscopic images (https://stockbeamer.com/2021/01/04/removing-video-noise-in-stock-footage; https://en.wikipedia.org/wiki/ Image_noise). Presence of noise obscures vital details of the image and makes it challenging to perform the various tasks in ALL-C system. Thus correct handling of noise is important to increase the accuracy of leukemia detection.

The noise removal algorithms can be broadly grouped into spatial domain algorithms and transformation based algorithms (Zhu *et al.,* 2021). Spatial domain algorithm, uses low pass filtering on a set of pixels and works on the basic principle that the noise exists only in high frequency bands. The main goal of these algorithms is to reduce noise by estimating each pixel's grey scale values based on the correlation between pixels and image patches. (Sena *et al.,* 2022). The spatial domain based denoising algorithms, while being very effecting in suppressing noise, also introduce blurs around edges and sometimes remove parts of edges. The algorithms under this domain can further be grouped as non-linear or linear algorithms. Examples of non-linear algorithms include median, rank conditioned, rank selection and relaxed median algorithms. Examples of linear include wiener filter and mean filter.

The transformation-based algorithm starts by converting the noisy image to another domain and using some features related to the image and noise present in it, remove noise in the transformed image. These algorithms work on the principle that the features of the image and noise are different in the transformed domain. The transformation-based algorithms can belong to two groups, namely data adaptive and data non-adaptive algorithms (Andrey *et al.*, 2020), depending on the basis function (Jain *et al.*, 1989) used. Popular methods used algorithms include spatial frequency filtering and discrete wavelet transformation based methods. Spatial frequency filtering algorithm applies fast Fourier transformation to obtain the low pass filter, from which noise is removed using frequency domain and adapts a cut-off frequency when the noisy regions are decorrelated from the useful signals in the frequency domain. The performance of these algorithms is dependent on the cut-off frequency and are normally time consuming. Moreover, these algorithms also produce artificial frequencies in the resultant enhanced images.

The wavelet transform based algorithms can be linear or non-linear. Wiener method, a popularly used algorithm of linear method, works efficiently when the object degradation can be modelled using a Gaussian process. These methods use the mean square error as accuracy criterion (Strela *et al.*, 2000). Popularly used non-linear method is threshold-based algorithms (Donoho *et al.*, 1992), which uses either soft or hard thresholds (Gabrea and Gargour *et al.*, 2004) along with a shrinkage method to remove noises. Shrinkage methods are threshold selection methods and include universal thresholding and subband adaptive thresholding method (Donoho and Johnstone *et al.*, 1995). Threshold are calculated using adaptive or non-adaptive methods. Examples include VisuShrink (a non-adaptive algorithm based on universal thresholding) (Donoho *et al.*, 1995) and data driven adaptive methods like SureShrink (Donoho and Johnstone *et al.*, 1995), BayesShrink (Chang *et al.*, 2000) and Cross Validation (Weyrich and Warhola *et al.*, 1998) algorithms.

Several algorithms have also used enhanced version of wavelet transformation. Wavelet packets, wavelet dual tree transformation, curvelets, etc, are some examples (Wolter *et al.*, 2022), Wanshan *et al.*, 2022). Sumanth *et al.*, (2018) have described the various advantages of using transform based method for removing noise in the images. Similarly, Fan *et al.*, (2019) have presented a detailed review of the various denoising algorithms and have listed out the merits and demerits of these methods. The same authors (Fan *et al.*, 2020), have proposed an optical flow-based algorithm combined with wavelet transformation for removing noise. On the other hand, Liu *et al.*, (2021), enhanced wavelet packets using fuzzy thresholding and correlation analysis to remove noises in images. The algorithm estimated optimal decomposition layer using the correlation function value difference between packet coefficients and used logarithmic entropy as best basis cost function.

A detailed explanation on the theory behind wavelets along with wavelets packets was provided by Bassam *et al.*, (2021). They have also discussed various applications where they have been applied successfully. A similar study report was also published by Dey and Siddiqui *et al.*, (2021). On the other hand, Gong *et al.*, (2021) discussed the application of wavelet family on signal denoising.

Even though noise removal is considered as a vital task in ALL-C systems, only very few authors have focused on enhancing microscopic images through noise reduction. Kaur and Maini *et al.*, (2016) compared five noise removal algorithms and studied their effect on removing noise from microscopic images. The algorithms selected were median filter, adaptive filter, contra harmonic mean filter, bilateral filter and alpha trimmed mean filter. These filters were analysed on their effectiveness in removing four type of noises, namely, salt and pepper, gaussian, poisson and speckle noise.

Prasad *et al.,* (2018) proposed microscopic image noise removal and sharpening algorithms. A median filter in spatial domain was used to remove noise. While two methods that worked with spatial and frequency domains were used to sharpen the microscopic image. The work proposed a method that combined both noise removing filter with the sharpening methods to enhance the microscopic image.

Giannatou *et al.,* (2019) proposed the residual learning Convolutional Neural Network (CNN) for noise removal in Scanning Electron Microscopic (SEM) images. This method is a residual learning method inspired by the CNN and trained to estimate the noise at each pixel of a noisy image. The input block in SEM denoising model consists of a convolutional layer followed by a ReLU and Batch Normalization. The output block consists of a convolution with one filter for reconstruction.

Devi and Patil *et al.,* (2020) also presented a comparative study on wiener and Median methods to filter the noise present in the microscopic images. According to their study median filter was more effective but Weiner filter was able to preserve details in a better manner.

Ilesanmi and Ilesanmi *et al.,* (2021) conducted a review of various denoising methods that were based on convolutional neural network. Various CNN techniques for image denoising were categorized and analyzed. The review was divided into two groups, where the first work reported studies that used general images during experiments, while the second group reviewed studies that focused on specific images.

Tian *et al.,* (2022) presented a noise removing system that can learn to denoise noisy fluorescence microscopy images. This system was designed as a self-supervised image noise removal method and has the capability to train an image denoising model based on single noisy observation. The training was done using paired noisy images of different dimensions.

Chang *et al.,* (2022) proposed an algorithm to remove noise from scanned microscopic images. They established a noise model of scanned electron microscopy and proposed an effective noise removal algorithm that preserved the structure of the desired region of interest. The proposed algorithm uses variance stabilization first to separate noise and other signals. Then a U-Net structure was used to perform noise removal.

2.2. WBC SEGMENTATION

The main method used for detecting and extracting WBC from microscopic images is segmentation. The main goal here is to extract WBCs, after removing the platelets and RBCs, from its background. The methods used for segmentation is grouped into three categories, namely, signal and image processing-based algorithms, machine-learning-based algorithms and deep learning-based algorithms.

Threshold-based algorithms are the simplest approach to segmentation and produce accurate results when the cells do not touch or overlap each other. It is also the right choice when the cells have a clear depth difference between objects and their background. The main challenge in this type of algorithms is the selection of correct threshold, which is difficult due to the complex nature of cells, intensity inhomogeneities and overlapping cells. The most commonly used algorithm is the Otsu's thresholding (Umamaheswari and Geetha *et al.,* 2018a).

Various other manner of thresholding have also been probed. Lam *et al.* (2021) presented a triple threshold-based method for segmenting WBCs from microscopic images. The proposed method first converted the microscopic image from RGB color space to HSV color space and then the Otsu's threshold was applied to the H component and the WBCs were extracted. In the third step, a kernel with two iterations was used along with the morphological open operator to refine the segmented results.

Thresholding method have also been combined with other segmentation algorithms. Li *et al.* (2016) suggested a combination of dual-threshold and morphological operations. This system was very effective in extracting WBCs and was able to achieve 97.85% accuracy. The dual threshold is a combination of RGB and HSV color space. The proposed method started with prepreocessing to obtain two images. The first is contrast-stretched image and the second is the H component derived after converting the RGB image to HSV color space. A golden section search method was used to estimate optimal threshold. Finally, a post processing procedure was used, where morphological operators and median filters were used to remove incomplete blood cells and unwanted noisy pixels.

Biswas and Ghoshal *et al.* (2016) proposed an algorithm to detect blood cells using a thresholding estimation that used watershed transformation. The algorithm used

Sobel filter in frequency domain to perform edge detection. The sobel filter was enhanced to use a specific window size that reduced noises and found fine edges. This window size also helped to increase the intensity of the edges with strong contrast. The watershed thresholding method using this edge was able to identify WBC more efficiently.

Sadeghian *et al.* (2009) proposed a method that used Zack thresholding algorithm to segment WBC and their nuclei. The method started by converting the RBG color space image into its gray scale form. Then, Canny edge detection method was used, followed by the application of gradient vector flow to connect the edges or boundaries of the nucleus. A hole filling algorithm was also used on the nucleus. The cytoplasm was extracted by subtracting the binary image obtained by using Zack thresholding algorithm from its gray scale version.

Mohammed and Abdulla *et al.* (2020) proposed a thresholding based WBC segmentation from microscopic blood images. The work used two thresholding methods, namely, global or single thresholding method and local or multiple thresholding. A cleaning post processing method based on morphological operations (dilation and erosion) was used to eliminate imperfections in the result.

Zhao *et al.* (2017) used morphological erosion and dilation operators, on microscopic images, during WBC extraction. The erosion operator was used to remove insignificant cells, while the dilation operator was used to grow the nucleus of WBCs. In the same year, Rawat *et al.* (2017a) proposed a method that combined morphological operators and thresholding method to segment the various components of the microscopic image. The morphological operator used was open and Otsu's method was used as the thresholding algorithm.

Dorini *et al.* (2007) also used morphological operators to extract WBC. This work combined morphological operator with scale-space analysis. This method had high misclassification rate and to solve this issue, the same authors Dorini *et al.* (2012) used a self-dual multi-scale morphological toggle operator to obtain a more accurate segmentation result.

Watershed algorithms have also been by several researchers, as it has the advantage to efficient segment overlapping and touching cells (Moshavash *et al.*, 2018).

The main issue of this algorithm is its over-segmentation that occurs because of the irregular shape of blood cells. To solve this issue, (Mishra *et al.*, 2017, 2018, 2019) used a marker-based watershed algorithm to produce a more segmentation result. These proposals worked in two steps. The first step extracted the markers and in the second step, the markers were imposed on the gradient to obtain the final segmented results.

Madhloom *et al.* (2015) proposed a hybrid model that combined watershed with region growing segmentation algorithm. First, the image was segmented using color information along with mathematical morphology. Then, a marker controlled watershed algorithm to separate overlapped blood cells. In the next step, a seeded region growing algorithm was used to segment the WBCs.

Sobhy *et al.* (2016) proposed two algorithms for segmenting WBCs. The first algorithm applied color correct technique first to estimate the mean intensity from the histogram of each color channel. Then the hue saturation intensity was also estimated after converting RGB to HSV color space. Then the two segmentation algorithms were applied on the S component. The first algorithm used was Otsu's thresholding and the second one was marker-control watershed algorithm. The exoskeleton algorithm was used to separate the overlapping WBCs.

Sukhia *et al.* (2017) proposed a method to differentiate individual and overlapped WBCS using watershed segmentation algorithm. The edge map, that fits a circle on each cell, was extracted to identify individual and overlapped cells.

Active contour and level set-based algorithm was adopted to perform blood cells segmentation based on boundary characteristics. The contours used by these algorithms are described as object boundaries that can define the region of interest (Hegde *et al.*, 2019). Emo *et al.*, 2006 proposed a region-based active contour algorithm to segment WBCs. The active contour algorithms cannot handle the topological variations that occur due to the splitting and merging, in the microscopic images. This issue was solved through the use of level-set algorithms. The level-set algorithms can handle contours of complex topology (Li *et al.*, 2010). Khadidos *et al.*, 2017) proposed a weighted level set algorithm to obtain highly accurate segmentation of medical images.

Marzukia *et al.* (2015) used active contour technique to segment WBCs. First the RGB was converted to grey scale image and then in the next step, the active contour algorithm was applied. The binary image of the result was obtained in order to find the roundness value in order to determine the grouped and single WBCs.

Apart from the above, the usage of machine learning classification and clustering-based segmentation algorithms have also been proved to be efficient.

Abdulhay *et al.* (2018) used support vector machine classifier to segment WBCs. On the other hand, Mohapatra *et al.* (2012b) used multilayer perceptron to perform the same task. These methods treat segmentation as a pixel classification problem and can segment the different components of microscopic images effectively.

Among the various clustering algorithms, the K-Means algorithm is the most commonly used approach. Examples include Savkare and Narote *et al.* (2015), Savkare *et al.* (2016), Vard *et al.* (2017), Ferdosi *et al.* (2018) and Negm *et al.* (2018) All these approaches were able to achieve an accuracy of 98%-99%.

Lim *et al.* (2015) grouped colors and morphological operations to segment blood cells in microscopic images. The algorithm also used K-Means clustering algorithm using colors to obtain the primary segmentation. Then morphological segmentation combined watershed algorithm based on gradient magnitude and skeleton was used to obtain the final result.

Gowda and Kumar *et al.* (2017) used K-means algorithm with Gram-Schmidt orthogonalization to segment WBCs. This algorithm used a preprocessing step that used median filter and image normalization to enhance the image first. Then the K-Means algorithm was used to segment WBC and its subtypes. Then the Gram-Schmidt orthogonalization was used to segment the nucleus from the cell.

Mohapatra *et al.* (2010), alternatively, used fuzzy c-means algorithm to segment WBCs successfully. The results from fuzzy c-means algorithm are low in the presence of noise and inhomogeneity of intensity. This was solved previously by the modified fuzzy c-means algorithm proposed by Chung *et al.* (2006). This method modified the membership function based on its spatial properties.

Mohapatra *et al.* (2012a) used a rough fuzzy c-means algorithm for WBC identification. This algorithm enhanced rough fuzzy c-means clustering based WBC extraction by boosting fuzzy membership values using cluster mean. This enhanced version outperformed K-Means, K-Medoid, conventional fuzzy c-means and rough c-means algorithms. Moradi Amin *et al.* (2016) also used fuzzy c-means to extract the nucleus from WBC.

Acharya *et al.* (2019), on the other hand, used K-medoid based algorithm to segment microscopic images. The medoid algorithm has heavy computations and is slower than K-Means, but its segmentation results are more accurate. Jha and Dutta *et al.* (2019) proposed a hybrid model that combined active contour and fuzzy c-means to enhance the task of segmentation to identify WBC from microscopic images.

Circular Hough Transformation was used by Fadhel *et al.* (2017) as a solution to handle the extraction of overlapped cells. The experimental results reported that the method proposed produced more accurate results, in a small time period, when compared to watershed algorithm.

Anita and Yadav *et al.* (2021), on the other hand, used an automated ellipse-fitting-based algorithm for detecting and extracting WBCs in microscopic images. In the following year, Das *et al.* (2022c) used a hybrid ellipse-fitting algorithm that produced highly accurate results with ALL, AML and sickle cell disease images.

Agrawal *et al.* (2010) utilized the GUI function of Matlab to select the best output using subjective assessment. This method helped to identify the best value for segmenting images. This method, designed to be interactive with the user, also had the advantage of allowing the user to select a specific region as region of interest and produced high segmentation accuracy.

Angkoso *et al.* (2018) implemented a segmentation algorithm that used the dynamic outline model based on color information. The algorithm used color features from various color space models like RGB, HSV, YCbCr, CieLab and grayscale. In order to reduce computation complexity, a method to select optimal color space channel was also proposed.

Zhong *et al.* (2019) proposed a constraint-based algorithm based on sparsity and geometry of blood cells and nuclei. The work combined the HSV and RGB color space channels and used the sparsity constraint to obtain a sparse image representation that contained useful information about nuclei. This was then used to extract the WBCs.

Another method used to improve WBC extraction is the design of hybrid systems. Example includes the hybrid system that combined the watershed-based segmentation algorithm has been combined with Otsu thresholding by several researchers (Bhavnani *et al.,* 2016; Quinones *et al.,* 2018; Safuan *et al.,* 2018; Salem *et al.,* 2016). These hybrid systems were able to an accuracy in the range of 93-99%. Ghane *et al.* (2017) proposed a hybrid system that combined thresholding, K-Means clustering algorithm with watershed algorithm. This algorithm started by segmenting WBCs and then extracting the nuclei from the segmented results. A step was also included to separate overlapping cells and nuclei.

Kumar *et al.* (2020) compared a set of segmentation algorithms that can extract WBC from microscopic images. The different methods compared were, threshold method, edge based method, clustering based method, ANN based method, region based method and watershed based method. The performance comparison was done in two manners. The experiments conducted showed that Canny and log edge methods, K-Means clustering based method, Otsu thresholding and ANN based method produced best results.

AL-Dulaimi *et al.* (2021) presented a detailed review of the various segmentation algorithms used to separate WBCs from microscopic images. The various algorithms discussed include edge boundary detection and image processing techniques (morphological operators and scale-space analysis, multiscale analysis, canny edge detection and snake model), color-space algorithm (RGB, CMYK and HSV with Otsu thresholding, color space-based K-Means clustering, color space-based morphological operation), thresholding algorithm (single threshold, dual threshold, Otsu's thresholding and marked watershed algorithm, hybrid thresholding), clustering-based algorithms (fuzzy c means, K-Means clustering, Watershed algorithm, gram-Schmidt orthogonal process) and signal processing algorithms (multispectral imaging algorithms, kevel set-based force and active contours, watershed marker-based distance) deep learning-based algorithms (self-supervised learning algorithms, convolutional neural networks).

Das *et al.* (2022b) proposed a 2-stage clustering algorithm to group blood cells in microscopic images. The proposed algorithm used eagle strategy based on stochastic fractal search for fuzzy clustering methodology in the first stage. In the second stage, morphological reconstruction was employed to filter the membership matrix, to obtain noise-immunity. The proposed system also included a non-parametric strategy for statistical validation, which was used to remove random effects in the achieved numerical results.

Thus, the signal and image processing-based category of algorithms are the most frequently used segmentation algorithms. From the literature survey, it is clear that this include threshold-based algorithms, morphological operation-based algorithms, watershed-based algorithms, active contour or level set-based algorithms and classification/clustering based segmentation algorithms.

2.3. MACHINE LEARNING CLASSIFIERS

ML and DL algorithms are widely used during ALL-C. This section presents some works that used conventional machine learning classifier to classify leukaemia. Supervised machine learning algorithms require labelled data to train the algorithm in order to achieve efficient classification results. Popularly used algorithms for ALL-C include K-Nearest Neighbour (KNN), Multi Layer Perceptron (MLP), Decision Tree (DT), Random Forest (RF), Support Vector Machine (SVM), Artificial Neural Network (ANN).

Prakisya *et al.* (2021) used KNN to classify WBC in AML M4, M5 and M7. Three distance measures (Euclidean, Chebychev and Minkowski) with weighted and unweighted KNN were analyzed. Five features, namely, area, nucleus ratio, circularity, perimeter, mean and standard deviation were extracted and used to train and test the KNN classifier.

Umamaheswari and Geetha *et al.* (2018b) proposed an ALL-C system, which started with a preprocessing step that, changed the input image size, adjusted brightness and contrast. In the second step, the nucleus region was segmented using morphological operators and Otsu's thresholding. Finally, the segmented regions were classified using a trained customized KNN classifier.

Gumble and Rode *et al.* (2017) proposed an ALL-C system that used morphological analysis to separate WBCs. It then evaluates the morphological index from the identified cells and classifies the absence or presence of leukemia using KNN classifier.

The shape and histogram features of microscopic images was used to train KNN to detect ALL by Purwanti and Calista *et al.* (2017). The KNN classifier was used as a binary classifier and classified the lymphocyte cells as normal or abnormal. This work used a combination of shape and histogram features and KNN classifiers was used with variations 1 to 15 in steps of 2.

Houssaini *et al.* (2022) compared different ML classifiers for detecting leukemia. The work compared five classifiers, namely, support vector machine, random forest, logistic regression, KNN and Naive Bayes.

Supardi *et al.* (2012) also used KNN classifier to classify the blasts in ALL samples. The classifier was trained using 12 main features (size, color and shape) and K values and distance metric used by KNN were tested using suitable parameters. The experimental results showed that KNN classifier with K = 4 and cosine distance metric produced maximum benefit.

Rawat *et al.* (2017b) classified ALL using hybrid hierarchical classifiers. The ALL-C system proposed segmented the microscopic image into different regions and then analyzed these regions to detect immature lymphoblast cells. Multiple features belonging to geometrical, chromatic and statistical texture features, were extracted. Feature dimensionality reduction algorithm based on Principal Component Analysis (PCA) was used to map the high feature space to a lower feature space. The classification was performed using various classifiers like SVM, smooth SVM, KNN, probabilistic neural network and adaptive neuro fuzzy inference system.

The MLP classifier was also used by several researchers in their quest to search for an efficient classifier to perform ALL identification. Examples include the proposals of Nazlibilek *et al.*, (2014), Neoh *et al.* (2015), Nasir *et al.*, (2013) and Halim *et al.*, (2019).

Salihah *et al.* (2013) proposed a classification system to detect ALL. This system used MLP and simplified fuzzy ARTMAP NN for this purpose. First, the WBCs were classified as lymphoblast, myoblast and normal. Two different training algorithms were used to train the MLP classifier. They are, Levenberg-Marquardt and Bayesian Regulation algorithms. Features like size, shape and color were extracted and used as input to train the classifier. The classifier that used MLP trained by Bayesian regulation algorithm produced maximum accuracy.

Another ML classifier used by researchers is the decision tree classifier. The decision tree classifier the complex classification decision is divided into the fusion of several simpler decisions (Safavian and Landgrebe *et al.* (1991). The most frequently used decision tree classifier is the C4.5 (Amin and Sibaroni *et al.* (2015) and its enhanced version EC4.5 classifiers (Lim *et al.*, 2000). ALL classification using decision tree classification was used by Negm *et al.* (2018), Mandal *et al.* (2019) and Ke *et al.* (2017).

RF classifier is one of the most powerful classifier that can achieve high classification accuracy (Pal *et al.*, 2005). This classifier is a tree structure based classifier, where each tree depends on the random vector value and the distribution of trees in the forest. The results are obtained by combining the results of all the decision trees used by the random forest classifier. ALL-C using random forest classifier was probed by Mishra *et al.* (2017, 2019), Breiman *et al.* (2001) and Freund and Schapire *et al.* (1996).

ANN is also used to perform ALL-C. ANN works on the principle of neuraon of the human brain. Examples of ANN include back propagation neural network, MLP (supervised) and self-organizing map (unsupervised). Negm *et al.* (2018), Acharya *et al.* (2019), Patra *et al.* (1994, 1999) and Al-jaboriy *et al.* (2017) have employed ANN to achieve efficient ALL classification.

SVM is yet another classifier that has been widely used by several researchers to perform ALL-C. The wide usage is due to its many advantages like generalization ability, discriminative power and optimal solution (Cervantes *et al.*, 2020).

The automated ALL-C system proposed by Patel and Mishra (2015) used K-Means clustering based segentation algorithm to detect WBC. Then histogram equalization and Zack algorithm were used to group WBCs. Mean, standard deviation, color, area, perimeter were extracted as features. Finally, the SVM classifier was used to classify the detected WBCs.

The system proposed by Das *et al.* (2020) started with the extraction of lymphocytes using a color-based K-Means clustering-based segmentation algorithm. Three sets of features, shape, texture and color, were then extracted from the segmented image. Next, the gray-level co-occurrence matrix and gray-level run-length matrix algorithms were used to extract features of the nucleus. Dimensionality reduction was then performed using Principal Component Analysis. In the last step, SVM classifier with radial basis function, was used to classify the detected WBC as normal or malignant.

Alagu *et al.* (2021) proposed a system to classify WBC in microscopic images. The system started with resizing all the images to the same uniform size. The next step used UNET-based segmentation algorithm to detect the nucleus, which had both healthy and blast cells. Deep features were extracted using a fully connected layer of different CNN models like AlexNet, GoogleNet and SqueezeNet, which were then fused to form a single super vector. Optimal features from this set were selected using MRMR and recursive feature elimination method. Statistical analysis was performed to obtain a robust and consistent set of features. Finally, SVM classifier is used to perform classification to identify normal and malignant cells.

Mishra *et al.* (2018) also used SVM to classify WBCs. The gray level run length matrix features were extracted from the cleaned microscopic images. The cleaning of images consisted of tasks like separation of grouped nucleus from the identified leucocytes and cleaning consists of a task that removed all components discovered at the edge of the smear. The effectiveness of the SVM classifier was analysing by comparing its performance with other standard classifiers like naïve bayes, K-NN and BPNN.

Mandal *et al.* (2019) also proposed an ALL-C system that used classifiers like SVM and gradient boosting decision tree classifiers. The classifiers were trained using presence of adjacent nuclei and measure of irregularity in the shape of a nucleus features.

Mohapatra *et al.* (2010), as mentioned earlier, using fuzzy-cmeans clustering algorithm to segment WBCs from microscopic images. Features like nucleus shape, texture, Hausdorff dimension and contour signature were extracted. These features were then used to train and test SVM to perform ALL-C.

MoradiAmin *et al.* (2016) have employed an ensemble of SVM classifiers with various kernels and parameters to classify three ALL subtypes: L1, L2, L3, and healthy WBC successfully.

James and Nair *et al.* (2014) presented a luekemia detection system from microscopic images of blood. The proposed system had a preprocessing step that converted RGB to CIEL color space and a used a wiener filter to remove noises. The using K-Means clustering the blood cell nucleus was extracted. Then features from the detected cell were used to train SVM classifier to group test images into cancerous or non-cancerous image.

Karar *et al.* (2022) proposed an intelligent medical IoT-enabled automated microscopic image diagnostic tool to detect acute blood cancers. The system had three stages. The first stage acquired blood samples using digital microscopy and then stored in a cloud server. In the second stage, the cloud server performed ALL to detect normal and malignant images using generative adversarial network classifier. Finally, the results were analysed by a haematologist.

2.4. DEEP LEARNING CLASSIFIERS

Rehman *et al.* (2018) proposed an ALL-C system based on DL classifier. A robust segmentation and deep learning techniques based on convolutional neural network were used to train the model on the bone marrow microscopic images to achieve accurate classification results.

Shafique and Tehsin *et al.* (2018a) used a pre-trained deep CNN for ALL detection and classification of its subtypes. In this work, instead of training the CNN from scratch, a pre-trained Alexnet was fine-tuned to the dataset used. The lat layers of this network was replaced by layers which can classify the input microscopic image into normal, L1, L2 and L3 classes. The overtraining issue of CNN was solved using image augmentation. The work also analyzed different color space models over different color images.

In the same year, the same authors ,Shafique and Tehsin *et al.* (2018b) also reviewed computer aided diagnosis systems regarding the methods used by them to perform various tasks in ALL-C. The tasks considered were enhancement, segmentation, feature extraction and classification.

Mallick *et al.* (2020) proposed a convergent deep learning model for leukemia classification. This method understood the convergence of training deep neural network. The DNN was designed to have five layers so as to classify ALL and AML samples.

Tran *et al.* (2018) used CNN to classify Leukemia disease in peripheral blood cell images. The proposed CNN was termed as LeukemiaNet and classified blood cells as ALL, AML and Normal. The dataset was extended using PCA color augmentation method.

Jiang *et al.* (2021) used Vit-CNN ensemble classifier, which combined the vision transformer model with CNN, to detect and classify ALL. The proposed classifier had the ability to extract features of cells images in two completely different manners to improve classification process. To handle the issue of data imbalance, differentiate enhancement-random sampling method was used. The proposed model also used a symmetric cross-entropy loss function to reduce the impact of noise in the data set.

Sampathila *et al.* (2022) proposed a customized deep learning classifier to detect ALL using blood smear microscopic images. This work trained a customized ALLNET model and tested in with the microscopic images available as open source data. The training was performed using Google Collaboratory.

Ahmed *et al.* (2019) also researched to find suitable method to classify leukemia subtypes using CNN. This work used two image databases, ASH-Image Bank and ALL-IDB. The results were compared with several ML algorithms like SVM, DT and KNN classifiers.

Ghaderzadeh *et al.* (2022) also used CNN to diagnose ALL and its further subtypes using microscopic images. This work compared 10 frequently used CNN architectures. They are, EfficientNet, MobileNetV3, VGG-19, Xception, InceptionV3, ResNet50V2, VGG-16, NASNetLarge, InceptionResNetV2, and DenseNet201. The CNN classifiers were tested using the dataset provided by Kaggle competition.

Qiao *et al.* (2021) proposed a compact CNN classifier that can be used to screen ALL in the preliminary stage. This classifier was tested using two datasets, namely, APL-Cytomorphology-JHH and APL-Cytomorphology-LMU. The proposed classifier was used to differentiate promyelocytes from normal leukocytes.

Jha and Dutta *et al.* (2019) designed as hybrid deep model based on mutual information to diagnose ALL. The deep learning model used was CNN classifier. The proposed scheme had four major steps, namely, preprocessing, segmentation, feature extraction and classification. Segmentation was performed using a hybrid model that combined active contour algorithm with fuzzy c means algorithm. Statistical and local directional pattern features were extracted from the segmented results and were used by the proposed Chronological Sine Cosine Algorithm-based Deep CNN to classify ALL.

Vogado *et al.* (2018) used three image databases to train hybrid model the combined ML and DL classifiers. The ML classifier used was SVM, while the DL classifier used was CNN. This hybrid model was able to achieve high accuracy, precision and recall.

He *et al.* (2020) used DNA sequence images along with DL and ML classifiers to detect ALL. The DL models used were CNN and long short term memory models and the ML classifiers compared were ANN, SVM and RF. The classifiers were used to identify four types of leukemia, namely, acute, chronic, myeloid and lymphatic.

The VCGNet was used by Sahol *et al.* (2020) to classify ALL and its subtypes. The proposed method was developed as a hybrid approach, which extracted features using VCGNet, a sophisticated CNN architecture, pretrained on ImageNEt. The features from microscopic images were extracted using statistically enhanced Salp Swarm Algorithm. This algorithm also selected only highly relevant features and removed highly correlated and noisy features.

Banik *et al.* (2020) evaluated CNN classifier for ALL classifier using four databases, namely, BCCD, ALL-IDB2, JTSC and CellaVision. This work started with color space conversion, followed by using K-Means algorithm based on nucleus properties to segment WBCs. A CNN-based model, which combined feature fusion, last convolutional layers and propagated the input microscopic image to the convolutional layer was proposed. The proposed CNN model also used a dropout layer to handle the issue of overfitting.

Naz *et al.* (2019) proposed a deep-learning based model to classify ALL. The proposed work had three main stages, namely, image augmentation, wavelet composition and decomposition for attaining high and low frequency bands of the cell image, CNN training model for the classification of leukocytes categories and prediction of leukemia. THe work was tested using two database, namely, LISC and Dhruv dataset.

Rehman *et al.* (2018) proposed a robust segmentation and DL algorithm based on CNN to perform ALL-C. The proposed system was compared with three CL classifiers, namely, Naïve Bayesian, KNN, and SVM. The experiments were conducted using a dataset provided by Amreek Clinical Laboratory.

Billah and Javed *et al.* (2022) proposed a Bayesian CNN-based diagnostic system for detecting Leukemia from microscopic images. This work experimented with different network structures and obtained a model that has high classification accuracy. The system while classifying cells into cancerous and non-cancerous also provided details regarding the uncertainty in predictions.

Suresh *et al.* (2021) proposed a ViT-CNN based ensemble classifier to group microscopic images into normal and cancerous. The proposed classifier combined vision transformer and CNN. The features were extracted in two manners. A difference enhancement random sampling method was used to enhance the data and to obtain a balanced dataset. The symmetric cross entropy loss function was used to reduce the impact of noise.

Abunadi *et al.* (2022) analyzed both ML and DL classifiers to detect ALL. The ML classifiers studied were ANN, feed forward NN and SVM, all of which used hybrid features combining Local Binary Pattern, grey level co-occurrence matrix and fuzzy color histogram. The DL classifiers examined were CNN based, namely, AlexNet, GoogleNet and ResNet-18, all of which were based on transfer learning method that used deep feature maps extracted from microscopic images. The study also proposed a hybrid classifier that combined AlexNet with SVM, GoogleNet with SVM and ResNet-18 with SVM.

2.5. CHAPTER SUMMARY

The investigation of the previous works related to the research topic exposed the fact that there is still room available to improve the performance of ALL-C systems. ALL detection and classification is a highly sensitive and complex issue that is related to human life and health, where correct detection is very important and should be impeccable, so that these automated systems can replace the human operators. Moreover, from the review it is also clear that the systems proposed to classify ALL into its subtypes, L1, L2 and L3 is less when compared to the binary classification of grouping images into normal and malignant. High interclass variability along with interclass similarity, makes the subtype classification a difficult task. However, as the subtype diagnosis is very essential to plan correct course of treatment, it is an aspect that is most desired by doctors. Thus, this research work proposed ALL-C systems that can improve the process of detecting ALL along with its subtype, while improving its detection accuracy. The methodological research design used to achieve this is presented in the following chapter (Chapter 3, Methodology) along with a brief introduction to the various enhancement algorithms proposed in each step of the proposed ALL-C system.