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Research Article

Detection and Classification of Leucocyte Types in Histological Blood Tissue Images Using Deep Learning Approach

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Abstract

The identification of leucocyte, also named white blood cells, types in histological blood tissue images is significant because it enables an opportunity for the diagnosis of various hematological diseases. In this study, for the diagnosis of lymphoma cancer, a hematologic disorder, we presented automatic detection and classification model using a deep learning approach. Faster R-CNN, which is a kind of region-based Convolutional Neural Network (CNN) model, achieves satisfactory performance on object detection and classification problems. To dispose of the feature extraction process in image-based applications, we offer a ResNet50 modified Faster R-CNN model for the detection and classification of leucocyte types which are lymphocyte, monocyte, basophil, eosinophil, and neutrophil in histological blood tissue images. In parallel with this purpose, a novel Faster R-CNN object detection model was designed by modifying ResNet50 model and the locations of leucocytes in the image were determined and classified. The efficiency of the proposed model was tested on a novel histological dataset including blood tissue images. The number of lymphocytes in the blood tissue is used as an evaluation criterion in the diagnosis of lymphoma cancer. Therefore, this study sets an example for clinical studies. According to the proposed model, firstly, the blood tissue images are normalized, and the implicit features are extracted by using the trainable convolution kernel. Then, for the reduction of the extracted implicit features, the maximum pooling is applied. After that, Region Proposal Networks (RPNs) are used to generate high-quality region proposals, which are used by Faster R-CNN for detection. Finally, the softmax classifier and regression layer are carried out to categorize the leucocyte types and estimate the boundary boxes of the test samples, respectively. Experimental results show the successful performance and the generalization capability of novel Faster R-CNN for the detection and classification of leucocyte types. This model demonstrates the potential to be deployed as a diagnostic tool for clinical studies because the method has been tested on a real-world histological data set.

Keywords: Artificial intelligence, Blood tissue, Classification, CNN, Detection, Faster R-CNN, Leucocyte types, Lymphoma cancer.

Derin Öğrenme Yaklaşımı ile Histolojik Kan Doku Görüntülerinde Lökosit Türlerinin Tespiti ve Sınıflandırılması

Öz

Histolojik kan dokusu görüntülerinde beyaz kan hücreleri olarak da bilinen lökosit türlerinin belirlenmesi, çeşitli hematolojik hastalıkların teşhisine olanak sağlaması açısından önemlidir. Bu çalışmada, hematolojik bir bozukluk olan lenfoma kanserinin teşhisi için derin öğrenme yaklaşımı kullanarak otomatik tespit ve sınıflandırma modeli sunulmuştur. Bir tür bölge tabanlı Konvolüsyonel Sinir Ağı (KSA) modeli olan Faster R-CNN nesne tespiti ve sınıflandırma problemlerinde tatmin edici performans elde etmektedir. Görüntü tabanlı uygulamalarda özellik çıkarma sürecini ortadan kaldırmak için, lenfosit, monosit, bazofil, eozinofil ve nötrofil olan lökosit

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türlerinin tespiti ve sınıflandırılması için ResNet50 ile modifiye edilmiş Faster R-CNN modeli önerilmiştir. Bu amaçla, ResNet50 modeli modifiye edilerek yeni bir Faster R-CNN nesne tespit modeli tasarlanmış ve görüntüdeki lökositlerin yerleri belirlenerek sınıflandırılmıştır. Önerilen modelin etkinliği, kan dokusu görüntülerini içeren yeni bir histolojik veri seti üzerinde test edilmiştir. Kan dokusundaki lenfosit sayısı, lenfoma kanseri tanısında değerlendirme kriteri olarak kullanılmaktadır. Bu nedenle bu çalışma klinik çalışmalara örnek teşkil etmektedir. Önerilen modele göre, öncelikle kan dokusu görüntüleri normalize edilir ve eğitilebilir konvolüsyon çekirdeği kullanılarak örtük özellikler çıkarılır. Ardından, örtük unsurların boyutlarının azaltılması için maksimum havuzlama uygulanır. Bundan sonra, Bölge Teklif Ağları (BTA'ler), tespit için Faster R-CNN tarafından kullanılan, yüksek kaliteli bölge önerileri oluşturmak için kullanılır. Son olarak, softmax sınıflandırıcı ve regresyon katmanı, sırasıyla lökosit türlerini kategorize etmek ve test örneklerinin sınır kutularını tahmin etmek için kullanılır. Deneysel sonuçlar lökosit türlerinin tespiti ve sınıflandırılması için yeni Faster R-CNN'nin başarılı performansını ve genelleştirme yeteneğini göstermektedir. Bu model klinik çalışmalar için bir teşhis aracı olarak kullanılma potansiyelini göstermektedir çünkü yöntem gerçek dünya histolojik veri setinde test edilmiştir.

Anahtar Kelimeler: Yapay zekâ, Kan doku, Sınıflandırma, CNN, Tespit, Faster R-CNN, Lökosit türleri, Lenfoma kanseri.

1. Introduction

The processing and analysis of biomedical images and the development of automated detection systems that can interpret the markings on these images have taken attention of the medical professionals. The biggest challenge among them is how to make sure about efficiency and how to handle satisfactory detection systems. In the medical image analysis field, it is not possible to process and analyze a huge amount of data manually, because the large volume of data results in time-consuming and job performance losses for experts. Deep Learning (DL) has an effective performance on classification and recognition systems due to its intense feature extraction ability. Deep CNNs, one of the DL methods, have commanded many tasks in computer vision applications. For object detection, region-based CNN (R-CNN) detection methods are such a rapidly developing area that three generations of region-based CNN detection models, from R-CNN to Faster R-CNN. These models provide more accurate results and faster processing speed in classification and detection problems. The main purpose of this study is to develop a blood smear image-based system to help diagnose hematologic diseases. For this, a system has been developed that can determine the location and number of white blood cells on the histological blood tissue images.

When the literatüre is reviewed, there are some histological blood tissue image analysis studies. Subsequent to this paragraph, some studies and their details are explained. Nazlibilek et. al (Nazlibilek et al., 2014) developed a system that counts the white blood cells automatically, determines their sizes exactly, and categorizes them into five leucocyte types. They aimed to help for diagnosing diseases with this system. Wang et. al (Wang et al., 2016) applied mathematical morphology-based methods and supervised method to extract spatial information and employ spectral analysis, respectively. They experimented that leucocytes can be segmented and categorized into five types with an overall accuracy of more than 90%. Shahin et. al (Shahin, Guo, Amin, & Sharawi, 2019) proposed a novel identification system for white blood cells based on deep convolutional neural networks. Two methodologies depending upon transfer learning are followed: transfer learning based on deep activation features and fine-tuning of available deep networks. Using several pre-trained networks, deep activation features are obtained and employed in a traditional identification system. Additionally, a novel end-to-end convolutional deep architecture called “WBCsNet” is suggested and built from scratch. Hegde et. al (Hegde, Prasad, Hebbar, & Singh, 2019) demonstrated the classification of six leucocyte types. They provided the comparison of the traditional image processing approach and deep learning methods for the classification of white blood cells. Gupta et. al (Gupta, Arora, Agrawal, Khanna, & de Albuquerque, 2019) proposed an enhanced version of the original Binary Bat Algorithm for the classification of different types of leucocytes. They implemented the proposed algorithm using four different classifiers which are K-nearest neighbors (KNN), Logistic Regression, Random Forest, and Decision Tree. López-Puigdollers et. al (López-Puigdollers, Javier Traver, & Pla, 2019) characterized the histological blood tissue images with the well-known visual bag-of-words approach. In their study, three fundamental point detectors and five regular sampling strategies were examined and compared. Patil et. al (Patil, Patil, & Birajdar, 2020) developed a new approach named Canonical Correlation Analysis (CCA). They claim the idea that the CCA method views the effects of overlapping nuclei where multiple nuclei patches are extracted, learned, and trained at a time. Due to the overlapping of blood cell images, the execution time is minimized, the dimension of input images gets compressed, and the network converges faster with more accurate weight parameters. Di Ruberto et. al (Di Ruberto, Loddo, & Putzu, 2020) suggested a novel and efficient method for detecting and quantifying microscopic red and white blood cells. The system is based on a region-based approach called Edge Boxes. They claimed that millions of candidate boxes are evaluated in an instant, providing a sorted list of a few thousand highest ranked and scored proposals. Anita and Yadav (Anita & Yadav, 2021) designed a complete automatic detection algorithm to recognize the leucocytes using artificial intelligence.

This study provides a novel ResNet50 modified Faster R-CNN model for both the detection and classification of leucocyte types. In addition to this, the number of leucocytes in the test image can be determined. This model demonstrates the potential to be deployed as a diagnostic tool for clinical studies because the method has been tested on a real-world histological dataset.

The complete structure of the paper is as follows. Section 2 describes the material and methods of the study. Section 3 represents experimental results and discussion of the study. Conclusions and recommendations are summarized in Section 4.

2. Material and Method

2.1. Deep Learning

The successful performance of DL has enabled the solution of various state-of-arts problems. DL methods are CNN, Recurrent Neural Network (RNN), Restricted Boltzman Machines (RBM), Long-Short Term Memory Networks (LSTM), and deep autoencoders (DAE). It is significant to determine the suitable DL method depending on the problem at hand. For example, RNN is used to solve time-dependent problems, while CNN is generally used for image-based applications.

2.1.1. CNN

CNNs are a kind of deep artificial neural network created using a multi-layered artificial neural structure with deep layers. It learns the features on the image along with the layers without requiring any preliminary feature extraction. The structure of CNN can be divided into two parts in general: feature learning and classification. The first part is formed by the succession of the input layer, the convolution layer, the activation layer, and the pooling layer. After the first part, the classification layer is in the second part. Fully-connected layer, dropout, and softmax are the basic layers in this section. In summary; the filters are shifted through the image and convolution operation is applied in the convolution layers. Feature maps, that is the output of the convolution layer, are passed to the activation function. Dimension reduction is performed on the pooling layer. In the fully-connected layer, the data in the preceding layer is organized as a one-dimensional matrix and each neuron is connected to the next neuron. Finally, the classification is performed in the classification layer.

2.1.2. Region-Based CNN

Significant improvement in image-based application due to CNN, faster and more accurate region-based classification and detection approaches such as R-CNN, Fast R-CNN, and Faster R-CNN have been developed. The main idea of these methods is that they attain the candidate region, and then classify and draw the borders for the candidate area. A summary of information on R-CNN and its variants is presented as follows:

R-CNN (Girshick, Donahue, Darrell, & Malik, 2014): This is the first region-based CNN model for the detection and classification of the object. The regions where objects may exist are discovered through a selective search algorithm and some candidate boxes are extracted to determine the boundary of the objects. After that, the features of each box are extracted with designed CNN. Classification is carried out using extracted features with the classifier.

Fast R-CNN (Girshick, 2015): Contrary to R-CNN, Fast R-CNN runs the neural network once on the entire image. Region of Interest (RoI) pooling layer slices out RoI from the output of the network, reshapes it and classifies it. Fast R-CNN operates a selective search algorithm to generate its region proposals.

Faster R-CNN (Ren, He, Girshick, & Sun, 2015): Region Proposal Network (RPN) and Fast R-CNN are the main parts of the model. Firstly, the convolution and pooling operations are applied to obtain image features. Feature maps are transferred to the RPN to perform preliminary border regression and classification and the candidate frame is determined whether it is the background or the object. The RPN gives the position and score information of the candidate frames. Then, a fully-connected layer forwards it to the Fast R-CNN. Finally, the final regression of the frame and the specific object categorization is performed.

All R-CNN models, except Faster R-CNN, use a selective search algorithm that is a slow and time-consuming process. Therefore, it affects the performance of the network to find out the region proposals. Instead of using a selective search algorithm on the feature map to identify the region proposals, a CNN model is used to predict the region proposals. For this study, ResNet50 model was tested as CNN model. The predicted region proposals are then reshaped using a RoI pooling layer.

For this study, a novel Faster R-CNN model was designed and used in the experimental studies for classification with detection.

2.2. Dataset

In this study, a novel histological blood dataset was created for the classification and detection task. Histological blood tissue images were transferred to the digital environment at different magnification ratios by using preparations and optical microscopy. The Olympus DP72 camera, as shown in Fig. 1, and the DP2-BSW program was used to take pictures at different magnifications. Sample images of the blood tissues are illustrated in Fig. 2.

The ethics committee report for the experimental studies was taken from the Faculty of Medicine at Selcuk University with the date and number 26.09.2019 and 2019/175 respectively.

As a dataset, 1336 blood tissue images were obtained. Finally, the dataset was separated into training and test set of the classification and detection task.

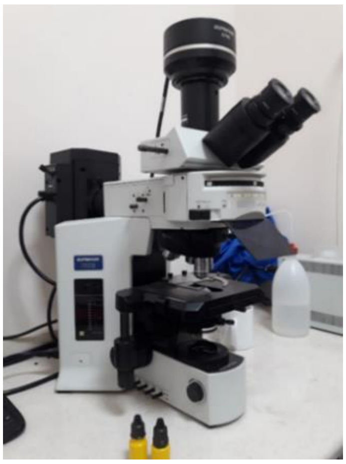

Fig. 1. OLYMPUS BX51 light microscope used in the process of data preparation.

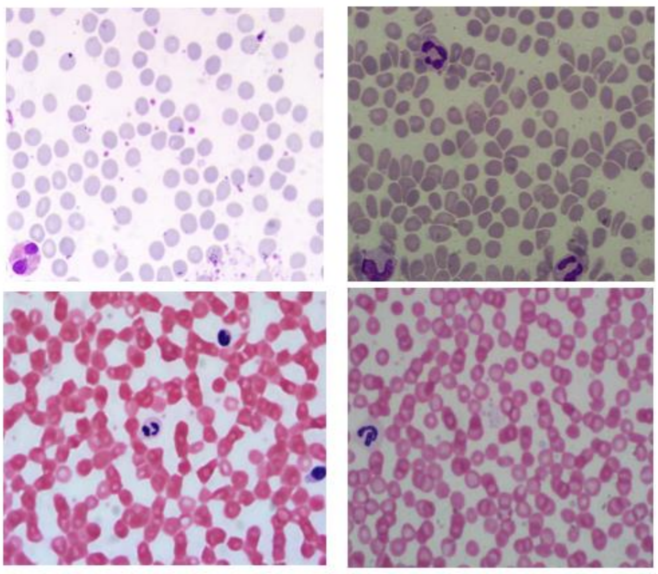

Fig. 2. Histological view of blood tissues with different magnifications.

2.3. Performance Measures

The success of the proposed model is calculated by the number of accurate estimates across all estimates. However, this information only gives classification accuracy and more performance measures are needed. To determine whether the proposed model is effective enough, a confusion matrix is preferred, which is a table that is often used to describe the performance of the classification model. The measures obtained using the confusion matrix are accuracy, precision, recall, and f1 score. Besides, cross-validation is a method used to increase the validity of the results. Cross-validation randomly separates the dataset into a specified number of identical size sets. After assuming one of the subsets as a test set, the system is trained with the remaining subsets. The processes are repeated until all subsets are tested in the system and the results obtained from these processes are generalized. As shown in Fig. 3, in this study, 5-fold cross-validation was used for the classification task.

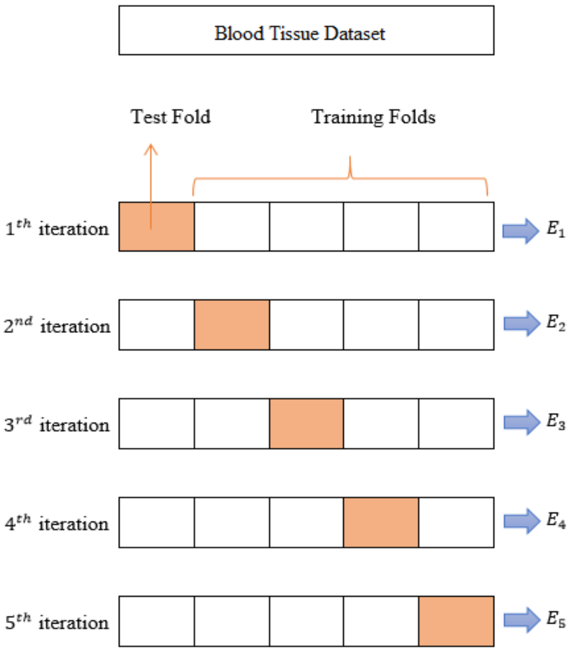

Fig. 3. An example of 5-fold cross-validation.

2.4. ResNet50 Model

ResNet (He, Zhang, Ren, & Sun, 2016) is a CNN model deeper than all models designed before it. ResNet, which contains a different logic than its predecessors, where network models are beginning to deepen; is formed by adding the residual block to the model, which feeds residual values to the next layers. With this feature, ResNet has a different structure than classical CNN models such as AlexNet(Krizhevsky, Sutskever, & Hinton, 2012) and VGG(Simonyan & Zisserman, 2014) created by adding standard layers consecutively. ResNet18, ResNet50, and ResNet101 are different variants of ResNet. Generally, this architecture consists of residual blocks as seen in Fig. 4.

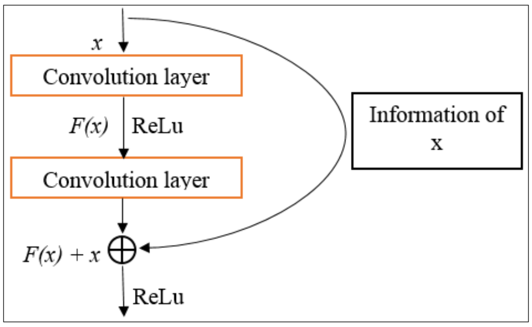

Fig. 4. The general structure of residual blocks.

In the residual block, *F (x)* result is obtained after the convolution-ReLu-convolution series of the input *x*. This result is then added to the original input x, and this operation is expressed as $H(x) = F(x) + x$. The proposed and designed Faster R-CNN model for object detection and classification was created by modifying the ResNet50 model.

3. Results and Discussion

Detailed information about experimental results was presented in this section. The primary motivation of this study is to find an effective model that can explicitly detect and classify leucocyte types in the blood tissue images into the class they belong to lymphocytes or others. To perform this task, a novel ResNet50 modified Faster R-CNN model was designed. The proposed model was tested with 5-fold cross-validation. Detailed information about this study is explained as follows.

3.1. Training Parameters

The training parameters of the proposed ResNet50 modified Faster R-CNN model are given in Table 1. The training was terminated after 50 epochs without overfitting the network. The drop factor is 0.9, the drop period is 5, the initial learning rate is 0.001, and the minibatch size is 4. Stochastic Gradient Descent with Momentum (SGDM) optimization algorithm was used in the training process.

Table 1. Parameter values in the training phase of the novel ResNet50 modified Faster R-CNN model.

Parameter	**Value**
Drop factor	0.9
Drop period	5
Execution environment	Multi GPU
Initial learning rate	0.001
Maximum epoch	50
Minibatch size	4
Optimizer	SGDM

3.2. Execution Environment

The training and testing were carried out on a computer with the following specifications: Intel Core i9-10920-X 3.50GHz processor, 128 GB of RAM, and four GeForce RTX 2080Ti graphic cards. The proposed region-based model was implemented on Matlab2020b using Deep Learning Toolbox.

3.3. Detection and Classification of Leucocyte Types

Lymphoma is cancer that starts in the infection-fighting cells of the immune system called lymphocytes and is the result of the uncontrolled growth of these cells. All lymphoma types grow at different rates and give various reactions to treatment. The number of lymphocytes in the blood tissue can be evaluated as a preliminary clinical study in the detection of this cancer. Sample images of leucocyte types are shown in Fig. 5.

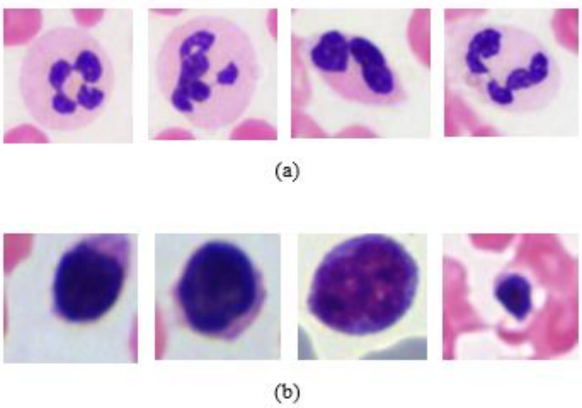

Fig. 5. Leucocyte types (a) Others, (b) Lymphocytes.

3.4. Experimental Results

In this study, detection and classification of leucocytes in the blood tissue images were carried out using the proposed ResNet50 modified Faster R-CNN model.

In the histological blood tissue images dataset, there is 1336 image with different magnification ratios. The original image size is 680x512x3 and has been resized depending on the designed CNN architecture. Table 2 lists the dataset with the number of images. At the step of training and test data determination, since 5-fold cross-validation was used, 267 images were separated for testing. After the data were separated into training and test data, both training and test data were shuffled in itself.

Table 2. The dataset with the number of images.

Number of samples in the dataset	Number of training samples	Number of test samples
1336	1069	267

The proposed Faster R-CNN model was obtained by transforming the pre-trained ResNet50 model into a Faster R-CNN object detection model. In order to design a region-based CNN model, RoI pooling layer, bounding box regression layer, and RPN are embedded in the ResNet50. Fig. 6 illustrates the designed ResNet50 modified Faster R-CNN model with layers.

The Matlab implementation details of the proposed ResNet50 modified Faster R-CNN model can be explained as follows:

1. The pre-trained ResNet50 model is loaded and the last three layers are removed. In addition to this, the number of classes the network should classify depending on the problem at hand is specified.
2. New classification layers are defined and they are added/connected to the network.
3. The number of outputs of the fully-connected layer is defined.
4. The box regression layers are generated and these layers are added to the network.
5. The regression layer is connected to the “avg_pool” layer.
6. Depending on the selected pre-trained CNN model, the feature extraction layer is determined. For ResNet50 model, feature extraction layer is “activation_40_relu”.
7. The layers appended to the selected feature extraction layer are disconnected.
8. RoI max-pooling layer is added and the feature extraction layer is connected to RoI max-pooling layer.
9. The output of the RoI max-pool is connected to the disconnected layers from above.
10. The anchor boxes are identified and the region proposal layer is generated.
11. The convolution layers for RPN are added and they are connected to the feature extraction layer.
12. The RPN classification output layers are added.
13. The classification layers are connected to the RPN.
14. RPN regression output layers are added.
15. The regression layers are connected to the RPN.
16. The classification and regression feature maps are connected to the Region Proposal layer inputs.
17. RoI pooling layer is connected to the region proposal layer output.

ResNet50 model that extracts features with high accuracy was modified. Root mean square error (RMSE) values of the ResNet50 model in the parts of the RPN are illustrated in Fig. 7. Average training accuracy and average training loss values during training are shown in Fig. 8 and Fig. 9 respectively.

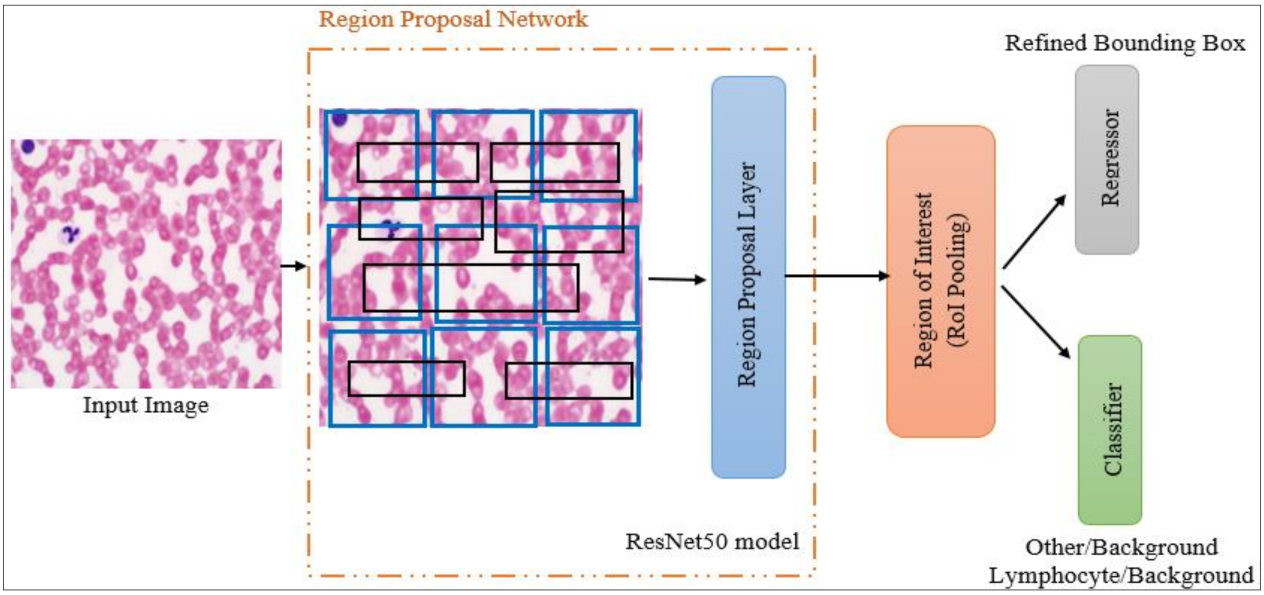

Fig. 6. Simulation of designed Faster R-CNN model structure with layers for detection and classification.

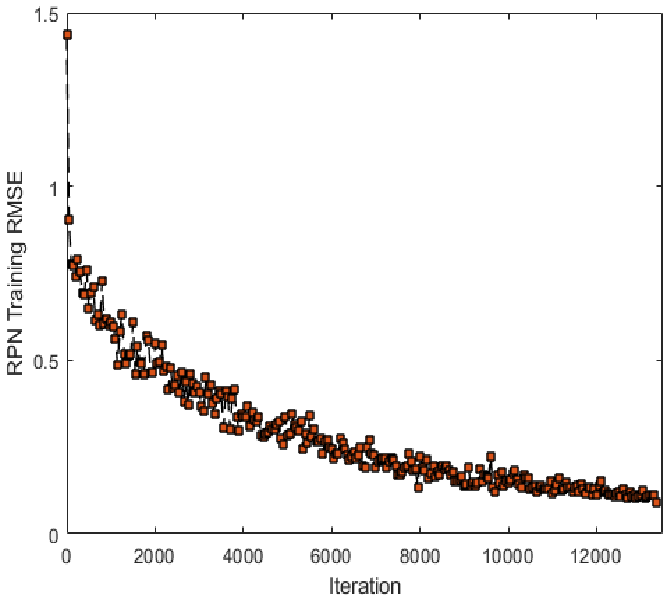

Fig. 7. RPN RMSE values during the training process.

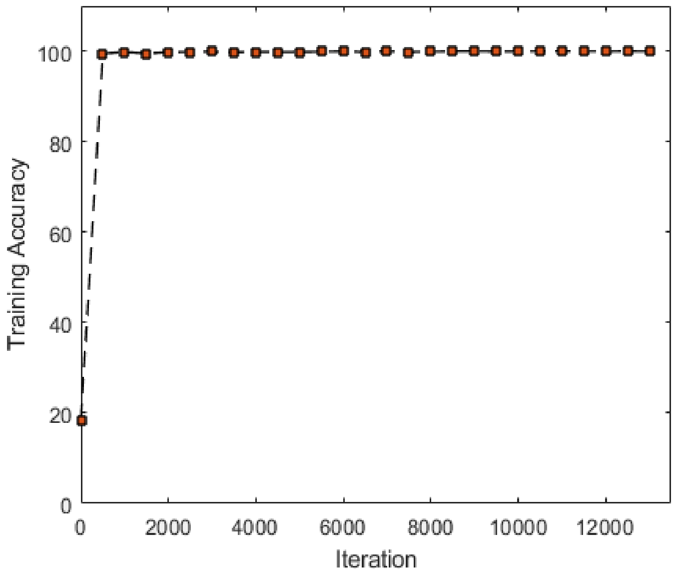

Fig. 8. Average accuracy during the training process.

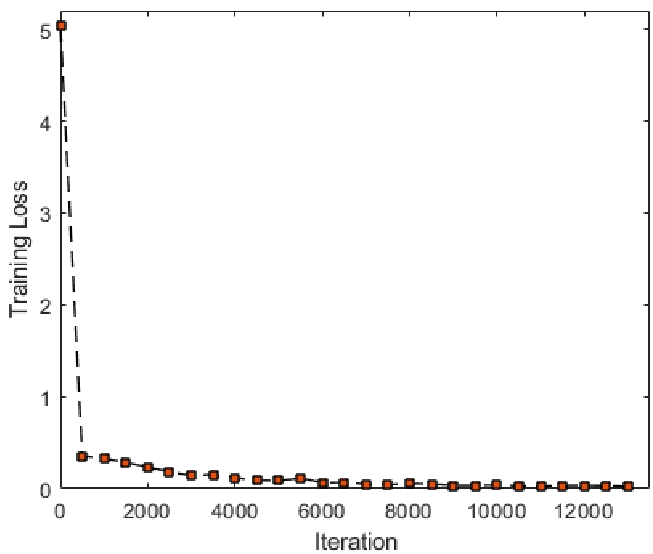

Fig. 9. Average loss during the training process.

The classification accuracy values obtained at the end of the training process are given in Table 3. The average accuracy value of the proposed detection and classification system is 95.81%.

Table 3. Performance values obtained for Faster R-CNN at the end of the test process.

Fold No	Labeled Object	Not Labeled Object	Number of the test images	Accuracy
1	256	11	267	0.9588
2	267	0	267	1
3	267	0	267	1
4	222	45	267	0.8315
5	268	0	268	1
			Average Accuracy	**0.9581**

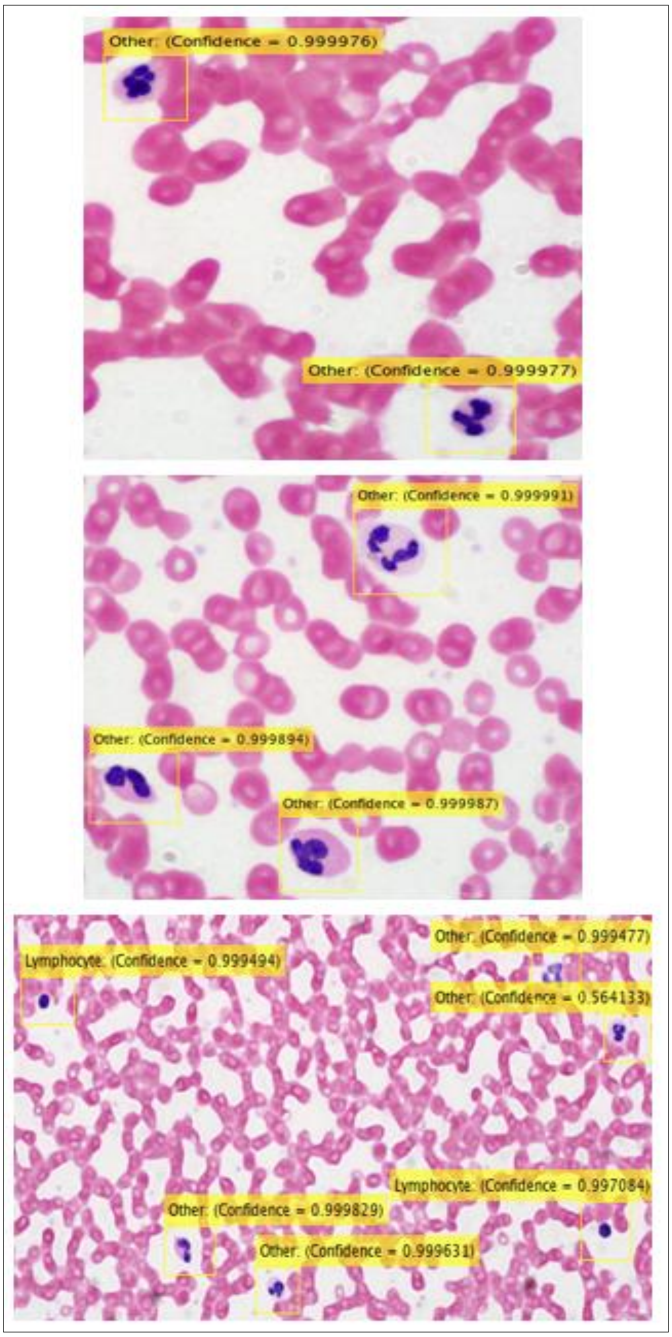

Fig. 10. The detection of leucocyte types and confidence values during the classification process.

As it can be seen in Fig. 10, the proposed ResNet50 modified Faster R-CNN model identifies the bounding box of the leucocytes and labels the region with high confidence scores. At the end of the test process, the class of the object in the bounding box was determined. In addition to this, the number of lymphocytes and other leucocytes can be determined. Considering the results, clinical preliminary evaluation can be made in the diagnosis of lymphoma cancer, taking into account the number and density of lymphocytes in histological image data.

3.5. Discussion

Object detection is a significant and challenging problem in image-based applications. Because the designed object detection algorithm searches to locate object instances from a large number of predefined categories in images. DL techniques have emerged as a powerful technique for learning feature representations directly from raw input data.

In this study, automatic detection and classification were provided without any preliminary feature extraction/selection and pre-processing on the images due to CNN models. The accuracy achieved by the novel Faster R-CNN model after 5-fold cross-validation of the blood tissue images dataset is 95.81%. The proposed ResNet50 modified Faster R-CNN model both finds the location of the leucocytes and classifies them with high accuracy. From the clinical perspective, this model demonstrates the potential to be deployed as a diagnostic tool because the method has been tested on a real-world dataset.

4. Conclusions and Recommendations

Within the scope of this study, the detection and classification of leucocyte types on the histological blood tissue images were performed. The positions and types of leucocytes were determined and the classification process was carried out. The purpose of the classification, which is divided into lymphocytes and others, is to analyze the density and number of lymphocytes in a certain part of the image. Because the number of lymphocytes in the blood tissue is an important parameter in detecting lymphoma cancer. The Faster R-CNN structure created by modifying the ResNet50 model gives satisfactory results in object detection and classification. This study, conducted using real-world data, also provides a preliminary outline of clinical experiments. Experimental studies can also be carried out using some other CNN architectures and different medical image datasets.

5. Acknowledge

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