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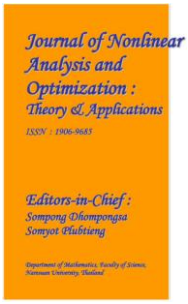

DEEP LEARNING MODELS FOR THE IDENTIFICATION OF BLOOD CANCER TYPES BY USING MICROSCOPIC IMAGES

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Abstract
The application of Mask R-CNN in deep learning models for cancer detection from microscopic images is noteworthy, as it leverages a Convolutional Neural Network (CNN) architecture derived from Faster R-CNN. Mask R-CNN excels in simultaneously detecting targets and performing semantic segmentation. However, empirical findings reveal that the model may not consistently excel in predicting intricate details of instances. This limitation can be attributed to the inherent characteristics of Mask R-CNN, particularly its scale-invariant fully Convolutional network structure. This design overlooks the disparities in spatial information across receptive fields of varying sizes. Notably, larger-scale receptive fields emphasize detailed information, while smaller-scale receptive fields prioritize semantic information. Consequently, the network may struggle to effectively capture the interpixel relationships at the edges of objects, leading to misclassification of these pixels.
Keywords: deep learning, R-CNN, Convolutional network

Introduction

Leukemia is a form of blood cancer originating in the blood and bone marrow, characterized by an overproduction of abnormal white blood cells, disrupting the normal production of red blood cells and platelets. Lymphoma, on the other hand, is a cancer affecting the lymphatic system, including lymph nodes, spleen, thymus gland, and bone marrow. It can manifest in various areas throughout the body, impacting the body's immune defense network[1]. Myeloma, or Multiple Myeloma (MM), is a cancer arising from plasma cells, a type of white blood cell. In healthy individuals, plasma cells produce antibodies to combat infections, but in MM, cancerous plasma cells accumulate in the bone marrow, displacing normal blood-forming cells and hindering the production of healthy blood cells. Instead of generating beneficial antibodies, these malignant cells produce abnormal proteins, leading to potential complications [2]. Multiple myeloma (MM) often presents challenges for early diagnosis due to a lack of initial symptoms. Common indicators may include bone pain, anemia, weakness, fatigue, weight loss, loss of appetite, upset stomach, constipation, confusion, frequent infections, severe thirst, and weakness or numbness in the arms and legs [3]. Factors contributing to the risk of the condition encompass obesity, exposure to radiation, a family history of the disease, advancing age, and exposure to specific chemicals. The diagnostic process entails conducting blood or urine tests, a bone marrow biopsy, and employing imaging techniques. Attaining remission is possible through the administration of steroids, chemotherapy, targeted therapy, and, in some cases, a stem cell transplant [4]. The ailment is manageable, yet fundamentally uncurable, and adopting remission strategies can help alleviate pain. Its onset is commonly observed around the age of 60, with a higher incidence among men [5]. Figure 2 illustrates the diagnostic and prognostic biomarkers utilized in predicting Multiple Myeloma (MM).

While a significant number of patients are identified in the early stages of the disease, the majority do not undergo treatment until they advance to overt myeloma. This stage is characterized by end-organ damage, including anemia, renal failure, lytic lesions, bone fractures, hypercalcemia, and manifestations associated with bone marrow failure [6].
Monoclonal gammopathy, a complex spectrum of clinical variants, spans from the relatively benign Monoclonal Gammopathy of Uncertain Significance (MGUS) and the indolent Smoldering/Indolent Multiple Myeloma (SMM) to the more aggressive, disseminated forms of Multiple Myeloma (MM) and Plasma Cell Leukemia [7]. The landscape has transformed with the advent of potent proteasome inhibitors like bortezomib and carfilzomib, as well as immunomodulatory drugs, heralding a new era in the management of these conditions. Over the last two decades, the use of Immunomodulatory Drugs (IMiDs) like lenalidomide has contributed to a notable improvement in overall survival (OS) for multiple myeloma (MM), with an increase from 3 to 6 years. However, despite these advancements, relapses remain a common occurrence in the treatment of MM [8]. In order to enhance the risk stratification of multiple myeloma (MM) patients for prognosis and therapy selection, there is a demand for novel approaches, as the current management tends to be uniform irrespective of individual risk factors [9]. Traditional algorithms for predicting and treating malignant melanoma (MM) were conventionally executed manually by skilled professionals, consuming significant time and often yielding results with considerable misdiagnosis or classification errors in determining the need for intensive treatment based on the high or low risk of MM [10].

In recent times, the integration of AI has brought significant enhancements across various facets of healthcare, ranging from diagnostics to treatment [11]. Within the realm of AI, Machine Learning (ML) and Deep Learning (DL) models have played pivotal roles in advancing disease prediction, particularly in the case of MM. ML endeavors to recognize correlations within data by employing numerical algorithms to decipher intricate patterns, thereby facilitating the automation of tasks involved in generating new hypotheses [12]. Machine learning algorithms, such as Support Vector Machines (SVMs), Genetic Algorithms (GAs), K-Nearest Neighbors (KNN), Random Forests (RF), Naive Bayes (NB), Artificial Neural Networks (ANNs), Decision Trees (DT), Bayesian Networks (BNs), and others, are commonly employed in cancer research for developing predictive models that enhance decision-making accuracy [13]. Nonetheless, the task of extracting valuable information from extensive databases poses a significant challenge for these ML algorithms. Furthermore, the computational complexity associated with ML approaches requires careful feature selection prior to training. Deep Learning (DL), a subset of Machine Learning (ML), has demonstrated success across diverse fields such as computer vision, speech recognition, and natural language processing. It has proven valuable in aiding medical professionals by assisting in diagnostic processes and identifying various chronic conditions [14]. DL models contribute to enhanced accuracy in diagnosing, prognosing, and determining treatment responses by rapidly analyzing significant and distinctive features present in relevant medical data. Convolutional Neural Networks (CNNs), Recurrent Neural Networks (RNNs), Long-Short Term Memory (LSTM) networks, Deep Belief Networks (DBNs), and other DL models play a crucial role in providing patients with multiple myeloma (MM) with quantifiable assessments [15].
Deep learning models have proven valuable in facilitating automated prediction and decision-making based on the vast datasets available in healthcare institutions. In the realm of Multiple Myeloma (MM), various deep learning frameworks have been developed to predict and categorize different types of MM. While significant progress has been made in the diagnosis and prognosis of MM, the precise approach to prevent MM remains elusive due to the absence of accompanying symptoms [16]. A novel deep learning approach, as presented in [17], has been introduced for the automated detection of whole-body bone lesions in multiple myeloma (MM) using a 3D methodology. This method effectively combines positron emission tomography (PET) and computed tomography (CT) features, leveraging both anatomical and molecular information derived from 68Ga-Pentixa PET/CT imaging. The utilization of digital phantoms and actual PET scans from MM patients enabled the extraction and learning of features from the datasets. The proposed method employs two convolutional neural

network (CNN) models, namely V-Net and W-Net, to perform segmentation and detection of MM lesions. These CNN models seamlessly integrate information from multimodal imaging, facilitating the identification of intermodality features crucial for accurate MM detection. The detection of multiple myeloma (MM) was addressed in a study [18] where a Deep Learning (DL) model was developed. This model incorporated Mask-Region Convolutional Neural Network (RCNN) and U-Net architectures for the segmentation of myeloma cells within bone marrow aspirate slides. The annotation of myeloma cell polygons was conducted on collected datasets through the VGG Image Annotation software. Subsequently, a Convolutional Neural Network (CNN) model was utilized for the purpose of MM detection. Another research [19] presented a CNN-based approach for the automatic detection of both Acute Lymphoblastic Leukemia (ALL) and MM in bone marrow microscopic images. The gathered datasets underwent augmentation through an edge detection model, involving rotation and extraction of edges from the images. Subsequently, feature selection was executed using the K-Means Clustering (KMC) algorithm. Finally, the prediction of ALL or MM was carried out using an optimized CNN model. The mentioned proposed models exhibit limitations such as susceptibility to overfitting when applied to extensive datasets. This research investigates challenges in blood cancer detection using deep learning methods and emphasizes addressing these issues by introducing novel approaches for more effective blood cancer detection solutions.

Problem Description

In the absence of data augmentation, the risk of overfitting increases, posing challenges for the model to effectively generalize to unseen examples beyond the training set. To address this issue, artificial expansion of the dataset can be achieved by applying diverse techniques to manipulate images. In [19], two specific methods were employed for data augmentation. The initial approach involves rotating images by 90 degrees to ensure the model's ability to recognize objects in various orientations. Subsequently, another technique is applied, which filters the image to produce an output containing only its edges or boundaries. Despite these modifications, the fundamental characteristics of the generated images using these techniques remain consistent. Consequently, these methods do not significantly enhance the diversity of the data. Designing an efficient Dense Convolutional Neural Network (DCNN), as discussed in [19], poses numerous challenges, particularly in the selection of layers and connections. These choices significantly impact the accuracy of trained networks, making it difficult to predict the optimal combination a priori. The effectiveness of a DCNN is largely attributed to its specific network architecture, determined by assigning values to numerous hyper-parameters, each influencing the resulting error rate. However, searching for optimal hyper-parameter values is a demanding task typically performed manually, requiring a substantial amount of effort.

Research Objectives

The primary goal is to safeguard the structural details within microscopy images to enhance blood cancer detection. This involves the introduction of a Resolution Enhanced and Noise Suppression Generative Adversarial Network (GAN) designed to produce high-fidelity microscopic images. In response to the shortcomings observed in the Mask R-CNN-based segmentation method, a novel attention mechanism and innovative semantic feature fusion methods are put forth to elevate segmentation accuracy. To address the performance challenges and inherent issues within Deep Convolutional Neural Networks (DCNN), a pioneering swarm intelligence optimization approach is applied to determine hyperparameters for the deep learning structure of the classifier dedicated to blood cancer detection.

Research Contribution

First contribution

Deep Learning (DL) architectures, particularly deep generative models like Generative Adversarial Networks (GANs), serve as a compelling alternative to address the challenge of limited data availability by creating synthetic samples that mimic the probability distribution of actual data. In the realm of computer vision, the advancements in GANs have paved the way for researchers to offer effective solutions in the domain of data augmentation. Numerous iterations of GANs have been

developed for diverse image augmentation tasks. Nevertheless, a notable limitation is that many GAN-based methods struggle to generate images that maintain consistency with their intrinsic structural information. In the initial stage of our research, we advocate the development of a novel Generative Adversarial Network (GAN) specifically designed for the generation of microscopic images depicting both normal and cancerous lymphocytes. This proposed model, termed Resolution Enhanced and Noise Suppression GAN (RENS-GAN), focuses on enhancing image resolution by directly utilizing directional view images as input. Within the GAN framework, the generator component undertakes the task of regressing high-resolution outputs based on low-resolution input images. Concurrently, the discriminator's role is to differentiate between the original microscopic images and those generated by the RENS-GAN. This dual functionality ensures the production of images with improved resolution while effectively suppressing noise in the generated microscopic lymphocyte images. In the generator component, we employ a series of consecutive residual blocks along with content loss to reconstruct a photo-realistic version of the original image. This process effectively restores edges and boosts resolution by factors of X2, X4, and even X8, all while maintaining high image quality.

The GAN introduces a novel method called Stochastic Variance Reduced Extra Gradient (SVRE) in which variance reduction and extrapolation are combined to effectively mitigate noise. This is achieved through a mutual game between the generator and discriminator networks, supplemented by additional training from the feature extractor network. The generator network is designed to perform a direct mapping from the noisy image domain to the noise-free image domain. Moreover, a new joint loss function is crafted to integrate information from image features and human visual perception into the task of mixed noise elimination, leading to improved image quality and visual effects. In another context, an optimized Dense Convolutional Neural Network (DCNN) from reference [19] is employed for the classification of blood cancer types. The proposed deep learning model for myocardial infarction (MI) detection is referred to as the Deep Blood Cancer Detection network (DeepBCDnet).

Second Contribution

In the second phase of the research, enhancements were made to the Mask R-CNN model through the incorporation of a bottom-up structure and attention mechanisms, facilitating the integration of deep semantic and shallow high-resolution features in both the Region Proposal Network (RPN) and Region of Interest (RoI) layers. This novel approach proves effective in accurately detecting and segmenting microscopic images at the pixel level. The introduction of a bottom-up structure within the Feature Pyramid Network (FPN) framework of Mask R-CNN serves to shorten the path between lower layers and the topmost layer. This optimization allows for more efficient utilization of lower layer features at the higher layers. Within the bottom-up structure, a channel-wise attention mechanism is implemented to assign weights to each channel, while a spatial attention mechanism assigns corresponding weights to each pixel in the feature maps. Furthermore, the original fully convolutional layer is replaced with an innovative semantic segmentation layer, which achieves feature fusion by constructing an FPN and summing the forward and backward transmissions of feature maps at the same resolution. This comprehensive approach results in improved performance and robustness in the detection and segmentation of microscopic images.

Third Contribution

The efficacy of a classifier primarily hinges on a specific network architecture, crafted by assigning values to numerous hyperparameters, each exerting influence on the resulting error rate. However, the quest for optimal hyperparameter values is a formidable undertaking, typically carried out manually and requiring a significant investment of effort. The hyperparameter optimization of Deep Convolutional Neural Networks (DCNN) is bolstered by the integration of the Osprey Optimization Algorithm (OOA). Addressing the inherent challenges of a combinatorial optimization problem, OOA offers solutions categorized into exact methods and heuristics. In this context, OOA serves as a meta-heuristic to pinpoint the optimal hyperparameters for DCNN, thereby enhancing the accuracy of lung disease detection. OOA stands out as a novel, nature-inspired meta-heuristic optimizer.

The foundational concept behind OOA draws inspiration from the hunting strategy employed by ospreys when capturing fish from the seas. Similar to this hunting approach, OOA operates as a random population optimization algorithm. However, challenges arise, particularly in managing population

diversity and avoiding local optima when confronted with a high number of parameters. The research introduces the Optimized Deep Blood Cancer Segmentation and Detection network (ODeepBCSDnet) as a solution to these challenges. The comprehensive flow of the proposed work is illustrated in Figure 1.

Dataset Description and Software Details

Acute Lymphoblastic Leukemia (ALL) image dataset

The accurate diagnosis of acute lymphoblastic leukemia (ALL), a widely prevalent cancer, typically involves invasive, costly, and time-intensive diagnostic procedures. Peripheral blood smear (PBS) image analysis serves as a crucial component in the initial cancer screening process, distinguishing between cancer and non-cancer cases [20]. However, the assessment of these PBS images by laboratory professionals is fraught with challenges, including diagnostic errors. The non-specific nature of ALL signs and symptoms often contributes to misdiagnosis during this examination.

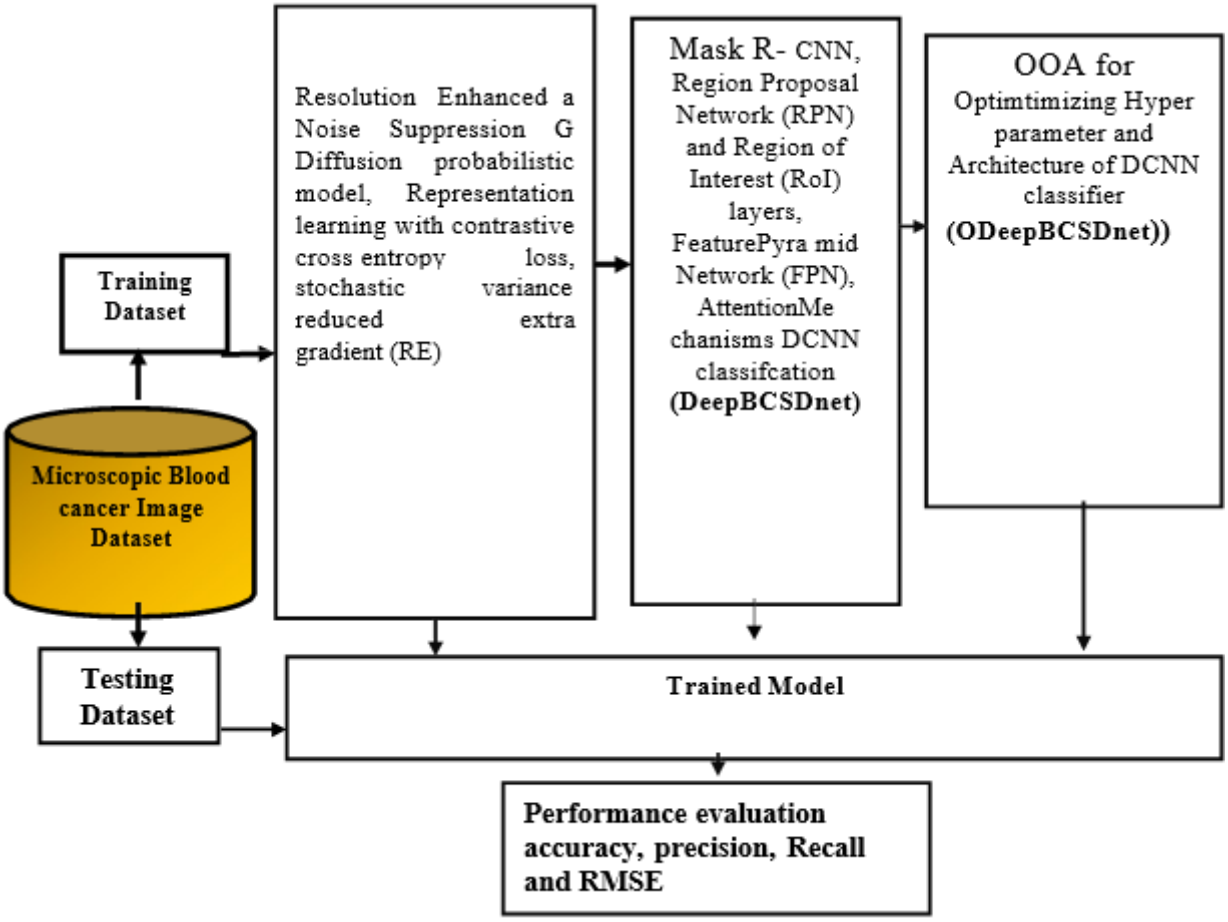

Figure.1. Methodology flow of the proposed modules

The dataset encompasses 3256 Peripheral Blood Smear (PBS) images derived from blood samples of 89 individuals suspected of Acute Lymphoblastic Leukemia (ALL), meticulously prepared and stained by proficient laboratory personnel at Taleqani Hospital in Tehran, Iran. These images are categorized into two classes: benign, represented by hematogones, and malignant, comprising three subtypes of ALL lymphoblasts—Early Pre-B, Pre-B, and Pro-B. Captured through a Zeiss camera at 100x magnification, all images are stored in JPG format. The definitive determination of cell types and subtypes was performed by a specialist using flow cytometry. Additionally, the dataset includes segmented images obtained through color thresholding-based segmentation in the HSV color space.

SN-AM Dataset: White Blood cancer dataset of B-ALL and MM for stain normalization (SN-AM)

Microscopic images were obtained from bone marrow aspirate slides of patients who had been diagnosed with B-lineage Acute Lymphoid Leukemia (B-ALL) and Multiple Myeloma (MM),

following standard guidelines [21]. The slides were stained using Jenner-Giemsa stain, and imaging was conducted at 1000x magnification using a Nikon Eclipse-200 microscope equipped with a digital camera. The images were captured in raw BMP format with a resolution of 2560x1920 pixels. The dataset comprises a total of 90 images of B-ALL and 100 images of MM. Notably, both MM and B-ALL images exhibit significant variability from one instance to another, providing a robust testing ground for any developed stain normalization methodology.

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