AI-enabled Microscopic Blood Analysis for Microfluidic COVID-19 Hematology

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***Abstract* — Microscopic blood cell analysis is an important methodology for medical diagnosis, and complete blood cell counts (CBCs) are one of the routine tests operated in hospitals. Results of the CBCs include amounts of red blood cells, white blood cells and platelets in a unit blood sample. It is possible to diagnose diseases such as anemia when the numbers or shapes of red blood cells become abnormal. The percentage of white blood cells is one of the important indicators of many severe illnesses such as infection and cancer. The amounts of platelets are decreased when the patient suffers hemophilia. Doctors often use these as criteria to monitor the general health conditions and recovery stages of the patients in the hospital. However, many hospitals are relying on expensive hematology analyzers to perform these tests, and these procedures are often time consuming. There is a huge demand for an automated, fast and easily used CBCs method in order to avoid redundant procedures and minimize patients' burden on costs of healthcare. In this research, we investigate a new CBC detection method by using deep neural networks, and discuss state of the art machine learning methods in order to meet the medical usage requirements. The approach we applied in this work is based on YOLOv3 algorithm, and our experimental results show the applied deep learning algorithms have a great potential for CBCs tests, promising for deployment of deep learning methods into microfluidic point-of-care medical devices. As a case of study, we applied our blood cell detector to the blood samples of COVID-19 patients, where blood cell clots are a typical symptom of COVID-19.**

Keywords – microfluidic device, microscopic pathology, hematology, mobilenet, deep learning at edge.

I. INTRODUCTION

Microfluidic techniques such as lab-on-chip and point-of-care diagnosis devices have recently been widely used in the biological and medical fields [1, 2]. These have revolutionized personalized medicine and rapid diagnosis of various types of diseases. Point-of-care (POC) diagnosis means that medical diagnostic testing can be at or near the point of care, or at the time and place of patient care. By contrast, the conventional method is normally conducted at hospitals, thus the results from the blood samples will usually take hours, or even days to be obtained if the hospital is quite busy. In this case, it will be hard for the doctor to make an early diagnose of diseases.

Complete blood cell counts (CBCs) are one of the most common diagnostic methods in medical institutions. For example, detection of different white blood cell counts can help to manage acute radiation syndrome. When a patient undergoes a radiation therapy or chemotherapy, CBCs are used as a routine indicator to evaluate the bone marrow to produce the necessary cells. In addition, inflammation, leukemia, immunodeficiency, etc. can be detected and identified using different white blood cell counts. Bone marrow fibrosis, lymphoma, aplastic anemia, and lupus erythematosus are closely related to the abnormal platelet counts. Excessive bleeding such as kidney bleeding is related to changes in the number of red blood cells [3, 4, 5]. Using a microfluidic detection technology to measure the number of blood cells, we can monitor the above-mentioned diseases more frequently and readily, and detect them much earlier, saving the lives of patients.

Microfluidics is a technology about controlling, manipulating and detecting complex fluids at a microscopic size. It was rapidly developed in the early 1990s and is an interdisciplinary field that combines physics, chemistry, biology, medicine, engineering, and other fields [6]. As the name implies, "micro" refers to a fluid with small size and high accuracy, which can be accurately observed and manipulated at a micro scale. "Fluid" is the object we observe and manipulate, which can be a solution, blood, gas, or even supercritical fluids. Modern microfluidic technology can integrate hundreds or even tens of thousands of functional units on a few square centimeters of glass or plastic chip substrates. Through simple experimental designs, researchers can manipulate hundreds or thousands of small-scale droplets, small bubbles or biological cells.

As the convid-19 virus gradually spreads through the whole world, recently many quick microfluidic test kits have been developed and launched [6], which can achieve a fast

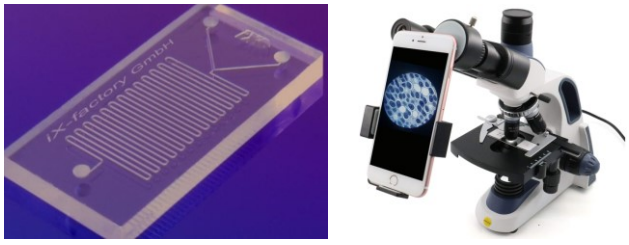

Figure 1. Typical microfluidic lab-on-chip device and the smartphone supported automated diagnosis system (The microfluidic lab-on-a-chip is often made of silicon or glass and so on. Channels in it enable fluid cross and manipulated by the researchers. This microfluidic device based diagnosis could be simulated as a combination of microscopic and smartphone camera. As the blood cell image acquired by the microscope camera, the smartphone app will analyze the pictures)

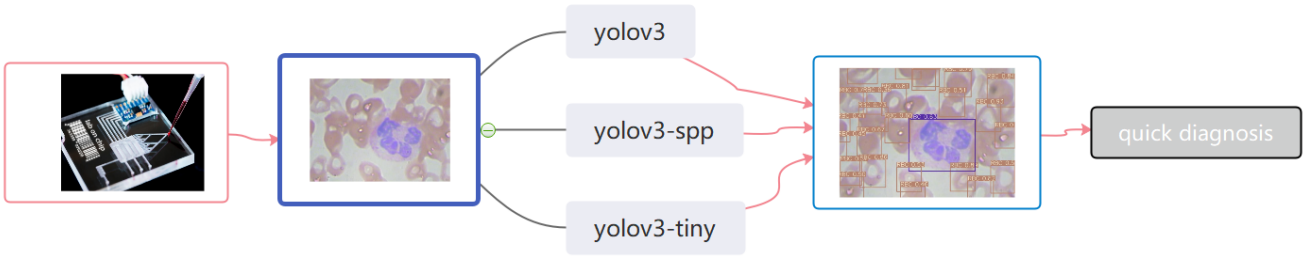

Figure 2. scheme diagram of deep learning based diagnosis [9]

detection of detection of IgM and IgG antibodies to COVID-19 in a single test within ~15 minutes. This clearly shows the importance of the microfluidic technology for the health care industry. However, many hospitals are relying on expensive hematology analyzers to perform these tests, and this procedure is often time consuming. There is a huge demand for an automated, fast and easy use CBCs method in order to avoid redundant procedures and minimize patients' burden on the costs of healthcare. Fig.1 illustrates such a mobile-based hematologic microfluidic system, which will be a platform for our microscopic diagnosis. In this research, we investigate a new CBC detection method by using deep neural networks, and apply state of the art machine learning methods in order to meet the medical usage requirements.

II. METHODOLOGIES

A. *Preliminary on YOLOv3*

Early blood cell detection methods apply the conventional computer vision techniques such as segmentation algorithms and create image descriptors such as SIFT/LBP/HPG [7, 8]. But a complete blood cell detection needs to overcome challenges such as cell overlap, small sizes, high background noise and so on. Recently, deep neural networks have attracted vast interest from research community, and from our recent studies [9-14] we have found these techniques can be a good answer for data-driven tasks. With benefits from the improvements of computing power and data acquiring technique, deep learning models such as CNNs (Convolutional Neural Networks) show a high performance in computer vision game and real application. Since 2012, several CNN based object detection algorithms have been proposed such as R-CNN, Fast-RCNN, Faster-RCNN, and Mask-RCNN [15-18]. In 2016, Redmon [19] suggested a new object detection method named YOLO which has a high detect speed but sacrifices some accuracy compared with those CNN region-based approaches.

The YOLOv3 [20] algorithm was further developed from the YOLO and YOLOv2 algorithms (also called YOLO9000) [21]. As contrast of those classical object detect algorithm such as faster RCNN, YOLO is a "one stage" object detection algorithm, which means it does not need proposal regions. The bounding box coordinates and probabilities for each class is computed by regression. These new methods boosted the network's detection speed significantly. In order to reach a fast speed, YOLO's detection error is often quite large. YOLOv2 algorithm is strengthened by importing Batch Normalization (BN) technique, high-resolution classifier, anchor boxes mechanism and other improvements. As for the YOLOv3, the most significant improvements are the introduction of pyramid networks and a new CNN feature extractor named Darknet-53. These changes make YOLOv3

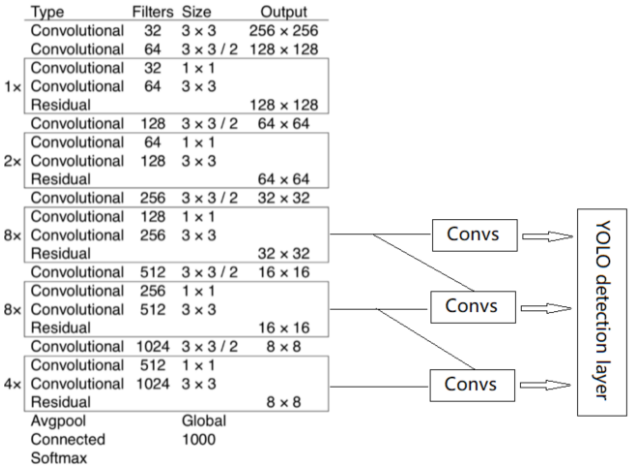

Figure 3. Network architecture of YOLOv3

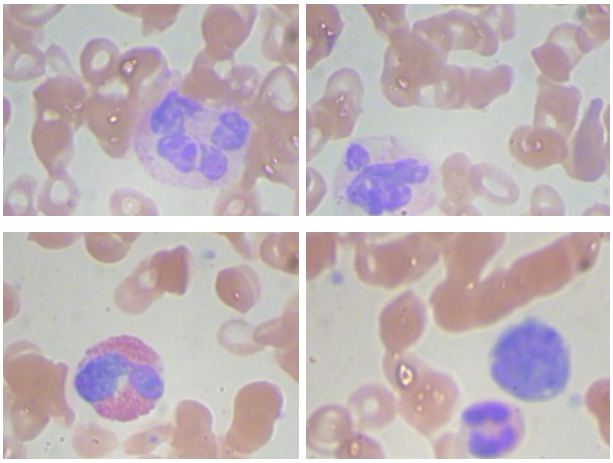

Figure 4. The sample of blood smear microscopic images

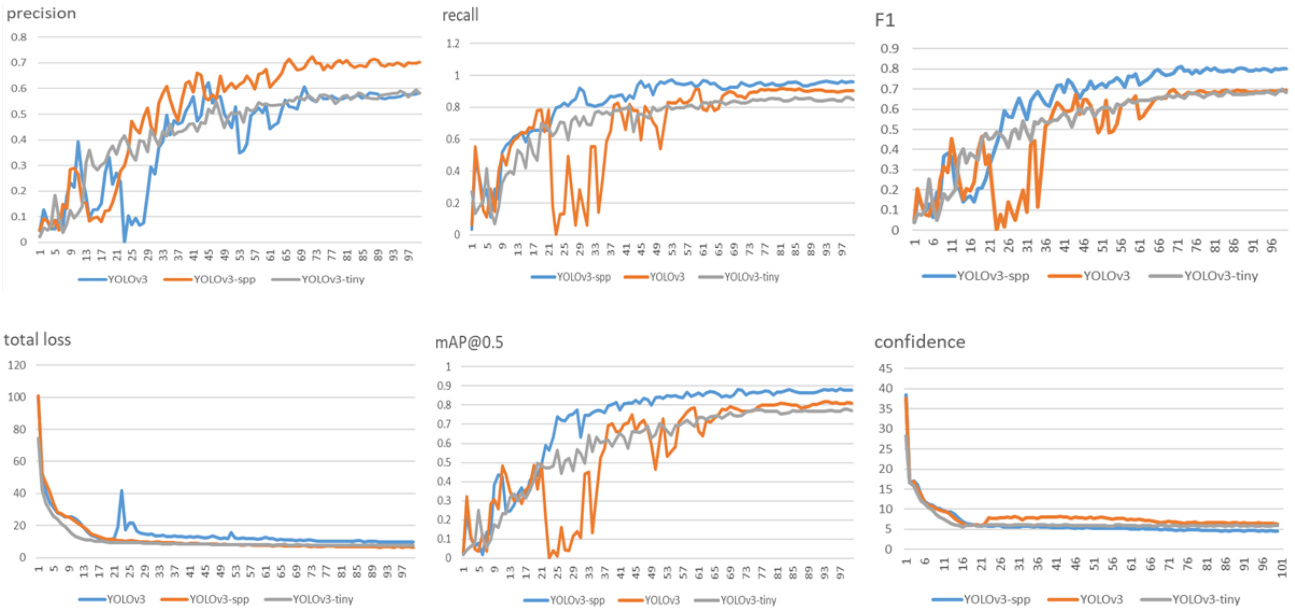

Figure 5. Test results of three different YOLO network on the blood cell dataset BCCD [22]. Top row, from left: precision, recall and F1 measure; Bottom row, from left: total loss, mAP, and confidence.

remaining the same performance at a double speed compared to that of YOLOv2.

In our experiments, we also used other two versions of YOLOv3 called YOLOv3-tiny and YOLOv3-spp [20, 21]. The YOLOv3-tiny uses only 7 convolutional and maximum pooling layers as its backbone network to achieve an easier and faster performance. Our framework is shown in Fig.2, and the network architecture of the YOLOv3 is shown in Fig.3.

B. Using YOLOv3 for Blood Diagnosis

The proposed system pipeline is shown in Fig.2. The obtained microscopic blood smear images are resized by YOLOv3 network into 416×416. After that, the localization and classification tasks will be fulfilled by the rest of the deep neural network. The qualified candidate detection network will serve the last stage of fast diagnosis process.

Considering the privacy of the patients and difficulty of obtaining a large amount of labeled datasets in medical field, we propose to apply transfer learning into this deep learning diagnosis method. The crucial concept of transfer learning is that the new model can use the previous one's knowledge to quickly master its present learning task. This is because in the processing of deep neural networks, the starting layers always detect lower level features such as curves, angles and lines no matter what we want to detect. However, for the last several layers we often need to train them separately to achieve a unique classifier in order to meet the required performance. We implement this by setting the gradients except three YOLO layers false and load the official YOLOv3 weights. Then we do not need to train the entire network from a scratch. This experience could be taken as an example to instruct other object detection tasks amid small dataset learning.

III. EXPERIMENT SETUP

A. Dataset

The data sets is an open source microscopic blood cell images which contains 364 images. These blood smear microscopic pictures illustrate three kinds of species, including red blood cells, white blood cells and platelets. Fig. 4 shows some input samples from the data set.

B. Evaluation

We have obtained some parameters widely used in evaluation of machine leaning model performance, including accuracy, precision, recall and F1 score. The confusion matrix is given in the table I below,

Table I. Definition of Raw Measures

	Positive	Negative
Positive	TP (True Positive)	FP(False Positive)
Negative	FN(False Negative)	TN(True Negative)

And the accuracy, precision, recall and F1 measure can be defined by,

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN}$$

$$\text{Precision} = \frac{TP}{TP + FP}$$

$$\text{Recall} = \frac{TP}{TP + FN}$$

$$\text{F1 score} = \frac{2 * (Precision * Recall)}{(Precision + Recall)}$$

With the above measures, we will be able to compare YOLO detectors and evaluate them over blood cell datasets.

IV. Experimental Results

Our raw samples are obtained from an open source datasets on GitHub [22], which contains 364 blood smear microscopic images. In order to utilize the values of small datasets, we only separate the images into training set and test set by a ratio of 8:2. We convert our datasets into the YOLOv3 format datasets and build the network based on Pytorch framework. Our experiments all run on a remote server with an 11G NVIDIA RTX 2080Ti GPU. The training is based on pre-trained weights, thus the training time is significantly shorter than training from scratch. The analysis using YOLOv3-SPP and YOLOv3 both take about half an hour to complete 100 epochs training process. Whereas YOLOv3-tiny takes only 10 minutes to finish the training. This is mainly because the size of YOLOv3-tiny is very small to reach a high training and detection speed. Figure 5 shows the test results on the BCCD dataset, and we can see that the YOLOv3-SPP has achieved the best accuracy when the model becomes converged.

From the test results, it is obvious that the white blood cells are easy to detect so that three models all produce very high mAP and F1 values. However, both the red blood cells and platelets represent a low precision with a high recall rate. This result directly indicates our method generates too many False Positive. From the detection of the samples, we can see that there are challenges including the large number and shape overlap of red blood cells, the large noises or low background contrast because of the tiny size of platelets.

Above all, model YOLOv3-SPP shows the best performance among three methods. Its mean average precision can reach 0.886 and the precision for three kinds of blood cells can exceed 80 percent, and especially that of the white blood cell is about 0.98. The detection time of YOLOv3-SPP can reach 0.132 s for four samples in Fig.6. Although the YOLOv3-tiny performs much more quickly for about 0.095 s on four samples, but its precision and recall become low when applied into real scenario. The detection examples of YOLOv3-SPP method is shown in Fig.6. Almost all the blood cells can be marked out by different rectangle boxes. The big blue rectangle boxes are white blood cells, while the yellow small boxes are platelets and those large amount targets are red blood cells.

In Fig.7, we further tested our system using the samples from a COVID-19 patients [23], where we can clearly see a blood clot in the 1st image. The test results show a perfect performance on these COVID-19 samples, implying a potential of this technology for automated hematology for COVID-19 medical analysis.

V. Conclusion and Future Work

In this work, we investigate three kinds of state of art deep learning methods to solve the CBCs testing problem. There are still further improvement in order to meet the requirements of practical uses for medication. However, it implies a tremendous potential that counting blood cells in microfluidic device for the POC services. While this is an initial proof-of-concept work, we have a list of tasks to do in our future work as listed below.

First of all, we need to improve the precision and recall of the test results. Ensemble methods [24-27] can usually work better, and likely we can integrate these methods into the classification scheme and improve the accuracy with various

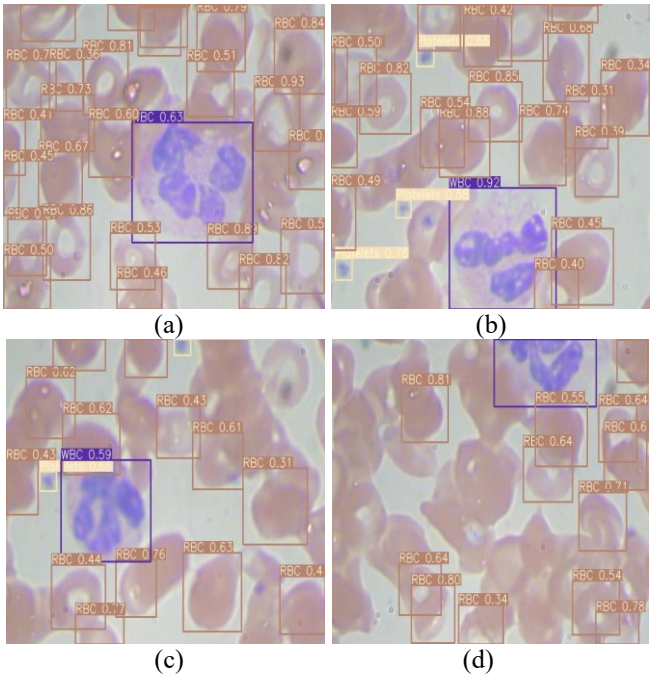

Figure 6. YOLOv3-spp detection results on blood smear microscopic images (a) (b) (c) (d).

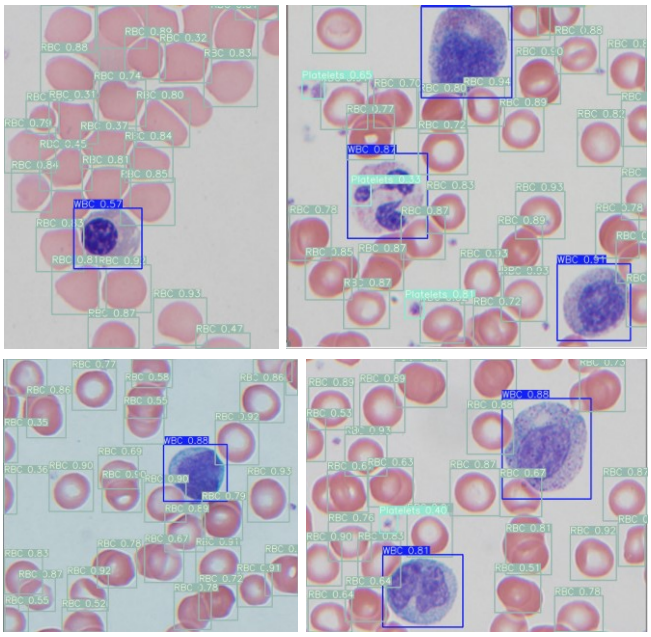

Figure 7. Further tests on COVID-19 samples from [23].

weak supervision schemes [28]. Secondly, given the situation of emergency breakout of COVID-19, we will exploit the use of such an automated hematologic POC device for assisting COVID-19 medical diagnosis. Thirdly, we need to make the model simpler and faster for mobile/edge-based computing. The default backbone of YOLOv3 is darknet 53, although the compute speed of darknet 53 is faster than ResNet-152 and ResNet-101. For some special scenarios, such a complex backbone might not be suitable. In our datasets, we might need to change the backbone into darknet19 or some lighter network such as Mobilenet. In addition, we also need to apply model compression methods such as model pruning, or quantize parameters of neural networks. Furthermore, while our work is targeted at the POC medical diagnosis, we will integrate the mobile based edge application with microscope and microfluidic substrates and investigate its practical use.

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