Combining VGG16 with Random Forest and Capsule Network for Detecting Multiple Myeloma

MSc Research Project
Data Analytics

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Project Submission Sheet
School of Computing

Student Name:	Deepak Kumar Swain
Student ID:	x19216769
Programme:	Data Analytics
Year:	2021
Module:	MSc Research Project
Supervisor:	Luis Gustavo Nardin, Paul Stynes, Pramod Pathak
Submission Due Date:	16/08/2021
Project Title:	Combining VGG16 with Random Forest and Capsule Network for Detecting Multiple Myeloma
Word Count:	4830
Page Count:	11

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Abstract

Multiple Myeloma (MM) is a common blood cancer linked to white blood cells. Patients' survival rates increase based on early diagnosis. Early diagnosis, however, has been a major issue. This study offers a model for detecting multiple myeloma from microscopic images of patients' blood cells that combines VGG16, capsule networks (CapsNet), and random forests (RF). The model is trained using 85 blood cell pictures, and accuracy and intersection over union (IoU) metrics are used to compare it to state-of-the-art (SOTA) models like U-Net and masked-RCNN. From the comparison of the results of both models, it was observed that VGG16-CapsNet model gave better accuracy, but VGG16-RF model performed better in terms of segmentation of myeloma cells. However, the achieved segmented output was not better than the masked-RCNN model.

1 Introduction

In the biomedical sector, detecting malignant white blood cells that are produced in bone marrow is a difficult process. In the human body, stem cells are responsible for the development of white blood cells (WBC), red blood cells (RBC), and platelets. WBC serve as a barrier to pathogens, while RBC operate as a route for oxygen to circulate throughout the human body. Platelets, also known as thrombocytes, are blood components that react to injuries or bleeding by causing blood to clot (McKenzie and Williams; 2015).

WBC are important components of the human body's internal defense system, and they are mostly produced in the red bone marrow. The thymus gland, lymph nodes, and spleen all generate different types of WBC. The human body requires that WBC divide in an organized way. Multiple Myeloma is a cancer that develops when a person's body produces too many aberrant WBC. These aberrant cells then quickly mutate, crowding out regular red and white blood cells. The yearly rate of new cases of cancer and deaths caused by MM per 100,000 on men and women from 2014 to 2018 in the US are 7.1 and 3.2 respectively. In 2021, around 35,000 new cases of MM cancer were detected and 12,410 deaths caused by MM in US.

Multiple myeloma affects plasmacytes, which are a kind of blood cell. Antibodies are produced by normal plasma cells to fight infections (Vyshnav et al.; 2020). A physical examination is usually used to discover the disease, with the doctor looking for physical symptoms such as spleen or liver enlargement, as well as lymphadenopathy. Blood tests are then performed to check for abnormalities in red or white blood cells, or bone marrow samples are removed and examined for multiple myeloma. The sample testing aids in determining the illness type and pace of progression. The mechanisms outlined above are quite effective at identifying malignant cells. These procedures, on the other hand, are laborious, time-consuming, and may result in human mistakes. Machine learning techniques have been successfully applied (Anilkumar et al.; 2020) in the healthcare in recent years on tasks like classification and identification of various diseases, as well as detection of uncommon disorders that are difficult to analyze from a microscopic image with the human eye.

Due to their effectiveness and accuracy in image segmentation, capsule neural networks (LaLonde et al.; 2020) and transfer learning (Karimi et al.; 2021) approaches have gained relevance in medical sectors in recent years for performing image segmentation effectively. For example, in transfer learning techniques, pretrained model's learings were used as the starting point for instead of starting from scratch. This process helps in training the models faster without decreasing the effectiveness in giving results. It is also helpful in the cases where the dataset is comparatively small for a research. To the best of our knowledge, capsule neural networks have not yet been employed for image segmentation of any form of blood malignancy, such as leukemia, myeloma, or lymphoma. So far, researchers have used autoencoder type models like U-Net, Masked-RCNN, Tiramisu, Faster-RCNN for image segmentations where the encoder is responsible to down sample the original images to generate learned feature vector and the decoder up-samples the learned features to give the original image/object as output. Transfer learning techniques have also gained popularity especially when the dataset size is small as the models are not trained from scratch (Zan et al.; 2020). The pre-trained parameters are used as starting point along with the desired dataset.

The proposed solution combines VGG16, CapsNet and RF to perform image segmentation. The aim of this research is to investigate how accurately transfer learning techniques are able to detect multiple myeloma from microscopic blood cell images. The following sets of study objectives were developed to answer the research question:

- Examine SOTA models like as U-Net and masked-RCNN, which have been widely applied in the biomedical fields.
- Design transfer learning models combining VGG16 with Capsule network and Random Forest for the segmentation of myeloma cells.
- Train and assess the performance of the models with small dataset (less than 100 images).
- Comparison of efficiency between SOTA models and transfer learning models.

Section 2 addresses related work with a focus on machine learning approaches for image segmentation and classification of multiple myeloma. Section 3 discusses the research methodology while section 4 discusses the experiments and results of applying the proposed approach. Section 5 concludes the research and discusses future work.

2 Related Work

Various research projects linked to image segmentation of blood malignancies such as leukemia, multiple myeloma have been undertaken in recent years, and some of the findings are presented in the following sub-sections. Multiple myeloma has been identified and classified using a variety of methodologies and approaches by researchers. Section 2.1 provides a literature review on existing work related to segmentation of blood cancer images. Section 2.2 provides a literature review on CapsNet and RF.

2.1 Segmentation of Blood Cancers Images

Image segmentation plays an important role in detecting cancerous cells in images. In past years, several researchers leveraged the effectiveness of image segmentation to improve the extraction of the necessary features from images. The followings are some the highlights of the research work done in the past.

Gautam et al. (2016) utilized the naïve bayes model to classify several kinds of white blood cells (such as neutrophils, eosinophils, basophils, lymphocytes, and monocytes). The image segmentation for feature extraction was done using Otsu's thresholding approach. Nobuyuki Otsu invented this approach for picture thresholding automation. It simply results single intensity level to separate the pixels into background and foreground which helps in extracting the region of interest. Anilkumar et al. (2020) investigated several image segmentation studies for leukemia diagnosis, including thresholding, region-based segmentation, clustering-based segmentation, and watershed segmentation. The thresholding (30%), clustering (26%), and watershed (15%) approaches were used in 71% of the research on image segmentation of blood smear images. Techniques such as active contour and neural network models were used to complete the remaining 29% of the task. In terms of image segmentation, machine learning and deep learning approaches received a lot of traction starting in 2016. Mishra et al. (2016) extracted features from blood smear images using marker-based segmentation (MBS) and grey level cooccurrence matrix (GLCM). For feature reduction, probabilistic principal component analysis (PPCA) was employed, and RF was used to determine if the blood tumors were benign or malignant. Acharya and Kumar (2019) presented a new method for segmenting white blood cells' nucleus and cytoplasm. The K-medoids method was used for image segmentation. They discovered that while the K-means clustering method is faster than the K-medoids algorithm, the K-medoids approach beats the K-means strategy in terms of resilience. For the picture segmentation of white blood cells, Bhattacharjee and Sainit (2015) suggested a new approach termed watershed transformation. For the categorization of normal blood cells and blast cells, these segmented images were input into two models: the gaussian mixture model (GMM) and the binary search tree model. In terms of data preparation, Saeedizadeh et al. (2016) used a unique technique. Using the K-means clustering technique, the input images in enhanced RGB (L*a*b) color format were categorized into four groups, and the clusters were then transformed back to RGB space. The watershed transformation technique was used to segment the images, and the segmented images were then input into a support vector machine model for myeloma cell categorization.

Vyshnav et al. (2020) investigated the benefits of deep learning neural networks for image segmentation of multiple myeloma, such as Masked-RCNN and U-Net. 85 publically accessible pictures were used to train the two models. The masked-RCNN could not execute segmentation where the cytoplasm and background color contrast was comparably low, according to this investigation. Sajjad et al. (2017) classified leukemia using a multiclass support vector machine (SVM) based on white blood cell types (e.g., basophil, monocyte, neutrophil, eosinophil, and lymphocyte). PCA was used to extract and select features from the training images. Based on feature extraction using PCA and classification using multiclass support vector machine, Mirmohammadi et al. (2018) enhanced the classification accuracy of Acute Lymphoblastic Leukemia (ALL) type (L1, L2, and L3). The researchers discovered that using PCA rather than other feature extraction approaches improves sensitivity and specificity. For image segmentation of leukemia, Jabeen et al. (2020) utilized a new method that used color filters to locate regions of interest (in this case, white blood cells) and feature extraction utilizing transformation techniques such as curvelet transformation and wavelet transformation. The collected feature vectors were then input into K-nearest neighbours (KNN) and support vector machine (SVM) models to verify the proposed algorithm's accuracy. Amin et al. (2014) utilized a binary support vector machine (SVM) model to categorize the pictures into malignant and noncancerous classes and used K-means clustering to separate the white blood cells. The model was tested using K-fold cross validation (k=10) to see if it was overfitting with data, and it was found that it was not. With the aid of a faster-region convolutional neural network (faster-RCNN) model, Hossain et al. (2020) suggested a method to detect malignant blood types in acute lymphoblastic leukemia. For image segmentation and classification of acute lymphoblastic leukemia, Sukhia et al. (2019) employed two distinct methods. The diffused expectation maximisation (DEM) method was used to detect three separate classes in the images: WBC, RBC, and background. The pictures were categorized into classes (normal blood cell and lymphoblast blood cell) using a sparse classifier after feature extraction and selection. Vincent et al. (2015) employed the stacking idea, in which a two-step neural network was used to provide two separate sorts of classifications. The blood smear picture samples were used as input in the first phase, and required characteristics were retrieved from the images. With the aid of a sequential neural network, the pictures were categorized into two groups (normal blood cells images and aberrant blood cells images) after feature extraction. The result of the first stage was utilized as input for feature extraction in the second step. Following feature extraction, the aberrant cell pictures were further classified into acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) with the help of another sequential neural network.

2.2 Capsule Neural Network and Random Forest

Capsule Neural Networks (CapsNet) have gained popularity in recent years in the area of image segmentation and classification. Apart from deep learning techniques, ensemble machine learning techniques like Random Forest (RF) have shown significant results in different research. This section provides a literature review on the use of CapsNet and RF for image segmentation.

Hinton et al. (2011) described how complex hand-engineered features such as the scale-invariant feature transform (SIFT) are employed in the field of computer vision to recognize objects. A concept termed capsules was proposed in their work as a means to deal with item change in location, orientation, size, and illumination in the simplest way feasible. It also discussed how convolutional neural networks (CNN) are mistaken in what they aim to do. Some key characteristics, such as the location and orientation of component features, are not recognized properly because to the pooling strategies employed in CNN. Sabour et al. (2017) established the working principle of CapsNet after a few years. Capsule, a collection of neurons that holds both scalar pixel values and directional values, has superseded the idea of pooling or sub-sampling. Even if the angular location of a component fluctuates, this helps the neural network grasp the components of the image better. LaLonde et al. (2020) extended the use of CapsNet to lung cancer image segmentation. Deconvolutional capsules were used to construct an autoencoder structure to compensate for global information loss in restricting the routing. This network was compared to cutting-edge networks like U-Net, Tiramisu, and P-HNN. Wu and Misra (2019) used RF, wavelet transform, and hessian matrix to segment images of organic shales. The existence of the four shale components, porosity, rock matrix, pyrite, and organic components, was determined using features extracted from pictures and put into a RF model. For automated identification of maize tassels, Zan et al. (2020) utilized transfer learning by merging VGG16 and RF, which is appropriate for complicated situations. First, the RF was used to partition drone images into tassel and non-tassel areas, followed by the morphological method to extract likely tassel region recommendations, and finally, false positives were removed using VGG16.

Due to its superior feature extraction method, machine learning-based technologies have been increasingly popular for image segmentation in recent years. For image segmentation, convolutional neural networks such as faster-RCNN, U-Net, masked-RCNN, and Tiramisu have been frequently utilized in research projects with excellent results. However, the most significant disadvantage of convolutional neural networks is that they require a huge amount of training data to obtain a good outcome. Another issue with convolutional neural networks is that they have trouble storing object orientation and location in pictures. This scenario arises as a result of the network's usage of the pooling approach, which can assist in locating the required component in an image but fails to comprehend the component's location. It just looks to see if the component is there in the image and then classifies it based on that. It is capable of accurately classifying a picture as a whole. However, it is impossible to overlook the importance of component placements, particularly in medical images. The issue with convolutional neural networks (CNN) has been well-known for years, and numerous studies are currently being conducted to address it. To address CNN's limitations, Hinton et al. (2011) proposed the basic principles underpinning capsule neural networks. Sabour et al. (2017) eventually deciphered the reasoning and presented the notion of dynamic capsule routing. This is a very new notion that is still being studied. Even though deep learning techniques are widely used in biomedical fields, it cannot be ignored that machine learning techniques perform excellently when it comes to tabular data. Among various machine learning techniques, Random Forest (RF) is widely used in biomedical fields as unlike other machine learning algorithms it is not prone to model overfitting and imbalanced data (Csaholczi et al.; 2021).

3 Methodology

The proposed method, as illustrated in Figure 1, performs image segmentation using the capabilities of image classification algorithms. The transfer learning approach has been adapted by using VGG16 model that has already been trained on ImageNet dataset (WordNet; 2021) that has 1000 classes. The weights of the final layer from the VGG16 model were chopped and the learnings (trained weights) were used as the starting point of training the multiple myeloma dataset using Random Forest and Capsule Neural Network. The training of both the models were done separately.

The current study makes use of a dataset from the Cancer Imaging Archive (TCIA) (Gupta and Gupta; 2019). The dataset contains microscopic images collected from bone marrow aspirate slides of patients with multiple myeloma who were diagnosed using standard methods. The slides were stained with Jenner-Geemsa stain. Images were captured

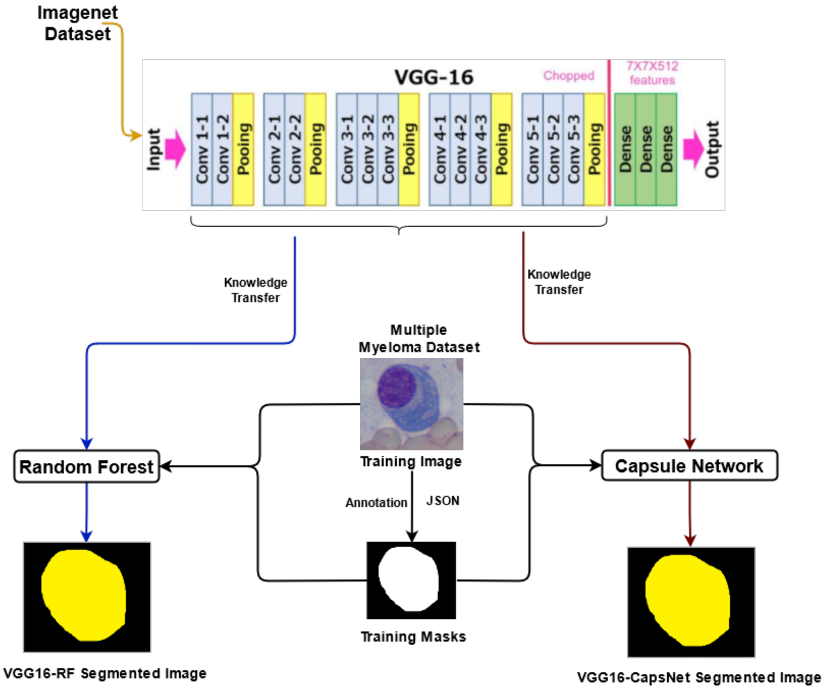

Figure 1: Proposed method where both Random Forest and Capsule Network models were trained separately by using VGG16 as backbone

at 1000x magnification using a Nikon Eclipse-200 microscope and a digital camera. The pictures were captured in raw BMP format at a resolution of 2560x1920 pixels. However, for the purposes of this project, these photos were converted to PNG format. There are 85 photos in total in this dataset. Before being used for segmentation, all 85 photos were stain normalized by professionals in the biomedical area. For convenience, these stain corrected pictures have been given as an annotated dataset with plasma cells recognized in all image slides of a presentation. Figure 2 depicts a selection of annotated pictures taken from the slides.

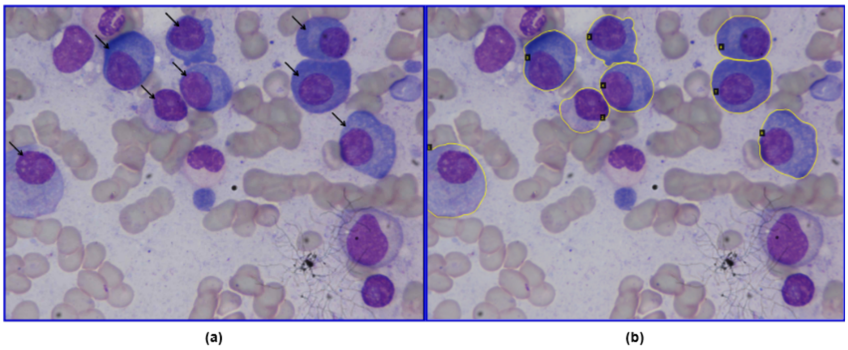

Figure 2: (a) Ground Truth Image, (b) Annotation Using VGG Annotator

For data preparation, images were annotated using VGG image annotator (Dutta and Zisserman; 2019) and then used as a JSON file for creation of masked images. To create masked images, K-means clustering and computer vision (OpenCV) techniques were used which are two of the most popular techniques to find contours in images.

However, OpenCV gave better result in terms of masked image creation. For creating masked images, the pixel coordinates of myeloma cells were taken from the JSON files and then bitwise AND operation was performed to get the contours of the myeloma cells in the images. This approach helped in getting the desired masked images which was difficult in K-Means clustering.

The chopped output of the VGG16 model containing pretrained weights was used as input for both RF and CapsNet models. For prediction of test images, the model returned the coordinates of the masked images which was then converted to images to visualize the segmented output.

4 Experiment and Result

The objective of the existing research and current research is to detect the multiple myeloma cells and provide the shape of the detected cell as output. In the existing work, accuracy was used to evaluate the model. The present study additionally compares the work to SOTA models using an accuracy metric. Apart from accuracy, another metric called Intersection over Union (IoU) has been used to evaluate current research. A detailed explanation is provided in the following subsections.

4.1 U-Net Model

To have better understanding and clarity, the existing work using U-Net was reproduced and hyperparameter tuned. Later, the results of reproduced work and existing work by (Vyshnav et al.; 2020). To reproduce the work, the masked images were created using VGG annotator and the data were trained on the reimplemented U-Net model. The U-Net model in the existing work achieved an accuracy of 89.62% whereas the reproduced U-Net model achieved validation accuracy of 94.62%. The difference in the accuracies may be due to the masked images used for training the model. The annotation in the current research is done manually since the masked images from the existing work were not received from the researchers.

4.2 VGG16 with Random Forest and Capsule Network Models

The implementation of proposed frameworks was done successfully where the models VGG16-RF and VGG16-CapsNet achieved accuracies as 92.4% and 99.38% respectively. Based on the accuracies it may be seen that the VGG16-RF model achieved better accuracy than U-Net. On the other hand, the VGG16-CapsNet model achieved better accuracy than both U-Net and Masked-CNN models. Figure 3 shows the results of State of the art models and proposed models on the same test data. However, it is clearly seen that even if VGG16-CapsNet achieved the best accuracy, the segmented output is worst among all the mentioned models. Hence accuracy is not the right metric to evaluate an image segmentation model.

One of the most popular technique called ‘Intersection over Union (IoU)’ was used as the metric to evaluate the proposed research. IoU is the appropriate metric to measure how well the predicted masked image is matching with the ground truth. The current research did manage to achieve better accuracy but when it comes to the image segmentation part, both VGG16-RF and VGG16-CapsNet did not give better result than the existing research. As per the output, it looks like the result of VGG-16-RF is close to

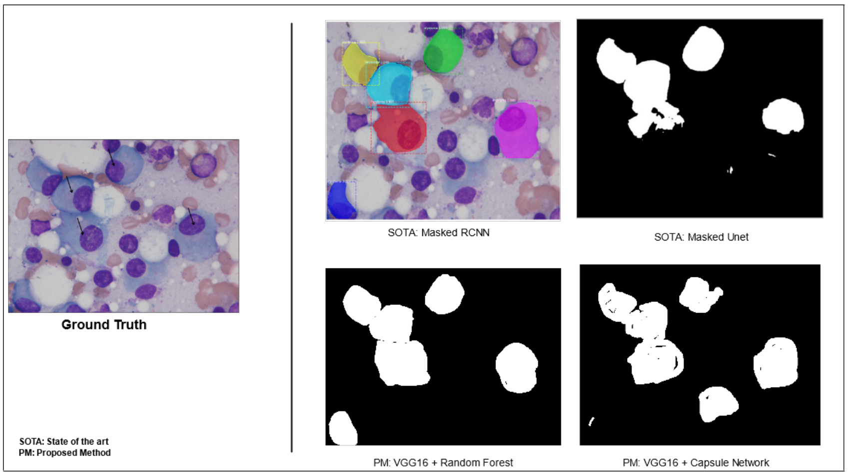

Figure 3: Output of state of the art models and proposed models on the same test data

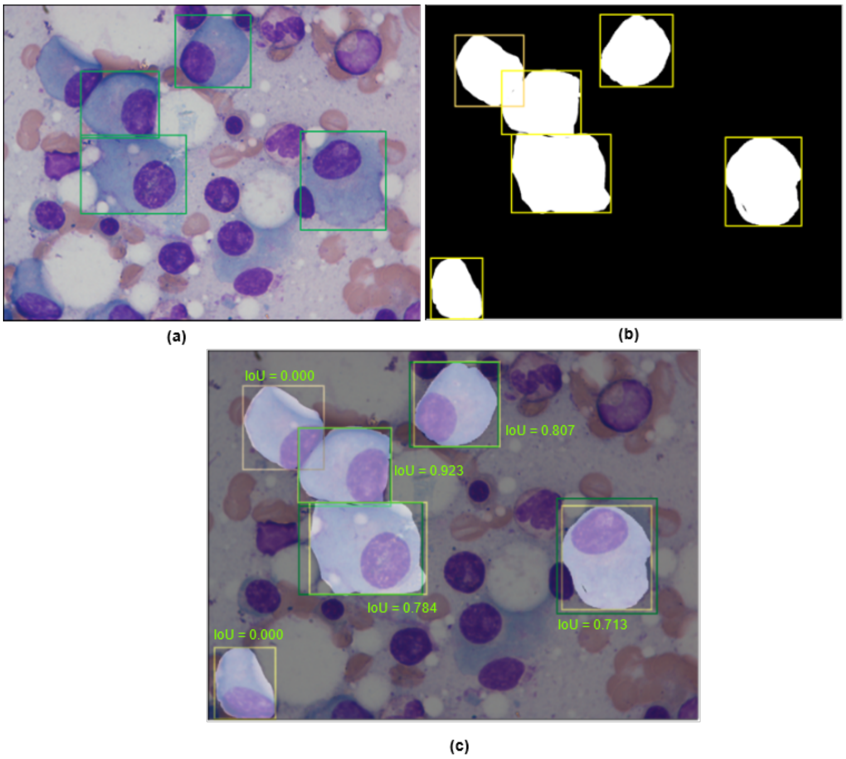

Figure 4: Visual Representation of IoU Values on a Test Image for VGG16-RF Model: (a) Ground Truth, (b) Prediction, (c) Ground Truth Vs Prediction comparison based on IoU values

the output of Masked-RCNN model. However, it is clearly seen that none of the model is giving accurate results as per the ground truth. In the ground truth image, there are only four myeloma cells but in the Masked RCNN and VGG16-RF model, six myeloma cells showing. This also clarifies the argument that the metrices like accuracy, precision, recall and f1-score are not the valid measures to evaluate these models. Hence, IoU has been used in the current research to validate each output myeloma cells. Figure 4 shows the IoU values for a sample image. The IoU values of individual myeloma cells are 0.713, 0.807, 0.923, 0.784, 0.000 and 0.000 respectively. For the invalid cells, IoU value is shown as 0.

4.3 Discussion

The VGG16-CapsNet model failed to achieve desired segmented output even if the it model achieved the hight accuracy. The VGG16-RF model achieve less accuracy than the Masked RCNN, but it managed to achieve similar result as shown in figure 3. This also justifies the argument that accuracy is not the correct measure for image segmentation. Hence, IoU is used to evaluate how accurately the models are able to perform the segmentation. As shown in figure 4, the VGG16-RF model managed to give good IoU values for the desired myeloma cells. However, the model gave some segmented cells in the output even if they are not myeloma cells. This occurred because the colour contrast was almost same as myeloma cells. Hence, the model failed to disregard these cells. The same output is received in the Masked RCNN model in the existing work. However, the existing work related to masked-RCNN hasn't been reproduced in the current research.

5 Conclusion and Future Work

The suggested study aims to see how effectively transfer learning approaches based on classification models can perform image segmentation for multiple myeloma patients. The VGG16-RF model managed to achieve the result as Masked-RCNN. In term of efficiency, the VGG16-RF model was faster than the other three models. However, As seen in figure 4, the output of the model still has flaws as it has detected some cells as myeloma cells even if they are not. This may be improved if the model is trained on a large dataset.

This research is limited to image segmentation of a particular disease called Multiple Myeloma that has blue coloured contrast in the training images. These contrasts appear in medical labs by mixing chemicals to the blood samples. If it is possible to give different colour contrasts to different types of blood cancers (occurring in WBC), the research may be extended to image classification after extracting the features from image segmentation.

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