Efficient Leukocyte Classification Based On Multimodal Light-source Images Using Ensemble-free Network

Litao Yang LITAO.YANG@MONASH.EDU
Deval Mehta DEVAL.MEHTA@MONASH.EDU
Zongyuan Ge ZONGYUAN.GE@MONASH.EDU
Monash Medical AI Group, Monash University

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Abstract

Classifying white blood cells (leukocytes) in a blood sample is essential for diagnosing the health condition of a person. Conventionally, this is accomplished in a central clinical laboratory with trained experts and sophisticated blood cell counter systems. Recently, there has been an increase in developing machine learning and deep learning techniques based on blood smear and fluorescent images for this task. In this work, we present an approach based on multimodal fluorescence and bright-field images of blood samples which are exposed to excitation wavelengths of different light sources. To this end, we collect a multimodal (four modalities) dataset of 6,700 white blood cells present in peripheral blood. Despite the multimodal nature of our dataset, we propose a low complexity ensemble-free deep learning network for performing leukocyte classification. In our proposed approach, multiple separated subnetworks of a single network can learn features from modality specific images. This enables our approach to provide an almost on par classification performance while having 4x fewer parameters than that of a traditional ensemble system employed for the same task. Our proposed ensemble-free architecture can achieve an overall accuracy of *96.15%* for 5-part differential leukocyte classification while having only *1.3M* parameters. We believe that our proposed approach can also help with developing an efficient point-of-care (POC) solution for leukocyte classification especially for resource poor environments.
Keywords: WBCs, fluorescence, bright-field, efficient, multimodal, ensemble

1. Introduction

A complete blood count (CBC) test is the foremost requirement for diagnosing any health-related condition of a person (Tkachuk et al., 2007). It is quintessential for doctors to analyse the blood count results for deducing conditions such as anemia, autoimmune disorders, leukemia, and any other bacterial infections (Walters and Abelson, 1996). A CBC test of a peripheral blood sample consists of the count of red blood cells (RBCs), white blood cells (WBCs) and platelets (Theml et al., 2004; George-Gay and Parker, 2003). Of the above, WBCs are further categorized into five parts: Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils and are responsible to defend body organs and heal any damage to the biological structures (Blumenreich, 1990). Thus, it is vital for doctors to know the count of WBCs amongst the different categories to diagnose any specific disease or underlying health condition.

The usual practice for recognizing the different WBCs in the blood has relied on performing a microscopic examination of the blood smear images by trained experts in this

field (Bain, 2005). The categorization of different cells is determined based on the distinguishing features in the morphological structure, size, cytoplasm, and nucleus of a cell under a microscope by the naked eye of a trained expert. This makes the process quite tedious and time-consuming while also being dependent on the human expert's subjective opinion and bias and prone to any recording errors (Fuentes-Arderiu and Dot-Bach, 2009). Another way employs sophisticated instruments such as hemocytometer (Lutz and Dzik, 1993) and flow cytometry (Bodensteiner, 1989) which provide a high accuracy in the classification of cells. However, these devices require a prior mixing of several reagents and lysing solutions with the blood sample and are also bulky and expensive, which are normally operated by trained professionals only in central clinical laboratories. These methods are not suitable contenders for Point-of-Care (POC) testing especially in resource poor settings.

Recently, due to the advent of machine learning and deep learning, there has been a rise in adopting techniques such as Support Vector Machines (SVMs), Multi-layer Perceptrons (MLPs), Convolutional Neural Networks (CNNs) for classifying the blood cell images. Most of these methods are based on blood smear microscopic images which provide reach features about the morphology and structure of the cells but still require manual preparation and staining of the slides by trained personnel (Ramesh et al., 2012). More recently, the research community has developed image acquisition of cell images by mixing Acridine Orange (AO) dye with the blood samples and exposing them to different light source excitation yielding intense green fluorescence like images (Das et al., 2021). AO dye has a natural affinity for nucleic acids and thus binds to the WBCs which then show up when excited with a light source (Melamed et al., 1972; Zheng et al., 2008). The fluorescence based imaging is more efficient and can be integrated easily into a POC setting compared to the one based on blood smears (Forcucci et al., 2015). However, fluorescence based imaging also suffers from phototoxicity and photobleaching, which makes the images less feature rich and thus the process of distinguishing between different cell types becomes more difficult as compared to the blood smear images (Ojaghi et al., 2020).

In this work, we develop an approach which is based on the multimodal images from fluorescence and three different bright-field lights. Relying on multiple modalities complement each other in enhancing the distinguishing features of different WBC cells. Thus, we collect a dataset of blood samples exposed to four different light sources at the same time and capture their excitation images under a microscope. Despite the multimodal nature of our dataset, we target to analyse these images in an efficient way. To this end, we develop an ensemble-free architecture for processing multimodal images at the same time. In particular, this work has the following major contributions:

- A multimodal approach to WBC classification based on fluorescence and bright-field microscopic images.
- A single ensemble-free deep learning network based on multimodal images for efficient WBC classification.

2. Related Work

Automated WBC Classification - There have been a plethora of methods developed for automated blood smear image based detection and classification of WBCs. They have var-

ied from utilizing traditional image based features such as hue, saturation values, connected component labeling (Cruz et al., 2017), local image descriptors such as Scale-Invariant Feature Transform (SIFT) (Lopez-Puigdollers et al., 2019) to widely used machine learning approaches such as Support Vector Machines (SVMs) (Rezatofighi and Soltanian-Zadeh, 2011; Putzu et al., 2014), Multi-layer Perceptrons (MLPs) (Nazlibilek et al., 2014; Su et al., 2014), Naive Bayes Classifier (Mathur et al., 2013; Prinyakupt and Pluempitiwiriyawej, 2015) and later have moved to deep learning approaches involving CNNs - utilizing pretrained Resnets, InceptionNets (Habibzadeh et al., 2013, 2018), custom CNN archtiectures (Zhao et al., 2017; Shahin et al., 2019; Jiang et al., 2018), dual-stage CNNs (Choi et al., 2017) and even adapting object detectors and classifier frameworks such as Yolo (Redmon and Farhadi, 2018), SSD (Liu et al., 2016), Faster RCNN (Ren et al., 2015) for automatically detecting and classifying WBCs in the whole image (Wang et al., 2019; Abas and Abdulazeez, 2021; Alam and Islam, 2019). Although most of the methods are based on blood smear images as the input, very recently some fluorescence based imaging methods have also been developed (Yakimov et al., 2019; Das et al., 2021). The existing work mostly concentrates on the classification performance and very less notice is being paid to the real-time feasibility of the models. A comprehensive review about various methods related to imaging and automated methods for WBC detection and classification is provided (Khamael et al., 2020).

Efficient Models - Although deep learning models have achieved state-of-the-art performance on many image related tasks, popularly adopted network families such as ResNets (He et al., 2016), DenseNets (Huang et al., 2017), InceptionNet (Szegedy et al., 2015) have very high number of computational parameters, which makes them unsuitable for implementing them on a low power device. Even the more recently developed lowest version of EfficientNet (B0) (Tan and Le, 2019) has 5.3M parameters. To solve this problem, the research community has explored to develop approaches for reducing the complexity of the deep learning networks and there have been many directions developed in this domain such as Knowledge Distillation (Gou et al., 2021), Quantization and Pruning (Han et al., 2015; Liang et al., 2021). These approaches have been fairly successful in making efficient networks while maintaining an equivalent performance to that of a highly complex network.

However, all the above developed approaches are targeted at the scenario when a dataset contains a single modality. For our WBC classification task, we have a unique dataset with four modalities - one from fluorescence and three from bright-field. As different modalities have their modality specific distinguishing features, the widely used approach for a multimodal dataset is building an ensemble (Hansen and Salamon, 1990) of modality specific networks for a better generalization and classification performance. Although ensemble approaches provide a high performance, they come with a huge added cost of complexity. Instead, we propose an ensemble-free network for our multimodal dataset.

The developments in the domain of network sparsity and pruning suggest that most of the network parameters are not utilized and can be pruned away without adversely affecting the performance (Zhu and Gupta, 2017; Frankle and Carbin, 2018). To this end, a recently proposed architecture trained multiple subnetworks (MIMO) for robust prediction (Havasi et al., 2020) and achieved significant performance improvement for datasets such as CIFAR-10, ImageNet. However, this approach is also limited to single modality datasets. Inspired from the sparse utilization of network parameters and the work from MIMO, we

propose a multimodal input and multimodal output approach for training modality specific independent subnetworks of a single deep learning network. Our proposed architecture treats the independent subnetworks as a combination of a traditional ensemble of modality specific networks. Thus, it is predicted to give a classification performance on par with a traditional ensemble while having the complexity of a single network. We explain our proposed architecture and training strategy in detail in Section 4 of this paper.

The rest of the paper is organized as follows. In Section 3, we give a description of our multimodal dataset and train test splits. In Section 4, firstly we introduce the baseline techniques and later we describe our proposed approach and training strategy. Section 5 deals with the experimental results of our proposed approach and benchmarking with the baseline techniques. Finally, we conclude this work in Section 6.

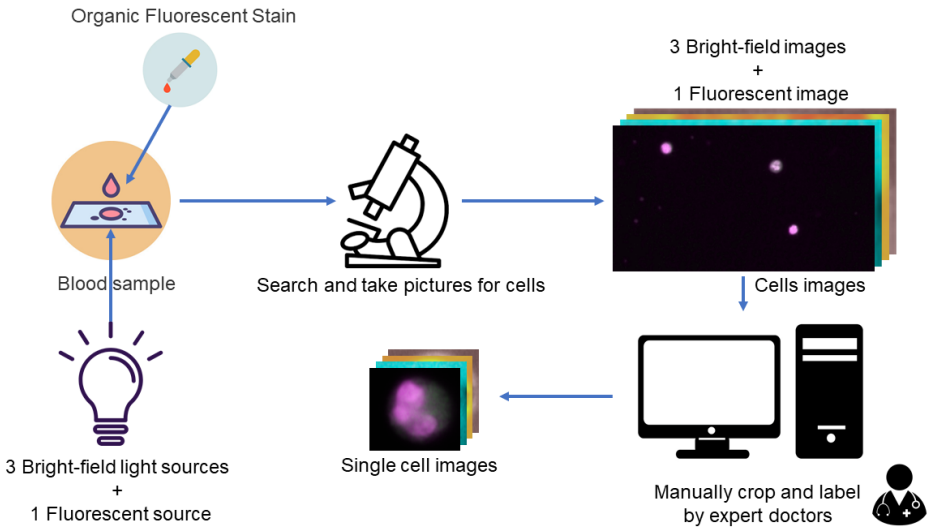

Figure 1: Overall process of data collection and annotation

3. Multimodal Dataset

We present the overall process of data collection and annotation in Figure 1. Please note that the colors of the images are for representation only and not the actual colors[1]. Firstly, we collect blood samples from a normal person which is then exposed to the three different bright-field light sources and the resulting three different bright-field images are captured by a camera module. For the fluorescent image, we then immediately stain the blood sample with an organic fluorescent stain and expose it to another light source before collecting the resulting fluorescent image. Thus, we capture four different modality images of a blood sample. The fluorescence image helps us to locate WBCs easily as they are the only cells

1. The technical details of excitation lights and actual colours will be released once the disclosure has been filed. Please also note that the artificial colour in the image does not affect the conclusion of this work.

captured suppressing the RBCs. Thus, we crop all the WBCs in the four different images which are then annotated and classified into five different categories by a trained pathologist. In total, our dataset consists of 6,697 WBC images which include 4167 Neutrophil (NEU), 2027 Lymphocyte (LYM), 82 Monocyte (MO), 378 Eosinophil (EOS), and 43 Basophil (BAS) with the class distribution shown in Figure 2. For training and testing our models, we split the dataset into 5-fold cross validation with stratified split strategy with the ratio of 80 (train): 20 (test).

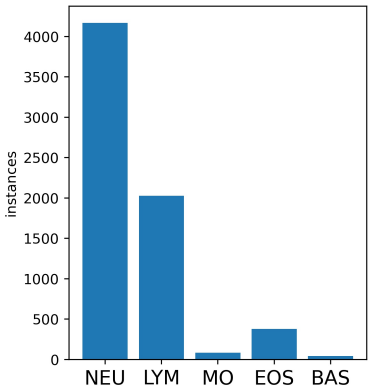

Figure 2: Class distribution amongst WBCs in our dataset

4. Multimodal Networks

In this section, we firstly describe the baseline techniques that we adopt for multimodal WBC classification. Later, we describe our proposed methodology.

Baseline Techniques - Let us represent $\{X_1, Y\}$, $\{X_2, Y\}$, $\{X_3, Y\}$, and $\{X_f, Y\}$ as the multi modal input images and their corresponding WBC cateogory of our dataset representing Color 1, Color 2, Color 3 and Fluorescence respectively. For creating baselines, we firstly train the individual networks $f(\theta_1)$, $f(\theta_2)$, $f(\theta_3)$, and $f(\theta_f)$ which learn distinguishing features for modality specific images. As we are targeting low complexity network, we select ShuffleNetV2 with 1.0x output channels (Ma et al., 2018) as our backbone. We train the individual networks with the standard cross-entropy loss for 5-class classification of the WBC cells for each of the four modalities. After training the individual modality baselines, for extracting the diverse features from the multimodal images, we build an ensemble of the individually trained modality specific network and average their predictions after the Softmax layer as shown in Figure 3. The ensemble architecture may achieve a higher performance but also increases the complexity to 4x of a single network.

Proposed Approach - Based on the previous studies of sparsity and pruning of deep learning networks, we experiment whether separated subnetworks inside a single network can be trained to learn the modality specific features. To this end, we develop two approaches as shown in Figure 4. In Figure 4 (a), we show our first approach, a Multimodal MIMO (MM-MIMO), where we adapt the original MIMO architecture and suit it for a

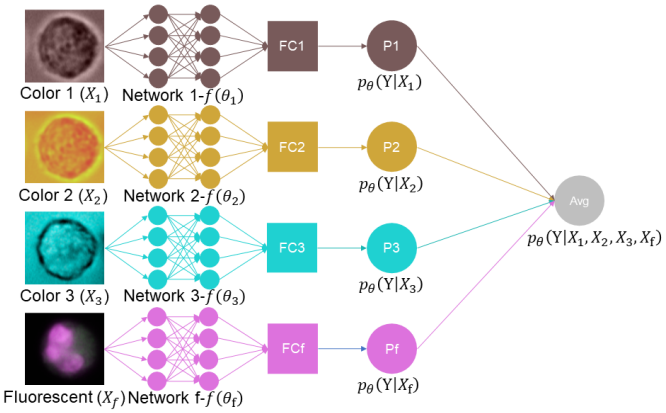

Figure 3: Traditional ensemble approach for our multimodal WBC dataset

multimodal dataset. In our adapted architecture, both the network module and fully connected (linear) layer are a part of ShuffleNetV2, which is the same as an individual modality specific network baseline except for the input and output channels. Firstly, for the inputs to the MM-MIMO, modality specific input images $\{X_1, X_2, X_3, X_f\}$ are sampled independently from the four modalities and concatenated to X_{123f} by Equation (1) in the channel dimension and supplied as the input to our MM-MIMO.

$$X_{123f} = f_{conact}(X_1, X_2, X_3, X_f) \tag{1}$$

Their corresponding WBC labels $\{Y_1, Y_2, Y_3, Y_f\}$ are used as the ground truth when training. The outputs of MM-MIMO are four modality specific predictions $\{p_\theta(Y_1|X_1), p_\theta(Y_2|X_2), p_\theta(Y_3|X_3), p_\theta(Y_f|X_f)\}$ based on the last hidden layer of the network. During training, the overall loss is the sum of the standard cross entropy loss for each of the four different modalities, which makes the whole network to classify their matching inputs, thus creating independent subnetworks within MM-MIMO. As we adopt independent sampling for each modality, the corresponding subnetwork will learn to ignore other input modalities to ensure that the modality specific prediction is independent. This way we get the independent subnetworks for each modality trained. During the testing phase, the four modality input images are of the same WBC category and the output predictions are averaged after the Softmax layer to get the final prediction.

In Figure 4(b), we show our second approach, Head Specific MM-MIMO, where we place specific heads in the initial and the end part of the MM-MIMO. Our reasoning comes from the idea that although MM-MIMO will learn independent modality specific subnetworks, the training of such subnetworks will be much more efficient if the inputs are not concatenated in the earliest stage and similarly the output heads are separated for training. Thus, in Head Specific MM-MIMO, we firstly extract the modality-specific feature maps $\{M_1, M_2, M_3, M_f\}$ from the inputs $\{X_1, X_2, X_3, X_f\}$ by using a single CNN block given by Equation (2).

$$M_i = CONV(X_i) \tag{2}$$

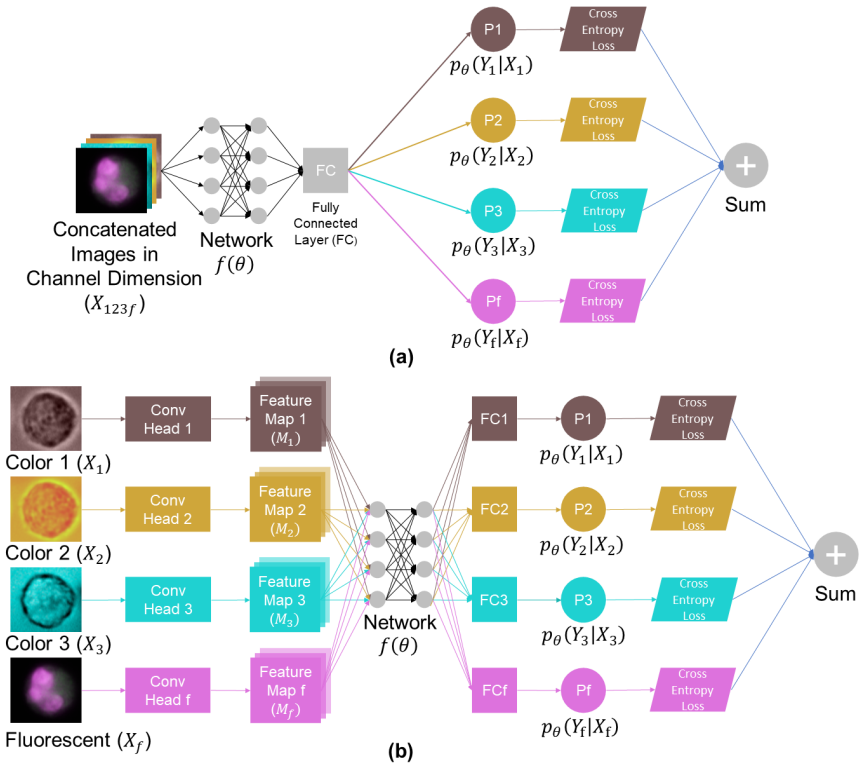

Figure 4: Our developed approaches (a): Multimodal MIMO - Adapted MIMO architecture for multimodal input; (b): Head Specific Multimodal MIMO - Multimodal MIMO with independent convolution heads and fully connected heads

Later, we concatenate the feature maps of all the four modalities to M_{123f} in the channel dimension and pass it to a single network. And finally, the end part of Head Specific MM-MIMO consists of modality specific separated heads with each head made up of one fully connected (linear) layer that outputs to the number of classes and we train it with the same strategy of MM-MIMO using corresponding ground truth labels $\{Y_1, Y_2, Y_3, Y_f\}$. To keep the Head Specific MM-MIMO efficient, the head specific CNN block is the first CNN block of the ShuffleNetV2 network and the head specific fully connected layer is the ShuffleNetV2 fully connected layer. The common module of the network is the ShuffleNetV2 network without its first CNN block.

5. Performance Results

In Table 1, we show the results of the individual network baselines for modality specific images. Since the fluorescent image has comparatively inferior features, it performs the worst amongst the four kinds of images. All the networks based on bright-field images perform better than that of the fluorescent image. We also note that the color3 image is

the best for leukocyte classification giving the highest accuracy of 95.72%, which is 1.78% better than that of fluorescent.

Table 1: Comparison of performance and network complexity for modality specific baselines

Light source	**Accuracy**	**FLOPs**	**Params**
Fluorescent	93.94±1.11	147.8M	1.259M
Color1	94.56±0.92	147.8M	1.259M
Color2	94.59±0.50	147.8M	1.259M
Color3	**95.72**±0.34	147.8M	1.259M

In Table 2, we show the results of our developed multimodal networks. Compared with the best individual baseline performance (Color3), all the multimodal networks perform better with the traditional ensemble giving the highest performance. This indicates that there are some diverse features which can be extracted from multimodal images. Although Ensemble performs the best, it has 4x times more parameters than that of a single baseline network. We can note that both our approaches MM-MIMO and Head Specific MM-MIMO give an increase in classification performance but have almost the same parameters as a single network. Specifically, for Head Specific MM-MIMO, we achieve 0.43% increase in accuracy with only 1.75% more parameters compared to a single baseline network.

Table 2: Comparison of performance and network complexity for our multimodal networks

Methods	**Accuracy**	**FLOPs**	**Params**
Ensemble	**96.33**±0.67	591.2M	5.035M
MM-MIMO (Ours1)	95.97±0.31	**172.2M**	**1.276M**
Head Specific MM-MIMO (Ours 2)	96.15±0.56	187.6M	1.281M

6. Conclusion

In this work, we present a novel way of classifying white blood cells (WBCs) based on multimodal images from fluorescence and bright-field light sources. Specifically, our dataset has three different bright-field image modalities and a single fluorescence based modality. We also propose an ensemble-free approach for our multimodal dataset, which attains an almost on par classification performance to that of a traditional ensemble but only has the computational complexity to that of a single network. We also develop two different configurations for the proposed ensemble-free approach, both of which perform better than the single baseline and have almost the same number of parameters. Our best configuration can achieve an accuracy of *96.15%* with only *1.28M* parameters. Thus, we believe that the proposed framework will also help to realize a Point-of-Care (POC) solution for leukocyte classification especially in resource poor settings.

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