AUTOMATIC DIAGNOSIS OF BREAST CANCER IN HISTOLOGY IMAGES USING DEEP CONVOLUTIONAL NEURAL NETWORKS

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ABSTRACT: Breast Cancer Disease is one of the most common diagnosed cancer in women, which accounts for 523,000 deaths each year. Traditionally, the current routine Breast Cancer diagnosis is performed manually by the visualization of the tissues samples which obtained from the patient biopsy. However, due to the large amount of data and complexity of the images due to the morphological appearances, molecular structures, behavior and response to therapy makes this task more time consuming. Histology image which contains morphological information and the biological characteristics of the cancer cells has been proven to effectively generate more valuable information for the breast cancer diagnosis. Hence, automatic diagnosis of Breast Cancer using histology images is essential for early detection of the cancer risk in order to provide more suitable medical treatment planning and prevent the potential of having malignant cancer. This paper presents a framework for automatic diagnosis of Breast Cancer in histology images based on Deep Convolutional Neural Networks. Specifically, we employed CNNs as a feature extractor and applied transfer learning technique to fine-tune the network to generate deep and more discriminative features hidden in the image. Due to the large difference between natural images and medical images, CNNs model which was previously trained on a large-scale natural image dataset was fine-tuned (i.e. transfer learning) to update the previous-learned weights to adapt with the specific task of medical images of breast cancer. Moreover, we present a new method to effectively generate more images to train for the CNNs model and compare with the most commonly used traditional data augmentation method. The dataset includes 400 microscopy images which collected from the ICIAR 2018 Grand Challenge on Breast Cancer histology images. We classify the images into 4 groups which indicates the aggressiveness cancerous levels labeled as normal, benign, in situ carcinoma or invasive carcinoma according to the predominant cancer type in each image. We used 70% of the image dataset to train our model, 10% for validation and 20% used for testing. Our experiments results show that our method can achieve a very high classification accuracy with 80% in distinguishing 4 types of cancer classes and 87.5% for differentiating carcinoma with non-carcinoma.

Keywords: Breast Cancer, Histology Images, Microscopy Images, Deep Convolutional Neural Networks (CNNs).

I. INTRODUCTION

Breast cancer is one of the most common leading cause of death in women according to the World Cancer Report [1], which accounts for 523,000 deaths each year and morbidity is ranked at second place after lung cancer. Early clinical diagnosis and prognosis of breast cancer followed with a proper treatment planning could help to prolong the patient's life. Among several medical imaging techniques, e.g., Computed Tomography, Magnetic Resonance, and Mammography for identifying the breast cancer, Hematoxylin and Eosin (H&E) histopathological slides of breast tissue is considered as a gold standard for prognosis. Specifically, H&E stained the biopsy samples of breast tissue purple and pinkish under the microscopes for primary diagnosis of breast cancer. Hereby, pathologists can accurately identify the presence and type of lesion in order to provide a proper medical treatment therapy. However, manual classification of breast cancer in histopathological images remains challenging due to some limitations. The classification examination requires professional background, rich experiences and expertise of pathologists, which can cause the high-cost and time-consuming or even misdiagnosis. Hence, an automated Computer-Aided Diagnosis (CAD) of breast cancer from H&E histopathological images is essential and high demanded for clinical diagnosis and prognosis, which aims to reduce the heavy workloads and avoids misdiagnosis of pathologists [2, 3, 4].

In recent years, there have been various dedicated approaches proposed for breast cancer classification. Conventional approaches mainly focused on the feature engineering followed by a classifier to classify the extracted features into different classes of breast cancer. These features can be hand-crafted features or feature descriptors, e.g., scale-invariant feature transform (SIFT) [5], gray level co-occurrence matrix (GMCL) [6], histogram of oriented gradient (HOG) [7], etc. Zhang et al. used hand-crafted features and applied Principal Component Analysis (PCA) to classify benign and malignant of breast cancer and reach an accuracy of 92% [8]. Spanhol et al. [9] applied machine learning methods for breast cancer classification based on the means of different feature descriptors and obtained accuracy of 80~85%. Wang et al. used 138 textual feature descriptors followed with an SVM binary classifier [10]. Despite feature engineering-based methods obtained a proper accuracy in breast cancer classification, such task requires extensive pre-processing, region of interests (ROI) segmentation and manual extraction, which is heuristics and human-dependent. Moreover, the hand-crafted features or feature descriptors are considered as low-level feature or unrepresentative surface features which cannot capture all the valuable information hidden in the image, e.g., morphological information, cell tissues structural information.

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Figure 1. Examples of microscopy image patches from BACH. (a) normal tissue; (b) benign abnormality; (c) malignant carcinoma *in situ*; (d) malignant invasive carcinoma. Normal and Benign classes are grouped as non-carcinoma class while (c) and (d) are grouped as carcinoma class.

Convolutional neural networks (CNN) have been demonstrated to exceed human performance in many computer vision tasks. Many CNNs model have been adopted for biomedical image classification including AlexNet [11], ResNet [12], Inception [13], Inception-V4 and Inception-ResNet [14]. Jaffar proposed to use CNN model to classify the mamogram-image and obtained out-standing results with an accuracy of 93.95% and AUC of 0.93. Qiu et al. [15] used CNN classifier to predict short-term breast cancer risk and achieved an average accuracy of 71.4%. Ertosun and Rubin [16] utilized CNN to visually search for masses as well as breast cancer classification and obtained an accuracy of 85%. Qui et al. [17] utilized CNN to classify benign and malignant cancer in the mammogram images. Similarly, in the same task, Jiao et al. [18] obtained an accuracy of 96.7%. Sahiner et al. [19] applied CNN classifier with spatial domain and texture images to classify mammogram images and achieved an ROC score of 0.87. Jadoon et al. classified three classes Mammogram which includes normal, benign, and malignant based on Descriptive CNN Features [20]. Araujo et al. utilized CNN to classify classes in 2 clinical important tasks: 1) Distinguishing 4 classes of Normal tissue, Benign tissue, In situ carcinoma, and Invasive carcinoma (as illustrated in Fig.1) and; 2) Differentiating 2 classes of carcinoma and non-carcinoma. For each task, they achieved an accuracy of 77.8% and 83.3%, respectively [21]. Spanhol et al. introduced an public dataset contains of 7909 breast cancer histopathology images and utilized CNN to classify the images into benign and malignant images and achieved some preliminary results ranges from 80 to 85% [22].

Inspired by above mentioned deep learning based breast cancer classification, we propose to use Inception-V3 [13] in our study. These images are classified into four classes of normal tissue (NT), benign tumor (BT), in-situ carcinoma (IS) and invasive carcinoma (IC). In this paper, we divide the task of breast cancer classification into 2 different clinical important tasks: 1) Differentiating between normal tissue (NT), benign tumor (BT), in-situ carcinoma (IS) and invasive carcinoma (IC) and; 2) Distinguishing non-carcinoma (normal tissue + benign tumor) with carcinoma class (in-situ carcinoma + invasive carcinoma). We mainly explore 3 critical factors which include data augmentation methods, stained image normalization and different classifiers. First, data augmentation is a crucial step for training a CNN model, in which CNN is able to capture more valuable information of the image, the more numbers of data generated the more robust of the classifier. We employed 2 strategies to generate more images in which our proposed augmentation strategy which preserves the morphological structural information achieved a better performance than the other strategy. Second, due to the large variations and differences in image color responses of the stained images according to slide scanners, and techniques of stain vendors or protocols. Experimental results show that the accuracy of training with stain normalized images achieves a higher accuracy than non-normalized ones. Third, for classification we compared softmax with the popular and most adopted Support Vector Machine (SVM) classifier. Our contributions can be summarized as follows:

- Our proposed image augmentation strategy which preserves the morphological information of the cell structural information could generate more valuable and representative images for the training, resulting in a more robust to data variations of the CNN classification model.
- We demonstrated that histology images with a normalization step to reduce the inhomogeneity of image color response yields a more accurate classification result compared with non-normalized ones.
- Our experimental results suggest that softmax classifier is more effective for high-dimensional feature analysis compared with SVM classifier.

Our paper is organized as follows. Section 2 describes the method for breast cancer classification. Section 3 presents the experimental results including dataset, experiments set up and results. Finally, section 4 is the conclusion of our paper.

II. METHOD

A. Data preparation

1. Image stain normalization



Figure 2. Histology image normalization. (a) Original image; (b) Normalized image

Due to differences of slide scanners, materials, techniques of stain vendors and protocols, histology image colors appear inhomogeneity among different images. Normalization is the crucial step for histological stained image for further processing and conducting any analysis. Prior to analysis, we employed stain normalization method described in [24] which consider the staining technique used for image preparation to normalize our images dataset. Specifically, logarithmic transformation is applied on the original images to convert the colors into optical density (OD). Then, a singular value decomposition (SVD) is calculated on the transformed OD and the higher variance is used to find the 2D projections. This 2D projections is then applied to the original image followed with the stretching of image histogram. Fig. 2 illustrates the effect of stain normalization of an example slide our collected dataset using the stain normalization technique. Algorithm of the method is described in the pseudo code.

Pseudo code: Stain normalization method for breast cancer images

Program stain_normalization(output)

Input: I: Breast cancer Image

Output: I_nor: Optimal Stain Vectors

```
1. Calculate OD = -log10(I) //Convert RGB to OD
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2. Threshold OD with \beta (\beta=0.15)
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3. Calculate single-value-decomposition (SVD) on the OD transformed pixels
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- 4. **Create** plane from the calculated two largest singular values of SVD directions corresponding.
- 5. **Project** OD transformed pixels onto the plane, and normalize to unit length

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6. Calculate angle of each point with respect to the first SVD direction
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- 7. Find robust extremes $(\alpha^{th} \text{ and } (100-\alpha)^{th} \text{ percentiles})$ of the angle
- 8. **Convert** extreme values back to OD space
- 2. Data augmentation for CNN training

The training of CNN requires a large number of labeling images. Such requirement may be difficult to meet in the medical domain due to the high-cost and time-consuming of manual labeling annotation. The most commonly adopted method used for increasing the amount number of images is linear transformation (e.g. random cropping, rotating, flipping and mirroring). Histology images which visualize the structures of cells and tissues captures valuable morphological information which is useful for the classification. Any non-linear method for image augmentation can lead to the loss of such information. Therefore, we attempt to generate images by applying linear transformation augmentation method, which denoted at AUG_1. First, the original image with a size of 2048×1536 is scaled to 397 x 299 (4:3 scale). To ensure the generated images capture most of the information of the image, the scaled image is cropped into 2 overlapped images with the same size of 299 x 299 (one from the left and one from the right), as illustrated in Fig. 3. The reason for this scale selection is that Inception-V3 requires the input image size of 299x299. Each image is then rotated, flipped, and mirrored to generate 7 images. As a result, 400 original images are augmented to 6400 images. 70% of the images are used for training and the remaining 10% and 20% used for validation and testing. The other method where the original image is simply rescaled from 4:3 to 1:1, then flipped and rotated is denoted as AUG_2. Since AUG_2 change the scale of the original image, it distorts the structure of the cell and tissue appeared in the image. It can also be considered as one of the non-linear transformation data augmentation methods. We will compare these two methods in the experiment to demonstrate the importance of preserving the morphological information in generating images used for training.



Figure 3. Example of our proposed data augmentation method. A original image; B black-color box cropped from A; C orange-color box cropped from A

B. Fine-tuning GoogleNet Inception_V3

Due to the limitation of images in medical domain, transfer learning or fine-tuning the pretrained CNN model using a small number of medical images is an efficient way to enable the network to learn features specific of different specific tasks in medical image processing. Tajbakhsh et al. [25] conducted several experiments on medical image dataset to investigate the impact of fully training and fine-tuning the CNN models. Their experiment results showed that fine-tuning a pre-trained CNN can lead to an incremental performance. Specifically, the weights of the pre-trained modeled which previously trained on a large scale of natural image dataset (e.g. ImageNet) are subsequently updated during the fine-tuning process. Inception-V3 is employed in our study to learn the discriminative features hidden in the image which can be beneficial for the classification performance. The Inception-V3 network employs factorized inception modules, allowing the network to choose suitable kernel sizes for the convolution layers and enable the network to learn both low-level features with small convolutions and high-level features with larger ones. The layout of Inception-V3 is given in table 1, interested readers can refer to [13] for more technical details about the network structure.

We modified the softmax classifier to be able to predict 4 classes instead of 1000 classes in the original architecture and fine-tuned the last layer fully connected layer of the Inception-V3. The model was trained with Stochastic Gradient Descent with a batch size of 128, and iterations of 5000. Learning rate and momentum was set at 10^{-4} and 0.9, respectively.



Figure 4. Inception modules . (a) 3 x Inception; (b) 5 x Inception; and (c) 2 x Inception

Туре	Patch size/Stride	Input size
conv	3×3/2	229×229×3
conv	3×3/1	149×149×32
conv padded	3×3/1	147×147×32
pool	3×3/2	147×147×64
conv	3×3/1	73×73×64
conv	3×3/2	71×71×80
conv	3×3/1	35×35×192
3 inceptions	as in Fig. 4 (a)	35×35×288
5 inceptions	as in Fig. 4 (b)	17×17×768
2 inceptions	as in Fig. 4 (c)	8×8×1280
pool	8×8	8×8×2048
linear	logits	1×1×2048
softmax	classifier	$1 \times 1 \times 4$ (4 classes) or
		$1 \times 1 \times 2$ (2 classes)

Table 1. Layout of Inception-V3 [13]

III. EXPERIMENTAL RESULTS

A. Dataset

The dataset used in this study is collected from the public dataset of ICIAR 2018 Grand Challenge on BreAst Cancer Histology (BACH) images [23]. This dataset comprises of 400 RGB microscopy images in .tiff format with a pixel scale of 0.42 μ m × 0.42 μ m. Images provided with a high-resolution (2048 x 1536) and labeled as normal, benign, in situ carcinoma and invasive carcinoma, each class contains of 100 images. All images were digitized using the same acquisition conditions, with a magnification of 200×. Two pathologists performed the labeling annotation without specifying the region of interest for the classification and images with disagreement were discarded.

B. Experiment designs

In this section, we conduct 3 experiment to explore the most critical 3 factors that most impact to the final classification of breast cancer. Noticeably, the training and testing dataset remains the same in all the experiments. Table 2 present the 3 conducted experiment. For each experiment, we select the factor which yield better result in each factor and apply in the next experiment. We implement these 3 experiments on the task of differentiating between normal tissue, benign tumor, in-situ carcinoma and invasive carcinoma. The selected factors are directly applied on the task of distinguishing non-carcinoma with carcinoma.

Experiments	Comparison		Classifers	Selection for next experiment
1	Linear transformation	Non-linear transformation	softmax	Linear transformation
2	Normalized images	Non-normalized images	softmax	Normalized
3	softmax	SVM	softmax vs. SVM	softmax

Table 2. 3 conducted experiment designs for breast cancer classification

C. Experimental results

Table 3. Results from 3 conducted experiments for the task of differentiating 4 classes of breast cancer.

Experiments	Methods			Patch-wise	Image-wise
I · · · ·				accuracy (%)	accuracy (%)
1	AUG_1	Normalized	softmax	74	80
1	AUG_2	Normalized	softmax	69.06	75.0
2	AUG_1	Normalized	softmax	74	80
	AUG_1	Non-normalized	softmax	73.2	76.25
3	AUG_1	Normalized	softmax	74	80
	AUG 1	Normalized	SVM	72.6	76.25

Table 4. Results for distinguishing non-carcinoma with carcinoma class of breast cancer

Methods			Patch-wise accuracy (%)	Image-wise accuracy (%)
AUG_1	normalized	softmax	82.27	87.5

Table 3 summarizes the results from 3 conducted experiments performed for the task of differentiating 4 classes of breast cancer. The best performance achieved with an accuracy of 80% with the use of the selected factors which are AUG_1, Normalized, and Softmax. We used this configuration for the task of distinguishing non-carcinoma with carcinoma class of breast cancer and achieved an accuracy of 87.5%, as shown in Table 4.

IV. CONCLUSIONS

This paper presents an automated diagnosis method of Breast Cancer in histology images based on Deep Convolutional Neural Networks. Several experiments have been conducted to explore some critical factors which have the most impact on the final classification. First, we found that different data augmentation methods have different impacts on the prediction of the model. The selection of augmentation method should be in consideration with different specific tasks to ensure that the generated images are meaningful and representative. In our paper, linear transformation achieved a better performance since it can mostly preserve the structural information of cells and tissues. Second, images should be normalized before training to reduce the inhomogeneity of image color response to make the model learn more effectively. Finally, the classification performance using softmax is better than the popular SVM classifier. Although there are still remaining many factors that could impact the classification performance. We only introduced only 3 most important factors which are essential for training any CNN model. Our work is the preliminary work for breast cancer classification based on deep learning and this domain still have a large space to improve. Our future work includes the employment of different architectures of CNN models and fully explores more critical factors which greatly impact the classification performance.

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CHẨN ĐOÁN UNG THƯ VÚ TỰ ĐỘNG THÔNG QUA ẢNH MÔ HỌC BẰNG MẠNG NƠ-RON TÍCH CHẬP SÂU

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TÓM TẮT: Ung thư vú hiện đang là một trong những căn bệnh ung thự phổ biến nhất ở phu nữ, chiu trách nhiệm cho khoảng 523 nghìn ca tử vong mỗi năm. Theo cách truyền thống, Ung thu vú được chấn đoán thông qua xem xét các mẫu tế bào sinh thiết của bệnh nhân. Tuy nhiên, với lượng lớn dữ liệu phức tạp có hình thái, cấu trúc phân tử, phản ứng đối với việc trị liệu khác nhau khiến việc này rất mất thời gian. Ảnh mô học chứa thông tin hình thái và các thuộc tính sinh học của tế bào ung thư đã được chứng minh là hữu ích hơn cho việc chẩn đoán ung thư vú. Do đó, chẩn đoán Ung thư vú tự động dùng ảnh mô học là rất cấp thiết cho việc phát hiện nguy cơ ung thư từ sớm nhằm đưa ra phác đồ điều trị hiệu quả hơn, từ đó ngăn chặn ung thư ác tính. Bài báo này cung cấp công cụ chẩn đoán Ung thư vú thông qua ảnh mô học dùng DCNN. Đặc biệt, chúng tôi dùng các CNN như một công cụ trích xuất đặc trưng và ứng dụng kĩ thuật huấn luyện trung gian (transfer learning) để tinh chỉnh mạng sâu và chứa nhiều đặc trưng ẩn trong ảnh đầu vào. Do có sự khác nhau giữa ảnh thông thường và ảnh y học, các mô hình CNN đã được huấn luyên trên tập dữ liệu ảnh thông thường được tinh chỉnh (thông qua transfer learning) để cập nhật các trọng số phù hợp với tác vụ đề ra. Ngoài ra, chúng tôi cũng đưa ra một phương thức mới để tăng cường dữ liệu cho việc huấn luyện các mô hình CNN và so sánh với các phương thức tăng cường truyền thống. Tập dữ liêu gồm 400 ảnh soi hiển vi thu thập từ cuộc thi ICIAR 2018 Grand Challenge on Breast Cancer. Sau đó chúng tôi phân loại ảnh thành 4 nhóm mức độ xâm lần của ung thư gồm bình thường (normal), lành tính (benign), carcinom tại chỗ (in situ carcinoma), và carcinom xâm lấn (invasive carcinoma) dựa theo loại ung thu chiếm ưu thế trên mỗi ảnh. Chúng tôi dùng 70 % ảnh để huấn luyện mô hình, 10 % để xác thực (validate) và 20% để kiểm thử (test). Kết quả thí nghiệm đạt được độ chính xác 80 % với phân loại 4 nhóm bệnh Ung thư và 87.5 % với phân loại ung thư hoặc không ung thư.

Keywords: Breast Cancer, Histology Images, Microscopy Images, Deep Convolutional Neural Networks (CNNs).