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Analysis of Histopathological Images for Prediction of Breast Cancer Using Traditional Classifiers with Pre-Trained CNN

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Abstract

Breast cancer is one of the most commonly found and dangerous cancer among women which leads to a major research topic in medical science. Most of the times, it is identified by using a biopsy method where tissue is removed and studied under a microscope. If a histopathologist is not well trained then this may lead to the wrong diagnosis. In order to facilitate better diagnosis, automatic analysis of histopathology images can help pathologists to identify malignant tumors and cancer subtypes. Recently, Convolutional Neural Networks (CNNs) have become preferred deep learning approaches for breast cancer classification and detection. In this research, two machine learning approaches i.e. Support Vector Machine (SVM) and Logistic Regression (LR) are used for comparative analysis. This paper mainly focuses on leveraging pre-trained (CNN) activation features on traditional classifiers to perform automatic classification of breast cancer images. For this purpose, a two-phase model has been proposed for automatic classification on the basis of magnification subsequently classify the samples for benign and malignant. This model is trained separately with respect to various image magnifications (40x, 100x, 200x and 400x). In this study, the dataset is partitioned into the following fashion: 80% for the training phase and 20% for testing phase The performance is analyzed by using Accuracy, Precision, Recall and F1-score in order to find out the best-suited model that can be used for automation system. The experimental results demonstrate that ResNet50 network has achieved maximum accuracy for LR in comparison to SVM in magnification factor. In addition, results show that the performance of CNN +LR is slightly better than CNN +SVM for classification of benign and malignant classes. The proposed model helps in extracting more accurate image features and significantly improves the overall accuracy of classification.

Keywords: Breast Cancer; Histopathology; Machine learning; Convolutional Neural Network (CNN); Support Vector Machine (SVM); Logistic Regression (LR)

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1. Introduction

Cancer is a type of disease that causes a change of cells in a body and rapidly spreads out of control in the body. One common variant of cancer is Breast Cancer. According to the World Health Organisation, Breast cancer is one of the most frequently diagnosed and life-threatening cancer among women which affects 2.1 million women per year. In 2018, approximately 627,000 women have died from this cancer which is approximately 15% of overall cancer deaths among women. The expected number of breast cancer patients will be more than 28 million in 2030[1][2].

Breast cancer develops from breast tissue identified by a lump in the breast and there are some changes in normal conditions. Breast cancer tumor can be categorized into two categories i.e Benign (Noncancerous) and Malignant (Cancerous). Various practicing methods have been used to detect breast cancer such as self-examination, Clinical examination, and screening tools which includes mammography. Detection of breast cancer might be a challenging job when it is said that it is not an individual disease but a combination of different diseases [3]. In Histopathology, a biopsy is a diagnostic method which can determine the cautious area is cancerous or not. The pathologist diagnosis is carried out by visual inspection of histopathological images under the microscope which is known to be the confirmatory gold standard for diagnosis[4].

Digital pathology image analysis often uses standard image recognition techniques but most of the techniques are replaced by deep learning methods used in ImageNet Large Scale Visual Recognition Competition (ILSVRC) 2012[5]. Various algorithms and investigation methods have been used by researchers to investigate breast cancer images from different perspectives depending on the disease demand, the status of the disease and the quality of the images [6][7]. In recent years, the use of deep learning architecture and more specifically Convolutional Neural Networks have become a major trend in computer-assisted medical image analysis**.**

The aim of this paper is to use Pre-trained CNNs on traditional classifier which automatically differentiates between healthy tissues and cancerous samples. For this purpose, a two-phase model is developed for the automated classification of histopathology images. In the first phase, a Pre-trained CNNs such as VGG16**,** VGG19, Xception and ResNet50 are used to extract features from histopathological images. In the second phase, these extracted features are used by machine learning methods i.e. Support vector machine (SVM) and Logistic Regression (LR) on different magnification factors (including 40x, 100x, 200x, and 400x).
CNN+SVM: refers to the SVM, with pre-trained CNN used as the fixed feature extractor.
CNN+LR: refers to the LR, with pre-trained CNN used as the fixed feature extractor.

More specifically, the contributions of this paper are as followings i) To propose a simple, efficient and effective model using CNN activation features for classification of histopathology images. ii) To compare the performance of the model on different magnification factor iii) To compare the performance of CNN+LR and CNN +SVM on magnification for binary and multi-class classification tasks.

The overall structure of this paper is divided into some sections. Section II shows a literature survey about related work. Section III gives an introduction about machine learning methods and combinations of a various classifier. Section IV shows statistics about Break his dataset including training and test samples. Section V discusses the proposed methodology, use of pre-trained CNN architectures and Model constructions. Section VI shows all the results obtained from the experiment.

2. Literature Survey

Several studies have been reported on breast cancer prediction. The studies from different approaches are applied to the given problem statement and showed high classification accuracies. Details of some of the previous research works are given in the following Table 1.

Table 1. Overview of papers dealing with Various methods and findings

Authors	Dataset	Methods	Findings	Accuracy
Myung Jaelin[8]	BreakHis	Transfer Learning, Data Augmentation, Data Pre-Processing, Data-Imbalance-Under sampling, applied on VGG16 and InceptionV3.	Binary Classification	98%
Dalal BarDau[9]	BreakHis	Approach-1 Extraction of a set of hand-crafted features was encoded by using two models i.e., Bag-of-words and Locality Constrained Linear Coding which was trained on SVM. Approach-2 Tested Data augmentation techniques to enhance the accuracy of CNN as well as "Handcrafted features +CNN" and "CNN Features + Classifier" The CNN is Custom Designed and traditional Classifier are K-NN, SVM and Random Forest.	Binary Classification Multi Classification	96.15% - 98.33% 83.31% – 88.23%
Neslihan Bayromoghu[10]	BreakHis	Designed Own CNN architecture for classification.	Magnification Benign and Malignant	77.3±5.91% - 83±8.54% 82.1±4.4% - 83.1±3.5%
Majid Nawaz[11]	BreakHis	Compared the results with LeNet, AlexNet and DenseNet.	Accuracy	95.4%
Zhongyi Han[12]	BreakHis	Compared the LeNet, AlexNet and CSDCNN with Raw Data and Augmented Data.	Accuracy	93.2%
Abdullah-Al Nahid[13]	BreakHis	Compared CNN, LSTM and CNN-LSTM Architecture using both softmax layer and SVM Classifier	Accuracy	91.00%
M. Jannesari [14]	TMA Database and BreakHis	Examined Different neural Networks such as Inception (V1, V2, V3 and V4) and ResNet (V1 50, V1 101 and v1 152)	Accuracy	98.4%
F. A. Spanhol[15]	BreakHis	Used AlexNet for Classification.	Accuracy	90.00%±6.7
Vibha Gupta[16]	BreakHis	Combined Some Colour-texture Image Descriptors such as Normalized colour space representation, Multilayer Coordinate Clusters representation, Gabor features on Gaussian Colour model, Gabor chromatic features, Complex Wavelet features and chromatic features and Opponent Colour Local Binary pattern (OCLBP) with Classifiers like SVM, Decision Tree, Nearest Neighbours, Discriminant Analysis and Ensemble Classifier.	Patient Score	87.53%

3. Machine Learning Methods

3.1. Feature Extraction Using CNN

Deep learning explores the possibilities of learning features directly from input data and tries to avoid hand-crafted features [17]. The main aim of Deep Learning is to achieve multiple levels of feature representation from an old one for more abstract semantics of the data. As a particular deep learning technique, Convolutional neural networks have achieved more popularity in image classification and its feature extraction. A CNN model is a combination of a few mathematical functions. In CNN, convolution is a function which takes inputs such as image and a filter or kernel to produce the output [6]. CNN is developed by using trainable layers which are stacked with each other. These layers are connected by a supervised classifier and some sets of arrays called feature detectors. These detectors map both

input and output of each layer. In CNN, generally, an input signal is an image where Feature Detector and maps help us to represent the image in a 2d array representation.

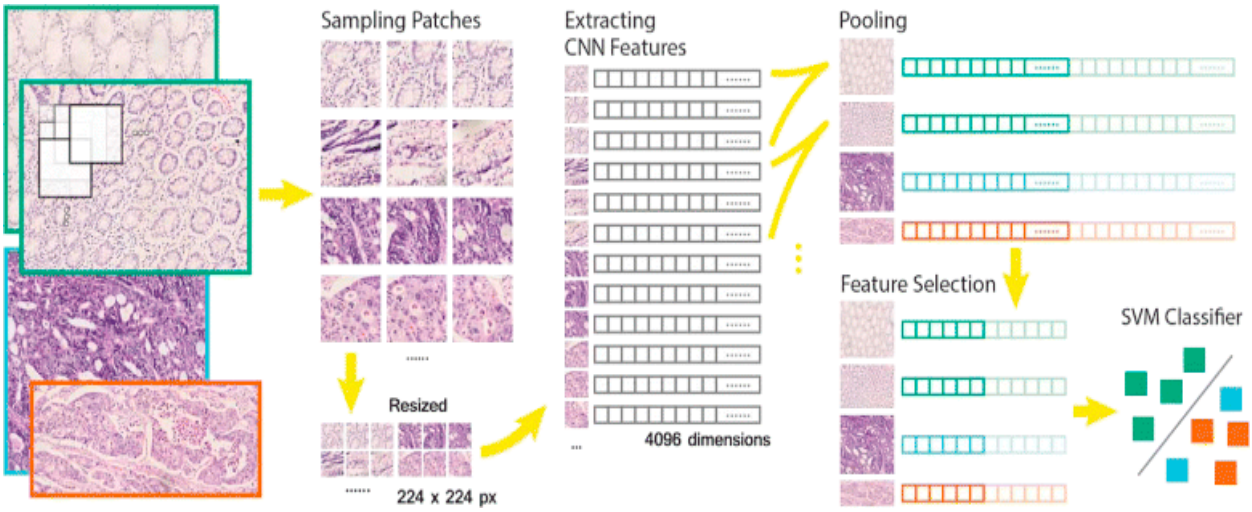

Figure 1. Feature Extraction Using CNN

There are 3 main parts for constructing CNN: Convolutional Layer, Pooling Layer and FC layer. In CNN, the main building block is the Convolutional Layer in which feature detector is used with an input signal as shown in Fig.1.This layer calculates the output of each neuron connected in local regions and for the next input, it computes a dot product of the weights. The region where neurons are connected to the input is called filter or kernel. There is a use of ReLU i.e. Rectified Linear Unit which is used for generating non-linearity in the given image [18]. A Pool layer is placed between two consecutive convolutional layers which are common in the trade. Pool layer resizes the input size for next convolution and it is generally used for producing a reduced progressive spatial size of representation [6]. A layer that is having connections to each activation function of the previous layer is known as Fully Connected (FC) layer. A Classifier is generally used in the end because it is presented in FC Layer. The main aim of using classifier is to analyse the proper class of image which is based on the detected features.

3.2 Machine learning Classifier

The process of predicting the particular class of given data point is known as Classification. Classes are referred by targets/ labels/categories in terms of classification problems. In predictive modeling, mapping function map Input Variables(X) to output variable(Y) for classification various data points.

3.1.1. Support Vector Machine

It is a supervised learning algorithm that is capable of making fine classifications through a separating hyperplane. In other means, trained labeled data (Supervised Learning) has been used and the algorithm returns an optimal separating hyperplane which classifies new examples. In 2D space, the hyperplane divides a 2-D plane into parts where each part represents some class according to the labeled data.

$$\frac{1}{2}\|w\|^2 + C\left(\sum_i \delta^{(i)}\right) \quad (1)$$

In the above equation, w represents the weights of class, C is the regularization parameter for the SVM and δ is the slack variable.

3.1.2. Logistic Regression

It is a Classification model which is very simple to implement and performs efficiently on linear separable classes. It is a Binary classification algorithm but can be implemented for multi-class classification by using OvR Method. Logistic Regression uses Sigmoid function with parameter z as net input: -

$$\emptyset(z) = \frac{1}{1+e^{-z}} \quad (2)$$

4. Dataset Description

In this proposed approach, we have used BreakHis Dataset which is also known as Breast Cancer Histopathological Images[19]. The BreakHis dataset contains overall 7909 images of histopathological Samples stained with Hematoxylin and Eosin. The Dataset has been divided into two categories i.e Benign and Malignant with respective to sample 2,480 and 5429. For implementation. our dataset is partitioned into the following manner: 80% for the training phase and 20% for testing phase as shown in Table 2.

Table 2. Training and Testing Samples used for the experiment

	Training Samples (80%)		**Testing Samples (20%)**	
Cancer Class	**Benign**	**Malignant**	**Benign**	**Malignant**
Number of Samples	1683	4637	792	788

These image samples are compiled from 82 patients tissue samples by using different Magnification factors (40x,100x,200x and 400x) as shown in Table 3.

Table 3. Number of samples in Benign and Malignant

Magnification	**40X**	**100X**	**200X**	**400X**
Number of total samples	1596	1687	1617	1420
Benign	424	446	424	389
Malignant	1172	1241	1193	1031

5. Proposed Methodology

A model has been developed for automatic classification on the basis of Magnification which classifies the samples for benign and malignant classes. The proposed system used in this work is illustrated in Fig.2. Each phase is described in the following subsection:

- Data Preparation & Pre-Processing-In this phase, the dataset has been loaded into google drive and applied Data Processing steps on it.
- Feature Extraction & Classifier –In this, Features are extracted using CNN's. After removing original classifier, a traditional supervised classifier is added to it i.e. SVM and LR.
- Model Development- Here, two models are generated which may or may not have dependency between them.
- Performance measuring parameters- Performance of the model is evaluated on the basis of accuracy, precision, recall, and F-values. It is calculated by using a confusion matrix
- Classifier Output –Results are analysed on the basis of cross-validation and test scores of SVM and LR

5.1 Image Pre-processing and Image Scaling

In this experiment, the rescaling method has been used. For this purpose, python-Keras ImageDataGenrator class is used for converting pixels scale form [0,255] to [0,1].

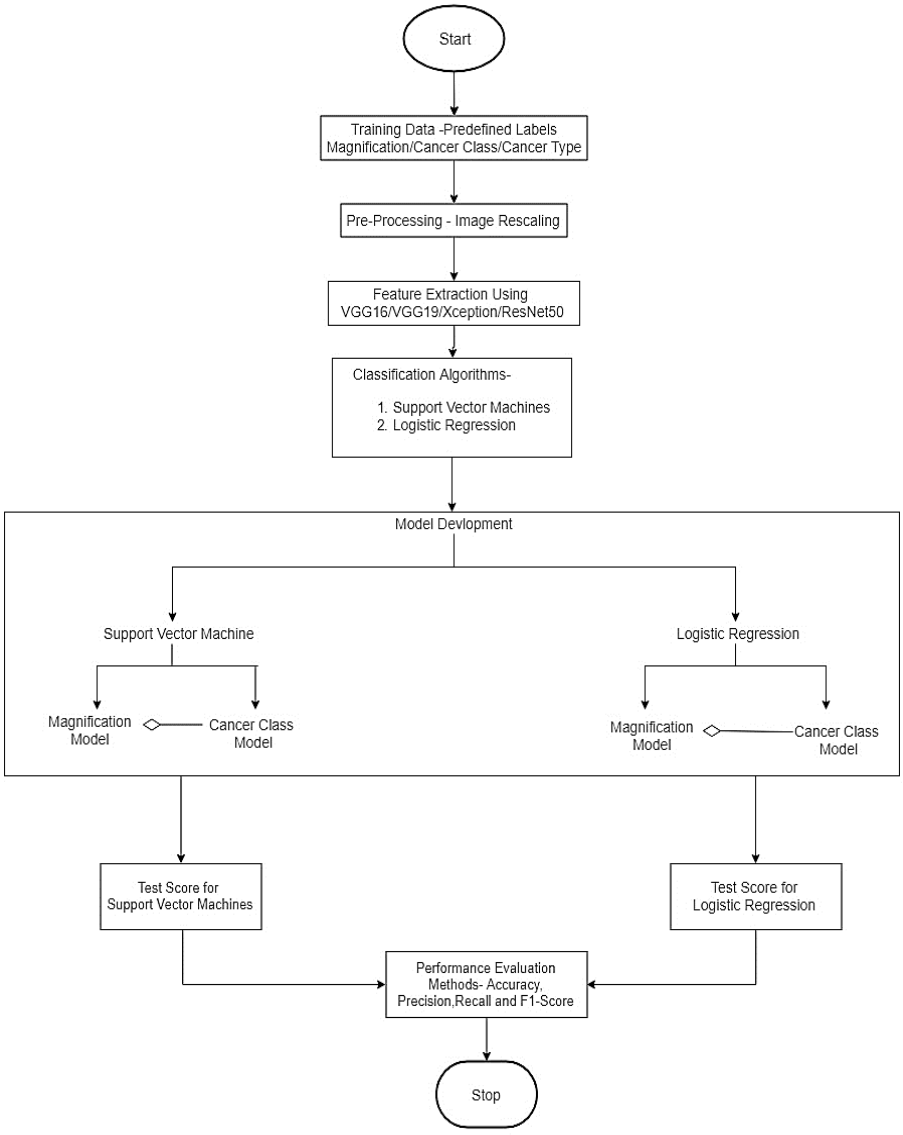

Figure 2. Flowchart of Proposed approach

5.2 Pre-Trained Deep CNN Architecture for feature extraction

In order to extract features from BreakHis Dataset, evaluation of Pre-trained CNN's Such as VGG16, VGG19, ResNet50 and Xception has been carried out [20][21][22]. The main aim of using a pre-trained model is to remove the top classifier from FC layers according to our need. The classifier which is removed from the FC layer is replaced by a traditional classifier which fits our purpose. According to below-mentioned strategies, fine-tune model is developed**.**

1) Training of the entire model**-** In this case, a pre-trained model is selected for training according to the dataset. After training of the model, it needs learning from scratch which results in the requirement of a large dataset and a lot of computational power.

2) Train a few layers and leave other layers frozen**-** As we know that lower layers refer to general features which are problem independent whereas higher layers refer to specific features that are problem-dependent. So, in order to solve

the problems of lower and higher layers, the weights of the neural network have been modified. To avoid overfitting in modified weights, one has to leave a greater number of layers frozen for a smaller dataset which consists of a large number of parameters as input.

3) Freezing of Convolutional Base- It corresponds to an intense situation for train/freeze trade-off. Here, the concept is to use the original form of convolutional base and feed outputs of the convolutional base to classifiers. A new fixed feature extractor has been used for this purpose which is developed from a pre-trained model. This approach can solve the problem in an efficient way when low computational power and smaller datasets are used.

5.3 Model Construction

In this research work, count tables have been used from Exploratory Data Analysis. These tables helped us for construction of model using neural network and classifiers. Firstly, the models are constructed by using scikit-learn library's function known as Grid SerchCV with Cross-validation parameter having value as 10 [23]. Two models such as Magnification Model and Cancer Class Models are produced for SVM and LR. The Extraction of features is done by using Google Colaboratory which is a free environment for research purposes and used for developments. Colab has been used for this purpose which permits a Tesla K-80 GPU instance, available for 12hrs. The models are as follows:

- Magnification Factor Model- This model gives the knowledge about magnification factor which is used during the study of whole slide imaging [16]. The magnification factors used in this dataset are 40x, 100x, 200x, 400x. Table no.3 is used for developing the model.
- Cancer Class Model- This Model predict whether the sample is non-cancerous i.e., benign or cancerous i.e. malignant. But it is not entirely dependent upon magnification models as there is an aggregation relationship between them.

After models have been structured, the reserved dataset is used for testing the models.

5.4 Measure for performance Evaluation

The result of each test is given in terms of accuracy (% of correctly classified instances). Several experiments have been applied to the challenging data set to evaluate the classification performance of the model. First, the overall accuracy of the model is assessed as the ratio between the number of images classified correctly and the total number of images evaluated in the cross-validated experiments. Accuracy is calculated from True positives(TP) and True negatives(TN) for binary classification and is as follows:

$$AC = \frac{(TP + TN)}{(TP + TN + FP + FN)} X\ 100 \tag{3}$$

In order to measure performance, we use Precision, Recall and F1-score which are calculated in terms of positives and negatives:

$$Precision = \frac{TP}{TP + FP} X\ 100 \tag{4}$$

$$Recall = \frac{TP}{FN + TP} X\ 100 \tag{5}$$

$$F1 = 2 * \frac{Precision\ X\ Recall}{Precision + Recall} X\ 100 \tag{6}$$

Where TP (True Positives)- Correctly classified as having breast cancer
TN (True Negatives)- Correctly classified as not having breast cancer
FP (False Positive)- Classified as having breast cancer but actually they don't have
FN (False Negatives)- Classified as not having breast cancer but actually they have cancer

6. Experimental Results

To study the performance of the model, 80% of training data and 20% of testing data is utilized. For this experiment, the images are organized into two classes i.e. Benign and Malignant. These images contain a magnification factor (40x, 100x, 200x, 400x).

6.1 Performance of CNN networks for SVM and LR

In this proposed model, four well recognized pre-trained deep CNN model: VGG16, VGG19, Xception and ResNet50 are used. The above mentioned pre-trained network is used as a feature extractor. Further, these feature vectors are used by the new classifier for learning the classification purpose. In this regard, Support Vector Machine (SVM) and logistic regression (LR) are utilized as a new classifier to make the final decision. Results of Support Vector Machines and Logistic Regression classifiers are compared with respect to accuracy using GridSearchCV.

Table 4. Classification Accuracy (%) of CNN for SVM and LR.

Model	CNN+SVM		CNN+LR	
	Validation Set (%)	Test Set (%)	Validation Set (%)	Test Set (%)
VGG16	83.1	90.2	83.33	90.06
VGG19	83.54	89.5	83.43	89.49
Xception	84.6	88.4	83.00	87.60
ResNet50	89.31	92.5	88.81	93.27

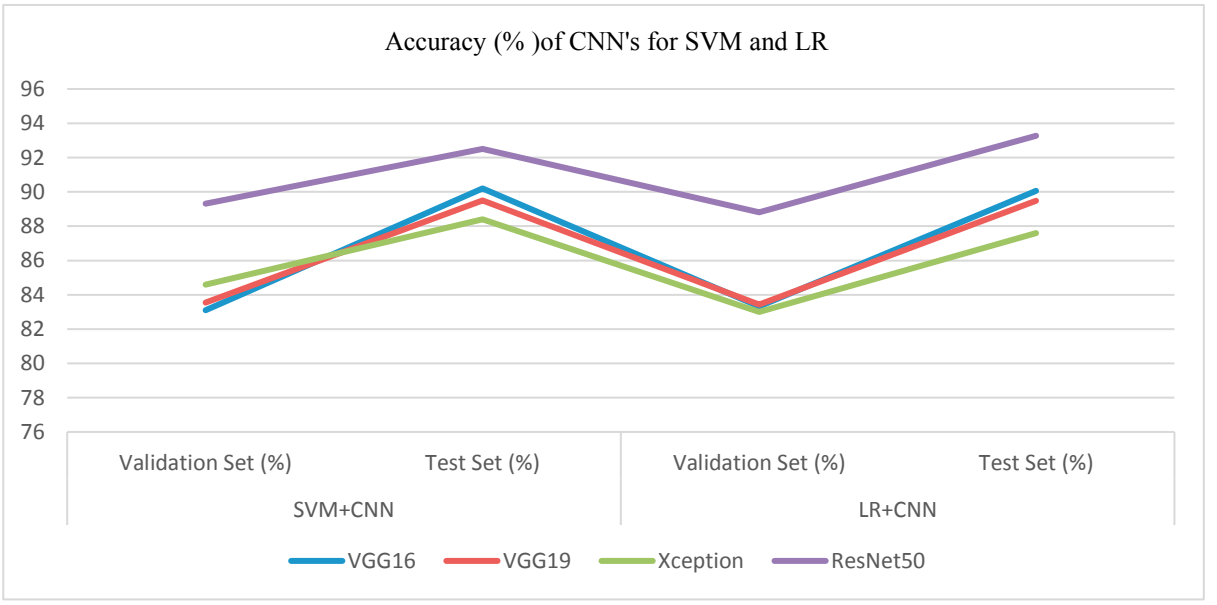

Figure 3. Classification Accuracy (%) of SVM and LR for Training and Testing

The result presented in Table 4 shows that among all four CNN networks, pre-trained ResNet50 network significantly

outperformed the VGG16 whereas the performance of VGG19 and Xception is comparable. Additionally, the results in Fig.3 illustrates that ResNet50+LR classifier has achieved the maximum accuracy (93.27%) for testing phase as compared to a 92.5% accuracy of ResNet50 +SVM Classifier.

6.2 Performance of CNN Network with Magnification for SVM and LR

Magnification is an important factor for analyzing microscopic images for diagnosis[15]. In order to validate the effectiveness of the proposed model, the results of CNN+SVM and CNN+LR are compared to different magnification factors (40x, 100x, 200x, or 400x).

Table 5. Multi Classification Accuracy (%) of CNN 's with Magnification for SVM and LR

	CNN's with Magnification			
Neural Net	**40X Mag.**	**100X Mag.**	**200X Mag**	**400X Mag**
		CNN+SVM		
VGG16	78.6	85.2	82	79.6
VGG19	77.3	79.1	83.0	79.1
Xception	81.6	82.90	78.4	76.30
ResNet50	86.4	86	84.3	82.9
		CNN+LR		
VGG16	78.84	85.20	81.21	79.09
VGG19	77.58	82.39	82.23	77.83
Xception	82.37	79.59	79.44	83.12
ResNet50	83.12	86.73	84.01	80.10

The results show that the magnification factors of the samples have an impact on training and testing accuracy. From above Table 5, it can be observed that ResNet50 network has shown better performance on 40x and 100 x as compared to other models. In addition, CNN+LR model has achieved the maximum accuracy of 86.73% in comparison of CNN+SVM as shown in Fig.4.

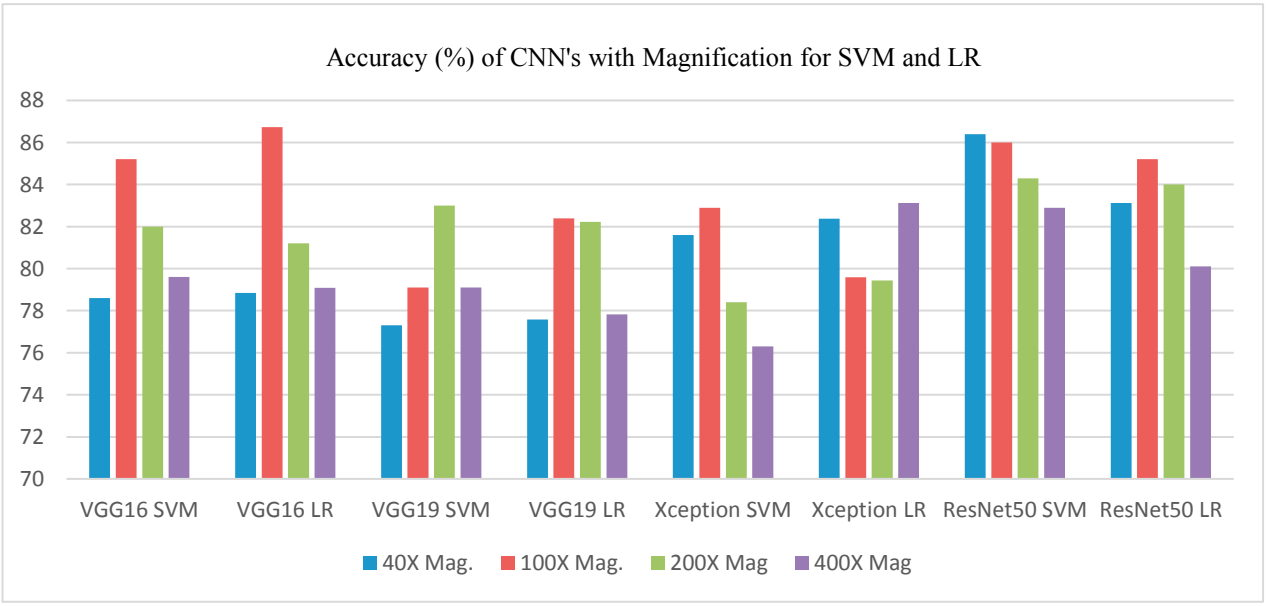

Figure 4. Comparison of Test score of SVM and LR

6.3 Performance of evaluation metrices per classes on SVM and LR using Magnification

In the proposed model, different evaluation metrics such as accuracy, recall, precision and F-measure values are used to evaluate the performance of a binary class system for benign (B) and malignant(M). The evaluation metric values are computed for SVM and LR in each magnification factor.

Table 6. Binary Classification Accuracy (%) per class with Magnification for SVM and LR

CNN+SVM

Magnification	Accuracy		Precision		Recall		F1-Score	
	B	M	B	M	B	M	B	M
40X	94.75	84.98	92.44	81.77	79.5	93.04	85.48	87.2
100X	95.87	97.03	90.34	82.40	80.71	91.28	85.24	86.61
200X	91.04	97.15	91.25	77.78	73.37	92.85	81.5	84.65
400X	84.37	97.50	81.05	79.22	78.17	82	79.58	80.5

CNN+LR

Magnification	Accuracy		Precision		Recall		F1-Score	
	B	M	B	M	B	M	B	M
40X	98.04	91.28	91.30	77.54	73.5	92.89	81.4	84.52
100X	95.83	94.02	94.4	81.2	78.1	95.38	85.55	87.78
200X	93.45	97.69	90.90	79.03	75.75	92.34	82.64	85.16
400X	96.87	98.63	86.93	80	77.66	85.16	82.03	84.08

From Table 6, it is observed that CNN +LR has shown better results for accuracy in comparison to other performance metrices. Fig.5 shows that CNN+LR has achieved 98.04 % accuracy for benign class on 40x magnification and 98.63% for malignant on 400x magnification so overall performance of CNN+LR is better than CNN+SVM in terms of accuracy. In these results, recall values show the relevancy of 78.1% and 95.38% for benign and malignant classes at 100X factor. Corresponding precision values shows that how correctly it can classify benign and malignant classes whereas F1 score stabilizes both precision and recall value for Accuracy.

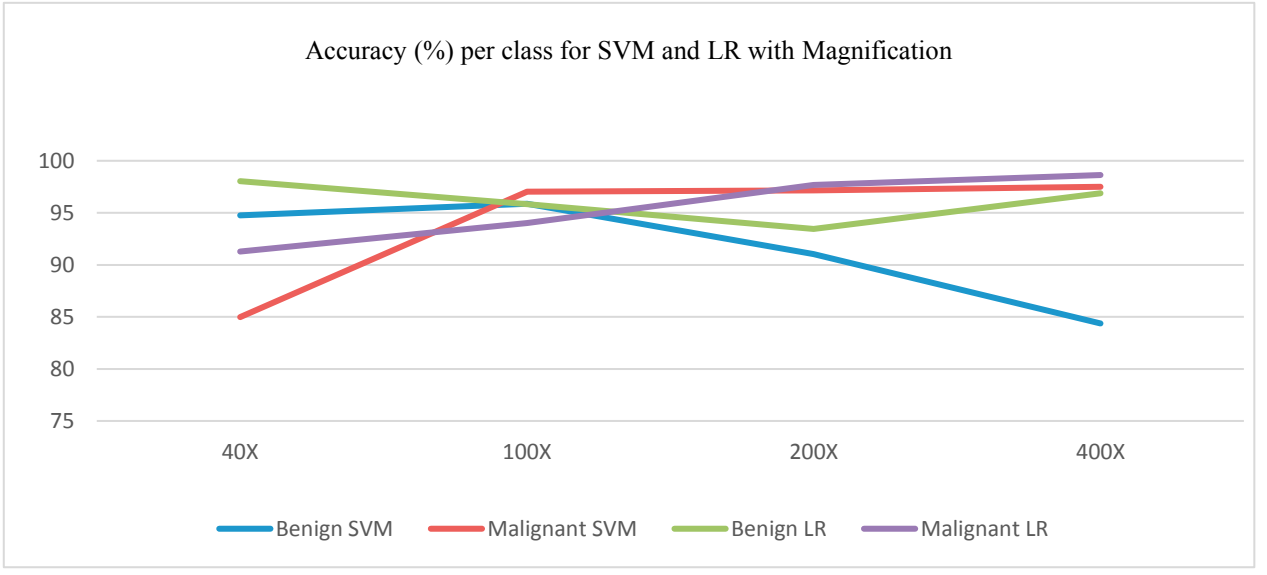

Figure 5. Binary Classification (%) with Magnification for SVM and LR

Discussion and Concluding remarks

In conclusion, Convolutional neural networks (CNNs) are the current state-of-the-art architecture for automatic classification of histopathological images. In our proposed system, we compared the performance of various combination of CNN+Traditional Classifier such as VGG16+SVM, VGG16+LR, VGG19+SVM, VGG19+LR, Xception+SVM, Xception+LR, ResNet50+SVM, and ResNet50+LR. From results, we observed that ResNet50 network achieved maximum accuracy i.e 93.27% and 92.5% for ResNet50+LR and ResNet50+SVM. Our model is also trained separately with respect to various image magnifications (40x, 100x, 200x and 400x) so the proposed approach has shown that 100 x and 40x specific model seem to yield better magnification performance as compare to 120x and 400x model. The reason could be the large difference in texture properties of image patterns. In addition, we have performed experiments considering binary and multi classification of instances i.e. classify instances (images individually or group of images belonging to a patient) into benign or malignant class. After evaluating performance, we observed that CNN+LR model has obtained 98.04 % accuracy for benign class on 40X and 98.63% accuracy for malignant class on 400X as compared to CNN+SVM model. Thus the experimental results show state-of-the-art testing accuracy for breast cancer detection as compared to existing methods. The presented work demonstrates the applicability and powerful classification capacity of machine learning approaches for the automatic analysis of breast cancer histopathology images. However, there are some limitations in this work. We can improve our performance if we provide larger datasets because limited raw data has an effect on accuracy results. As future work, we plan to extend the classification problem to more tissue categories i.e subtypes of benign and malignant classes by using data augmentation techniques. In the long run, we plan to design a complete framework for the analysis of Whole Slide Histopathology (WSI) by adding multi-classification of benign subtypes i.e. Adenosis, Fibro Adenoma, Tubular Adenoma, Phyllodes and Malignant types i.e., Ductal Carcinoma, Lobular Carcinoma, Mucious Carcinoma, Pappillary Carcinoma. Having that in mind, we would like to emphasize the need of data augmentation technique to solve the class imbalance problem.

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