Learning by Sampling for White Blood Cells Segmentation

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Abstract. The visual analysis and the counting of white blood cells in microscopic peripheral blood smears is a very important procedure in the medical field. It can provide useful information concerning the health of the patients, e.g., the diagnosis of Acute Lymphatic Leukaemia or other important diseases. Blood experts in clinical centres traditionally use these methods in order to perform a manual analysis. The main issues of the traditional human analysis are certainly related to the difficulties encountered during this type of procedure: generally, the process is not rapid and it is strongly influenced by the operator's capabilities and tiredness. The main purpose of this work is to realize a reliable automated system based on a multi-class Support Vector Machine in order to manage all the regions of immediate interests inside a blood smear: white blood cells nucleus and cytoplasm, erythrocytes and background. The experimental results demonstrate that the proposed method is very accurate and robust being able to reach an accuracy in segmentation of 99%, indicating the possibility to tune this approach to each couple of microscope and camera.

Keywords: Automatic detection · Biomedical image processing · Segmentation · Machine learning · White blood cell analysis

1 Introduction

The main purpose of this work is to develop an automatic system able to extract appropriate information from blood cell images taken by microscopes in order to easily perform a useful activity on them, e.g., white blood cells count. Ideally, there are several useful operations for what this method can be used for: essentially, identify, analyse, classify or count the white blood cells held in one or more microscopic images. Nevertheless we can say that the most important and key step of the entire automatic process is, certainly, the image segmentation, which differentiates meaningful objects from the background. It is a crucial step because its accuracy greatly affects both the computational speed and the overall accuracy of the whole system. However, it is also a very difficult problem to manage because of the complex nature of the cells, low resolution of microscopic images and the presence of complex scenes, e.g. cells can overlap each other or

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cells can have different sizes or shapes. On the other hand, the colour and the contrast between the cells and the background can vary very often according to the frequent, inconsistent staining technique, thickness of smear and illumination. Although a standardization is useful to avoid superfluous differences in the features of similar images, a robust segmentation approach can cope with the described issues. One natural way for colour image segmentation is to perform pixels clustering or classification in colour space. Unsupervised and supervised schemes [1], such as k-means, neural network et al., have been widely used for this purpose even if there are many disadvantages to deal with. Generally, the biggest problem of an unsupervised clustering scheme is how to determine the number of clusters, which is known as cluster validity. And as for a colour image, the selection of colour space is quite critical. The supervised scheme needs training. The training set and initialization may affect the results, and overtraining should be avoided. So a supervised clustering/classification algorithm with good generalization property is most appealing. Our method aims to solve the segmentation problem in a non-linear feature space obtained by kernel methods in order to overcome the non-linearity of data distribution and the shift/offset of colour representing the different regions of interest inside a blood sample: mature erythrocytes, nuclei and cytoplasm of white blood cells. We want to develop an automatic machine learning to perform image segmentation of blood and bone marrow cells images. SVM (Support Vector Machines) and ANN (Artificial Neural Network) are machine learning models with excellent performances in classification, but their main drawbacks are that a training phase is absolutely necessary to make them work and the training phase could be computationally hard with large datasets.Our solution has been developed following the suggestions of [2–4]. We have used the ALL-IDB dataset [5], a public and free dataset that contains microscopic images of blood samples, specifically designed for the evaluation and the comparison of algorithms for segmentation and image classification. Our idea is to use a part of this dataset as a training set for our learning by sampling algorithm. The first step of the algorithm is to apply a classic segmentation method to obtain pure samples related to the regions of white blood cells nucleus and cytoplasm, mature erythrocytes and background. As a comparison, we have also realized a method based on three Mean Shift procedures in order to search the clustering modes corresponding to the colour of the above defined three regions. Then we prepared the training samples by adapting sampling from the regions obtained from the classic segmentation phase so as to perform the training process of a multi-class SVM in order to correctly classify all the pixels of a given image. Finally, the SVM is used to segment the image for extracting whole white cells, using a classification phase by means of a classification model. Since the size of training set could be controlled and reduced in sampling, SVM training is really fast. Section 2 introduces a brief summary about the classic segmentation methods, known in literature. Section 3 describes Mean Shift theory and its application to image segmentation. Section 4 presents SVM basis theory and how it can be used for our purposes. Section 5 shows the proposed solution and some experimental results and comparisons with other methods. Discussions, conclusions and future aspects are given in Section 6.

2 Background and Related Works

A typical blood image usually consists of three components: red blood cells or erythrocytes, white blood cells (WBCs) or leukocytes, and platelets. Leukocytes are easily identifiable, as their nucleus appears darker than the background. However, the analysis and the processing of data related to the WBCs are complicated due to wide variations in cell shape, dimensions and edges. The generic term leukocyte refers to a set of cells that are quite different from each other (Fig. 1). Leukocytes containing granules are called granulocytes, and they include neutrophils, basophils and eosinophils. Cells without granules are called mononuclear, and they include lymphocytes and monocytes. Furthermore, lymphocytes suffering from ALL, called lymphoblasts, have additional morphological changes that increment with increasing severity of the disease. In particular, lymphocytes are regularly shaped and have a compact nucleus with regular and continuous edges, whereas lymphoblasts are irregularly shaped and contain small cavities in the cytoplasm, termed vacuoles, and spherical particles within the nucleus, termed nucleoli. In Fig. 1 some examples of healthy and sick WBCs belonging to the ALL-IDB database [5] are showed. The ALL-IDB is a public image dataset of peripheral blood samples from normal individuals and leukaemia patients. These samples were collected by the experts at the M. Tettamanti Research Centre for childhood leukaemia and haematological diseases, Monza, Italy. The ALL-IDB database has two distinct version (ALL-IDB1 and ALL-IDB2). The ALL-IDB1 can be used both for testing segmentation capability of algorithms, as well as the classification systems and image pre processing methods. This dataset is composed of 108 images captured with an optical laboratory microscope coupled with an Olympus Optical C2500L camera or a Canon PowerShot G5 camera. All images are in JPG format with 24-bit colour depth. The first 33 have 1712×1368 resolution, the remaining have 2592×1944 resolution. The images are taken with different magnifications of the microscope ranging from 300 to 500 which brings the colour differences that we managed grouping the images with same brightness characteristics together. The ALL-IDB2 is a collection of cropped area of interest of normal and blast cells extracted from the ALL-IDB1 dataset. It contains 260 images and the 50% of them represent lymphoblasts. According to the literature, few examples of automated systems are able to analyse and classify WBCs from microscopic images, and the existing systems are only partially automated. In particular, a considerable amount of work has been performed to achieve leukocytes segmentation. For example, Madhloom [7] developed an automated system to localise and segment WBC nuclei based on image arithmetical operations and threshold operations. Sinha [8] and Kovalev [9] attempted to differentiate the five types of leukocytes in cell images. Sinha used k-means clustering on the HSV colour space for WBCs segmentation and different classification models for cell differentiation. Kovalev first identified the nuclei and then detected the entire membrane by region growing techniques. Few papers sought to achieve robust segmentation performance under uneven lighting conditions. However, a study by Scotti [10], used a low-pass filter to remove background, different threshold operations and image clustering to segment WBCs. Moreover, other authors proposed methods

for automated disease classification. In particular, Piuri [11] proposed an approach based on edge detection for WBC segmentation, and used morphological features to train a neural network to recognise lymphoblasts. Halim [12] proposed an automated blast counting method to detect acute leukaemia in blood microscopic images that identifies WBCs through a thresholding operation performed on the S component of the HSV colour space, followed by morphological erosion for image segmentation. Although the results of this study seem very encouraging, there is no method to determine the optimum threshold for segmentation, and no feature or classifiers were presented. Mohapatra [13] investigated the use of an ensemble classifier system for the early diagnosis of ALL in blood microscopic images. The identification and segmentation of WBCs is realised through image clustering followed by the extraction of different types of features, such as shape, contour, fractal, texture, colour and Fourier descriptors, from the subimage. Finally an ensemble of classifiers is trained to recognise ALL. The results of this method were good, but they were obtained by using a proprietary dataset, so the reproducibility of the experiment and comparisons with other methods are not possible.

3 On Mean Shift Technique

Mean Shift technique was originally proposed in 1975 by Fukunaga [2], then adapted by Chen [1] and generalized for image analysis purposes. More recently it have been extended to low-level vision problems [14], including segmentation, adaptive smoothing and visual tracking. Basically, it is used as a non-parametric technique for the estimation of the density gradient in image analysis field, even if it was developed in order to perform mode finding on clustering procedures. In contrast to the classic K-means clustering approach, there are neither a priori assumptions about the point distribution nor the number of modes and clusters:

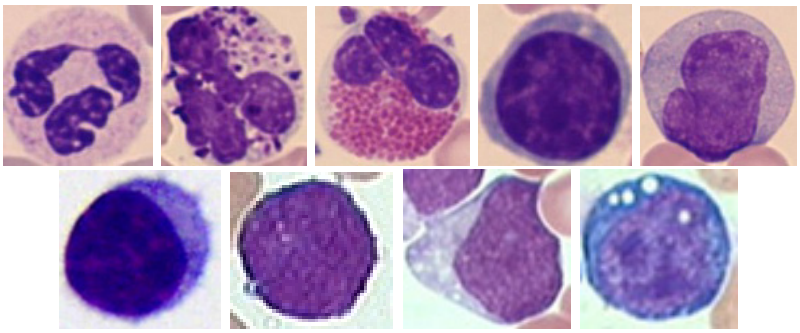

Fig. 1. (Top) A comparison between different types of WBCs: neutrophils, basophils, eosinophils, lymphocytes and monocytes. (Bottom) A comparison between lymphocytes suffering from ALL: a healthy lymphocyte, followed by lymphoblasts classified as L1, L2 and L3, respectively, according to the FAB [6].

they are computed by the Mean Shift procedure itself. Furthermore, Mean Shift has been adapted to become a very effective image segmentation technique, even if it was born as a clustering method of data analysis. It allows to attenuate shape or colour differences between the objects inside the considered images; for these reasons it works as a local homogenization technique. Considering its operating principles, the objective is to substitute every single pixel value with the mean of the sampled pixel values in a certain neighbourhood, within a certain radius R and a certain colour distance D; both of them are usually input defined by the user which generally has a deep knowledge about the context or uses some pre-processing technique to obtain the best values of R and D. Typically, Mean Shift requires at least three basically information to gain the best results; first of all, we have to define a certain kernel, which uses a distance function, to measure the pixel distance in every single iteration of the procedure: examples are the Gaussian kernel and the Epanechnikov kernel. Secondly, it needs two distance values: an R radius and a D colour distance. Then, iteratively, the procedure finds the modes of an input given image and calculates new values for every single pixel, according to the chosen kernel function and the distance parameters. It is worth mentioning that Mean Shift algorithm is not well defined at the boundaries, because it does not consider the non-existent neighbour pixels. Consequently, a strategy to handle them is necessary. For example, we have studied a padding of the image to process boundary pixels correctly.

4 SVM for Segmentation

Remembering that our starting objective was to segment blood cells images, now we explain how this classification method can be used to reach our segmentation purposes and targets. Support Vector Machine (SVM) has been chosen in order to perform a classification of every single pixel belonging to the images we have to segment, according to the method proposed in [1]. Once the Mean Shift has been performed on a certain training set, we use a set of these produced images to train the different SVM we realized. As a comparison, we also segment every single dataset image with classic segmentation methods. It is done to execute a more in-depth analysis of our study. The **first strategy** works as a normal binary SVM classifier, hence we have exactly two classes in which the pixels will be classified: the positive class groups together the white blood cell nuclei and cytoplasm pixels, instead the negative class represents pixels belonging to erythrocytes or background. Fig. 2 shows the segmentation result using this solution, in which the WBC is exactly recognized and segmented, but the lighter region of erythrocytes is misclassified as WBC region. The **second strategy** substantially works like the first one, with the main difference that we exclude from the training samples all the pixels belonging to the cytoplasm, in order to avoid misclassification due to similarities with the lighter region of erythrocytes. Fig. 2 shows the segmentation result using this solution. Again the nucleus is well detected but for determined classes of WBCs the cytoplasm is not well detected. The **third strategy** is based on the results obtained with the two previous versions. In fact the classifier needs more valid training samples for cytoplasm only.

So, in last version we perform a three-class SVM, using both the pixels belonging from WBCs nuclei (class 1) and both pixels belonging to the WBCs cytoplasm (class 2). Thus, pixels belonging to erythrocytes or background are labelled with class 3. Note that for this approach only classic segmentation have been used to produce pure samples for the SVM, because Mean Shift segmentation merge together both WBC nucleus and cytoplasm. A Mean Shift alteration could be done to adapt it for our purposes, but we have chosen to use classic method for simplicity. Fig. 2 shows the segmentation result using this solution in which both nucleus and cytoplasm are well detected.

5 System Implementation

For each strategy, the training set is formed by sampling pixels from the images belonging to the ALL-IDB2 presenting healthy WBCs chosen to make part of the available training images. On the other hand, the test set is formed of the first 33 images of ALL-IDB1, acquired in the same lighting conditions and with the same camera.

5.1 First Step

According to the prior knowledge defined about Mean Shift and classic segmentation methods, we have used two strategies to perform the first phase of our algorithm. Both of them are focused to offer the SVM a sufficient set of possible training samples. We have used either classic methods or Mean Shift to obtain this training set. The main objective is to train the SVM with the most accurate pixels related to white blood cell nuclei and cytoplasm. Once the pre processing strategy has been used, the next step is the classic or Mean Shift segmentation method. As said before, we have used both the approaches to experiment their

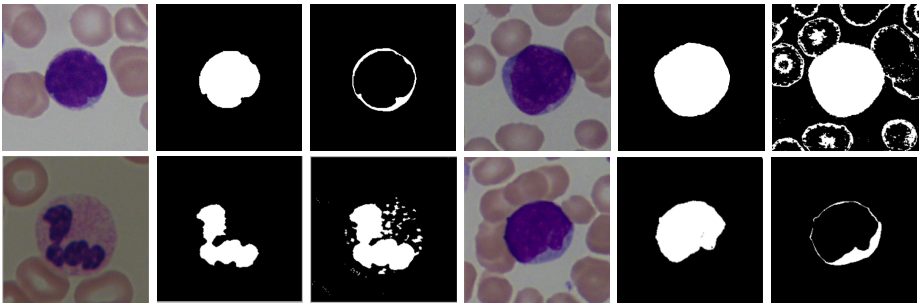

Fig. 2. (Top) From left to right: training original image from ALL-IDB2, manually segmented nucleus and cytoplasm; test original image, segmentation result for nucleus and cytoplasm with the first strategy. (Bottom) From left to right: test original image, segmentation result for nucleus and cytoplasm with the second strategy; test original image, segmentation result for nucleus and cytoplasm with the third strategy

behaviour in relation to the SVM training set building. With the classic segmentation methods, we have obtained two binary masks. The first one contains the white blood cells segmented in their entirety while the second one contains only the white blood cells nuclei. From these images, the segmented cytoplasm region could be easily obtained performing a difference operation between the first image and the second one and remembering that the cytoplasm region is always placed around the white blood cell nucleus. Thanks to this process we can easily perform the training of the SVM in the next phase, according to a defined strategy. Overall, we have obtained, in both cases, a certain set of images in which the regions have been pointed out. Mean Shift method, instead, produces only a set of images in which the regions of interest are marked with different colours, obtained by finding the dominant colour modes of the three main regions: erythrocytes, white blood cell and background. It is important to note that this phase is crucial to detect pure candidate pixels to perform the SVM training in the next phase, therefore we make a comparison between the results obtained in our method, realized without using Mean Shift, and the method inspired to the theory expressed in literature.

5.2 Second Step

Now our interest is to perform a properly training phase over the given pixels obtained in phase one. The chosen pixels must be the most various possible all over the regions obtained in phase one, in order to realize a proper classification model during SVM training phase. According to our implementation, we have chosen to use classic segmentation to perform phase one, and Mean Shift to realize a secondary implementation to show and compare the obtained results. Note that Mean Shift technique can be easily adapted to our purposes, but the final method should be adapted to be a three phases method, as long as Mean Shift does not directly offer pixels belonging to cytoplasm. They could only be obtained performing a two-phase SVM training. Now, we show a strategy to train the SVM in order to produce a classification model. Once we have obtained pixels belonging to cytoplasm, white blood cell nucleus and red blood cells regions, the remaining step to perform is to accurately choose these pixels with a uniform sampling, in order to consider every single image available in the group of images given for the training set. Thus, four different regions form candidates of training set for SVM. We mark nucleus pixels of white blood cells with class label I_1, cytoplasm pixels with class label I_2, instead mature erythrocyte and non-cell region pixels are marked with I_3. To avoid uncertainty, the following property has been set:$I_1 \cap I_2 \cap I_3 = \emptyset$ (empty set). SVM implements a classification strategy that exploits a margin-based ?geometrical? criterion rather than a purely ?statistical? criterion. It does not estimate the statistical distributions of classes for classification, while defines the classification model by exploiting the concept of margin maximization. There are two types of margin in SVM. Hard margin classifier works well in no-noise cases, but fails with noisy data due to overfitting. Soft margin classifier may achieve much better generalization results by relaxing the hard margin and ignoring the noisy data. So, removing

noisy samples from the training set may benefit to training; for this reason we have produced pure samples of the three classes. Statistics theory has revealed that, through uniform, or Monte Carlo sampling, a subset could be produced to represent the entire data set approximately while retaining the distribution of data effectively [17]. The essential steps of this phase can be summarized as follows:

- sample N pixels from I_1, I_2, I_3 regions. There are N/4 pixels sampled respectively from four regions (cytoplasm, nucleus, mature erythrocytes and background region) to keep the size of the training set balanced;
- train a SVM online, taking the reduced training set defined at point one and a RBF kernel and generate a classifier model;
- use this model to classify the image pixels which are represented by $(R, G, B)^T$.

We have performed two main experiments. The first one has been realised to verify our implementation performances over single WBCs and in order to identify the most suitable parameters for the SVM. Thus, through a 10 fold cross-validation each time we have divided the original training set in two subsets, the first one to train the SVM and the second one to test the obtained model. An ideal average accuracy value has been reached by choosing the parameters c and γ as $1e3$ and $1e1$ respectively. The second and final experiment have been realised to verify the segmentation performances of the proposed method. Thus the whole original training set has been used to create the SVM model. The first 33 native resolution images has been used as test set and to check the method applied to a natural image composed of several white blood cells of many different classes.

5.3 Third Step

Once the first (visual) results have been obtained we have started experimenting with various features that can be used to train the classifier. In fact, even though we are talking of a segmentation technique, pixels are used as features for the SVM classifier. Until now the only descriptors used are the colour values. Although in many cases these features are enough to reach a good segmentation result, in other cases a poor feature set like this is not able to discriminate pixels belonging to regions with wide variations in colours. Thus the first intuition has been to add the average colour values of each pixel neighbourhood. These average values have been tested for neighbourhood of size 3×3, 5×5 and 7×7. For the same neighbourhood we have also computed other statistical features that are often used for segmentation purposes: standard deviation, uniformity and entropy. While the segmentation accuracy highly benefits from the use of these new features, the overall system became to slow, both in training and segmentation phase. Furthermore, the step of samples selection, used to train the classifier, became too complex, due to a higher number of samples with different values. For all these reasons the features previously mentioned have been extracted only for neighbourhood of size 3×3, showing excellent performances

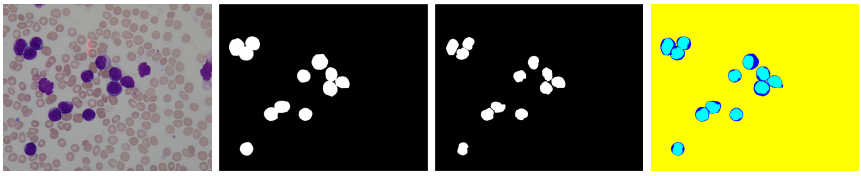

Fig. 3. Original images from the ALL-IDB1 database, ground-truth for whole leukocyte, ground-truth for leukocyte nuclei and final segmentation result.

Table 1. Segmentation performances.

	Otsu	Zack	Our Approach
Accuracy	77.67 ± 0.6	74.76 ± 3.6	97.61 ± 1.7
Sensitivity	76.70 ± 8.3	85.43 ± 6.8	98.45 ± 0.3
Specificity	85.62 ± 4.6	81.27 ± 5.4	97.56 ± 1.2
Precision	53.55 ± 12.8	79.12 ± 8.6	70.45 ± 5.8
F-measure	45.18 ± 5.3	55.15 ± 3.3	82.13 ± 2.3

as showed in fig. 3, outperforming previous results. After the segmentation, all the images have been automatically cleaned, as we have already proposed in [18], in order to remove small artefacts from the background and to give to the reader an idea about the goodness of the results. In order to evaluate the segmentation performances of the proposed method, a subset of images (10 random samples) belonging to the ALL-IDB1 have been manually segmented by skilled operators, creating two ground-truth images for each sample. These images display respectively each blood cell present in the image and the white blood cell nuclei. Fig. 3 shows some images belonging to the ALL-IDB1 and their relative ground-truth images. Finally, the ground-truth images previously described have been compared with the automated segmented images in order to calculate the most common metrics for segmentation evaluation, that are: accuracy, sensitivity, specificity, precision and F-measure. Our segmentation approach has been compared with some well know segmentation algorithms like Otsu [19] and Zack [20]. Table 1 shows the average performances obtained with the ten tested samples. As it can be seen the most important values obtained with our approach are higher than the other segmentation approaches.

6 Conclusions

This work proposed and investigated a new automated white blood cell recognition method that can be applied to support some existing medical methods, like the WBCC, White Blood Cells Counting. It is realized using lots of notions already known in literature but combining them to build an essentially brand new method in which the major innovation is brought by the use of multi class SVM. Whereas the aim of a fully automated cell analysis and diagnosis of white blood cell has not yet reached, many important steps in the image segmentation

using Learning by Sampling method have been realized. We proposed a segmentation approach using several variations in the schemes. One of these variation consists in using classic segmentation methods or the Mean Shift. The experimental results demonstrate that the new approach is very accurate and robust in relation to some traditional methods such as the already mentioned Mean Shift combined with two-phase SVM training method. The performances achieved with the ALL-IDB often reaches the 99% of accuracy, but in particular we want to highlight the possibility to tune this approach to each couple of microscope and camera using only few image samples. Despite the good results, we do not consider the development of our project totally concluded. Our purposes and hopes are certainly to continue the work in order to experiment several new investigations that could potentially bring to better results. Among the future works we can indicate the extension to different colour spaces in which segmentation process could be achieved easily and more effectively. A further step will include analysis and recognition of the different types of healthy and blasted white blood cells. Finally, our idea is to export the whole procedure to bone marrow images, in which the first segmentation phase is more difficult than in the peripheral blood images, since the brightness conditions could be very different and large clusters of cells can exist.

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References

1. Pan, C., Lu, H., Cao, F.: Segmentation of blood and bone marrow cell images via learning by sampling. In: Huang, D.-S., Jo, K.-H., Lee, H.-H., Kang, H.-J., Bevilacqua, V. (eds.) ICIC 2009. LNCS, vol. 5754, pp. 336–345. Springer, Heidelberg (2009)
2. Fukunaga, K., Hostetler, L.: The estimation of the gradient of a density function, with applications in pattern recognition. IEEE Transactions on Information Theory **21**(1), 32–40 (1975)
3. Shapiro, L.G., Stockman, G.C.: Computer Vision, chap. 12, pp. 279–325. Prentice Hall, New Jersey (2001)
4. Gonzalez, R.C., Woods, R.E.: Digital Image Processing, 3rd edn. Prentice Hall Pearson Education Inc., New Jersey (2008)
5. Donida Labati, R., Piuri, V., Scotti, F.: ALL-IDB: the acute lymphoblastic leukemia image database for image processing. In: Macq, B., Schelkens, P. (eds.) Proceedings of the 18th IEEE ICIP International Conference on Image Processing, pp. 2045–2048. IEEE Publisher, Brussels (2011)
6. Bennett, J.M., Catovsky, D., Daniel, M.T., Flandrin, G., Galton, D.A., Gralnick, H.R., Sultan, C.: Proposals for the classification of the acute leukemias. French-American-British (FAB) co-operative group. British Journal of Hematology **33**(4), 451–458 (1976)

7. Madhloom, H.T., Kareem, S.A., Ariffin, H., Zaidan, A.A., Alanazi, H.O., Zaidan, B.B.: An Automated White Blood Cell Nucleus Localization and Segmentation using Image Arithmetic and Automated Threshold. Journal of Applied Sciences **10**(11), 959–966 (2010)
8. Sinha, N., Ramakrishnan, A.G.: Automation of differential blood count. In: Chockalingam, A. (ed.) Proceedings of the Conference on Convergent Technologies for the Asia-Pacific Region, vol. 2, pp. 547–551. IEEE Publisher, Taj Residency (2003)
9. Kovalev, V.A., Grigoriev, A.Y., Ahn, H.: Robust recognition of white blood cell images. In: Kavanaugh, M.E., Werner, B. (eds.) Proceedings of the 13th International Conference on Pattern Recognition, pp. 371–375. IEEE Publisher, Vienna (1996)
10. Scotti, F.: Robust segmentation and measurements techniques of white cells in blood microscope images. In: Daponte, P., Linnenbrink, T. (eds.) Proceedings of the IEEE Instrumentation and Measurement Technology Conference, pp. 43–48. IEEE Publisher, Sorrento (2006)
11. Piuri, V., Scotti, F.: Morphological classification of blood leucocytes by microscope images. In: Proceedings of the IEEE International Conference on Computational Intelligence for Measurement Systems and Applications, pp. 103–108. IEEE Publisher, Boston, July 14–16, 2004
12. Halim, N.H.A., Mashor, M.Y., Hassan, R.: Automatic Blasts Counting for Acute Leukemia Based on Blood Samples. International Journal of Research and Reviews in Computer Science **2**(4), August 2011
13. Mohapatra, S., Patra, D., Satpathy, S.: An Ensemble Classifier System for Early Diagnosis of Acute Lymphoblastic Leukemia in Blood Microscopic Images. Journal of Neural Computing and Applications (article in press, 2013)
14. David, J.F., Comaniciu, D., Meer, P.: Computer-assisted discrimination among malignant lymphomas and leukemia using immunophenotyping, intelligent image repositories, and telemicroscopy. IEEE Transaction on Information Technology in Biomedicine **4**(4), 12–22 (2000)
15. Lezoray, O., Elmoataz, A., Cardot, H., Gougeon, G., Lecluse, M., Elie, H., Revenu, H.M.: Segmentation of Color Images from Serous Cytology for Automated Cell Classification. Journal of Analytical and quantitative cytology and histology/the International Academy of Cytology [and] American Society of Cytology **22**(4), 311–322 (2000)
16. Vapnik, V.N., Vapnik, V.: Statistical learning theory, vol. 1. Wiley, New York (1998)
17. Caflisch, R.E.: Monte Carlo and quasi-Monte Carlo methods. In: Acta Numerica, vol. 7, pp. 149. Cambridge University Press (1998)
18. Putzu, L., Di Ruberto, C.: Investigation of different classification models to determine the presence of Leukemia in peripheral blood image. In: Petrosino, A. (ed.) ICIAP 2013, Part I. LNCS, vol. 8156, pp. 612–621. Springer, Heidelberg (2013)
19. Otsu, N.: A Threshold Selection Method from Gray-Level Histograms. IEEE Transactions on Systems, Man, and Cybernetics **9**(1), 62–66 (1979)
20. Zack, G., Rogers, W., Latt, S.: Automatic Measurement of Sister Chromatid Exchange Frequency. Journal of Histochemistry and Cytochemistry **25**, 741–753 (1977)