Automatic System for Detecting Invasive Ductal Carcinoma Using Convolutional Neural Networks

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***Abstract*—Invasive ductal carcinoma (IDC) is the most common type of breast cancer. Every year a numerous number of women in this world are diagnosed as having IDC. Accurately detecting IDC is a time consuming and challenging task as the pathologists need to focus on the specific regions of whole slide images (WSI) that contain IDC. Precise and early diagnosis of IDC is a must because it helps to estimate the subsequent tumor aggressiveness that can be caused by this type of breast cancer. The goal of this research is to create an automated system that will analyze the whole mount slide images of breast cancer specimens to indicate the exact positions of IDC inside of the slides and give a decision based on the results. A multilayered convolutional neural network is designed which is trained over a large number of whole slide images. The dataset consists of 162 cases of patients diagnosed with IDC. We found an accuracy of 89.34% in f1 score using convolutional neural network to achieve the state of the art result on IDC classification.**

***Index Terms*—data source; related work; convolutional neural network; methodology; model architecture and training; experimental analysis**

I. INTRODUCTION

Cancer is one of the most concerning public health problems in the 21st century. As stated in the International Agency for Research on Cancer (IRAC), part of the World Health Organization (WHO) we know that 8.2 million people died because of cancer in 2012 and 27 million more deaths to be expected to occur until 2030 [1]. Every day a great number of women are being identified with different types of cancer all over the world. Excluding skin cancer, breast cancer is the second most common cancer type for women and the mortality of breast cancer is much higher compared to any other cancer types. Invasive ductal carcinoma (IDC) (also known as infiltrating ductal carcinoma) is treated as the most common type of breast cancer of them all as almost 80% of all breast cancers are invasive ductal carcinomas. American cancer society (ACS) states that each year more than 18,000 women suffer from invasive breast cancer and a majority of them have IDC [2]. The reason why IDC is such an alarming problem for the world is that of its low survival rate. Especially the survival chance decreases for a diagnosed patient if it is identified at a later stage of the disease. The cancer is then already spread to a greater extent and curing it becomes much harder. According to The American Cancer Society, the five-year survival rate after diagnosis for people with stage 4 breast cancer is only 22% [3].

IDC breaks through the wall of the milk duct and spreads to the surrounding breast tissues. The cancer begins in the milk ducts of the breasts, which are kind of like pipes that carry milk from milk-producing lobules to the nipple and invades the tissues of the breast. As time progresses, IDC may spread to the lymph nodes and in other different areas of the body too. IDC can affect woman of any age but woman older than 55 have a higher risk of being affected [3]. Regions containing invasive cancer determines the aggressiveness of the disease. In order to identify the presence of IDC, we have to distinguish the tissue regions containing invasive tumor from the non-invasive healthy tissues. An automated system based on identifying IDC should isolate the regions and give a prediction regarding it.

In the traditional method, doctors analyze the reports of patient's current conditions and take instant decisions depending on their skills, intuition and experience based on visual interpretation. Sometimes, this may lead to errors which can even lead to tragic results like death. An automated system can help with this type of pathological decision making especially while treating a fatal disease like breast cancer in order to diagnose the patient's current situation accurately. It gives doctors some extra assistance and confidence for such kind of critical diagnosis so it can help them to become more productive, objective and consistent. The use of this type of automated system in medical science has been increased lately. A pneumonia detection system on chest X-Ray image named CheXNet [4] claimed to have a better performance than average radiologists. As time plays an important factor in this type of cancer diagnosis, the proposed IDC detection system works to generate both accurate and fast result.

The automatic image processing for breast cancer detection in histopathology images has been a research topic for some time. It is a challenging task because the related images are complex in nature and structure. Petushi et al. [5] introduced a methodology of classification for tissue micro texture. The classification was between different grades of tumor cells and adipose tissue. Naik et al. [6] presented an automated detection and segmentation methodology of glands and nuclei in the histopathology images. Using nuclear centroids, the malignant areas were distinguished from the benign areas from the whole slide images which had an accuracy of 80%. George et al. [7] proposed a diagnosis system using the nuclei segmentation of cytological images. Couple of different machine learning models i.e. neural

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network and support vector machine were used which had an accuracy in the range of 76% to 94% in a rather small dataset of only 92 images. Dundar et al. [8] introduced a prototype system for distinguishing between usual ductal hyperplasia and actionable subtypes. It automatically classified breast microscopic tissues to achieve this. Cruz-Roa, Angel, et al. [9] proposed one of the first deep learning model using CNN to a visual semantic analysis of histopathology images for diagnosis support for IDC detection. The model had an F1 score and balanced accuracy of 71.80% and 84.23% respectively. Spanhol, Fabio Alexandre, et al. [10] also proposed a similar CNN based model which was trained by the extraction of image patches and then the combination of these patches for final classification. They also showed that the combination of different CNN models gave an improvement in recognition. In [11] an open source framework (Caffe), with a singular network architecture was used for IDC detection (F-score of 0.7648 on 50 k testing patches).

The method of an automated system is that it automatically gives a prediction from different classes for some given input data. It is trained on a comparatively big dataset to be able to distinguish between different classes. Nowadays, deep learning approaches i.e. convolutional neural network is very successful in producing state of the art accuracy in the automated segmentation and classification of disease extent on histopathology images [12][13]. A convolutional neural network (CNN) introduced by LeCun [14] is being used to achieve state of the art result for different pattern recognition problems [15][16]. CNN is now being used for mitosis detection in breast cancer histopathology images [17][18][19].

II. Data Source

The original dataset consists of digitized histopathology slides from 162 specimens diagnosed with IDC at the Hospital of the University of Pennsylvania and the Cancer Institute of New Jersey [9][11]. The images are scanned at 40x magnification via a whole-slide scanner in order to produce digital slides. Whole slide images (WSI) are one of the recent imaging modality that is now very popular among the pathologists worldwide for diagnostic, educational, and research purposes [20]. Especially in breast cancer classification, WSI images are being used vastly [7][21][22]. These images emulate the slide viewing on a computer screen by a conventional microscope. From the dataset, 277,524 patches of size 50x50x3 (RGB) were extracted. 198,738 patches were IDC negative and 78,786 were IDC positive shown in figure 1. Each patch's file name has the format: u_xX_yY_classC.png, where u is the patient ID, X is the x-coordinate of where this patch was cropped from, Y is the y-coordinate of where this patch was cropped from, and C indicates 0 for non-IDC and 1 for IDC.

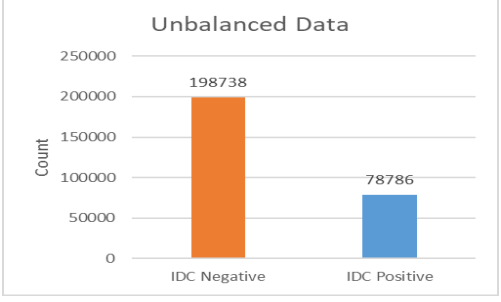

Fig. 1: Number of IDC(+) of IDC(-) images

An example is 8863_idx5_x51_y1251_class0.png. Where 8863_idx5 denotes patient's id, 51 is the x coordinate, 1251 is the y coordinate, and class0 denotes that it is non-IDC. Figure 2 shows a couple of random whole slide images from the dataset defining if IDC is present or not.

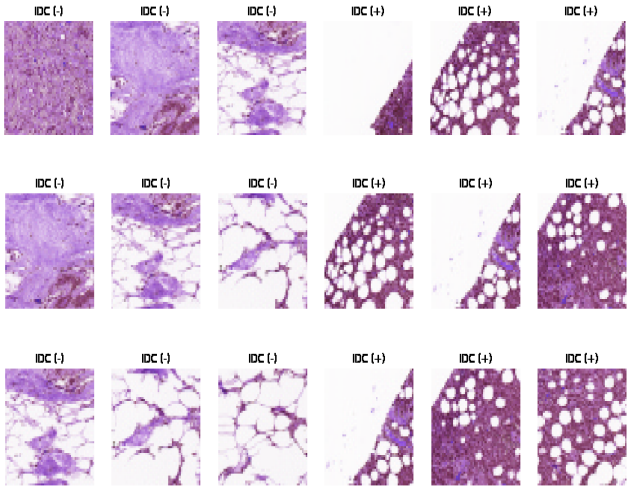

Fig. 2: Couple of whole slide images from the dataset defining IDC (+) and IDC (-)

III. Convolutional Neural Network

Image classification based on some particular visual information has always been a difficult task even for the human visual system. Considering the microscopic images from histopathological sections, they are much more difficult to classify because of their complex geometrical shape as well as the inter-intraclass variability in the images [23]. Convolution neural network (CNN) is a trainable deep learning architecture. This was encouraged by animal optical system [24] that learns features directly from the given input data avoiding the hand-crafted feature. CNN consists of multiple nonlinear transformations in several steps and in each step it works to reduce the error to accurately classify. In summary, a CNN is made of multiple trainable stages composed like a stack of data top of each other followed by a supervised classifier. Each stage has a set of arrays named feature vectors which represent the input and output vectors respectively [24]. CNN needs a huge amount of labeled samples and computational power to train the network. Because of the growth of the available digital data and powerful computational resources i.e. graphics processing unit (GPU), [25] the required time is being reduced significantly than before while training the network. This convenience can help us to train deeper CNN architectures in our environment to achieve a greater result.

CNN is a structured neural network which requires minimal preprocessing where the first couple of layers are sequentially interconnected in order to process visual information. CNN is feed-forwarding in nature since the output of the current layer becomes the input of the next layer. Neurons in the CNN have learnable parameters such as weights and biases. The network starts training itself with a forward pass. A list of connected layers transform the input volume into an output volume. The prediction in the output layer is computed as probability that represents class scores. The predicted outcome is then compared with the true result

to compute the error. In backpropagation, the computed error generates the gradient that flows in the backward direction. At each step, the parameters are tuned in such a direction that it tries to reduce the previously generated error [26][27][28]. This process continues in an iterative way until the model converges.

A typical CNN architecture has the following components:

- **Input layer:** This layer loads the input data and feeds it through the next layers.
- **Convolution layer**: Due to the advantages of parameters sharing and sparsity of connections, convolution operations are used in CNN [15]. In convolution layers, a number of filters (or kernels) of small sizes (e.g., 3x3, 5x5 or 7x7) convolute the input data i.e. 2D image for extracting different features. It produces the output by sliding over all spatial locations of the input image using the dot product between their weights and local regions connected to the input followed by adding a bias parameter. The following equation expresses the convolution operation where w is the filter weights, x is the input image and b is the bias term:

$$y = w^T x + b \tag{1}$$

  The filters are shared across neurons in order to learn frequent patterns that appear in the images [23].
- **Activation layer:** The activation layer introduces non-linear properties to the network followed by convolution layers. Their main purpose is to convert an input signal of a node into an output signal. The generated output will be passed towards the next layer. The Rectified Linear Unit (ReLU) activation function is mostly applied in most real-life practice as it is computationally efficient and converges much faster than most other activation functions [15].
  The following function expresses the ReLU nonlinearity where it takes input x:

$$f(x) = \max(0, x) \tag{2}$$

- **Pooling layer:** The pooling layer is generally introduced between two successive convolution layers to reduce the number of parameters and computations required by the network. It helps to overcome the overfitting problem while training the dataset. Max pooling function is a very common pooling technique to use because it produces better results in real life applications than other pooling techniques [15][29]. It applies a window function in the input patch and computes the maximum in the neighborhood.
- **Dropout:** It is a regularization technique for eliminating the overfitting problem [30]. In each forward pass, at every layer, it randomly sets a portion of neurons to zero. So, a subset of the network is used in that iteration. Figure 3 shows how some neurons have been turned off so only a subset of the original network is being used.
- **Fully connected layer:** The fully connected layers (FC) have full connections to all the activations of the neurons in the previous layer. They treat both the input and output as simple vectors. The final fully connected layer of the network produces the net output with an activation function i.e. softmax function depending on the number of classes in the classification problem. The following function expresses the softmax function:

$$L(x) = -\log\left[\frac{e^{x_i}}{\sum_j e^{x_j}}\right] \tag{3}$$

  where x_j corresponds to outputs of fully-connected layer multiplied by logistic model parameters.
  In the binary classification task, the last layer consists of two neurons that produce the score that represents probability of each class.

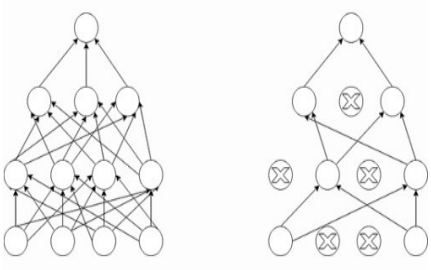

Fig. 3: Dropout used in a network

A typical CNN architecture consists of these types of several components. An example of a typical architecture would be:
[(CONV-RELU)*N-POOL?]*M-(FC-RELU)*K,SOFTMAX
where N is usually up to ~5, M is large, 0 <= K <= 2
Figure 4 shows how a typical CNN architecture looks like:

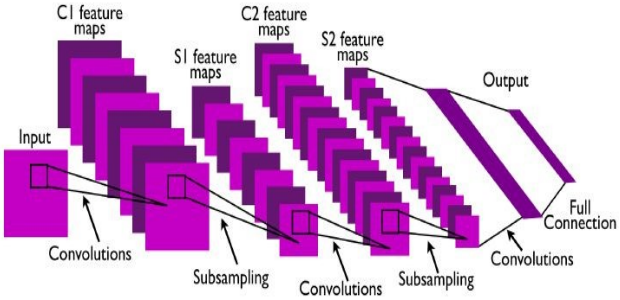

Fig. 4: A typical CNN architecture extracted from [24]

IV. Methodology

IV-A. Balancing Dataset

In our dataset, the class imbalance problem arises as the IDC (-) has much more members than the IDC (+) class. This problem affects classification systems such as neural network in accurate decision making [31]. The huge difference in number between the class members can be seen in figure 1. The difference needs to be balanced out before training the network. To solve this problem, an equal number of specimens (78786 images) were selected from both IDC (+) and IDC (-) classes. From the selected images, 63032 and 15754 images were selected from both the classes for training

dataset and test dataset respectively. So, our training dataset contained 126064 images and test dataset contained 31508 images in total can be seen in figure 5. The images were selected randomly to avoid bias.

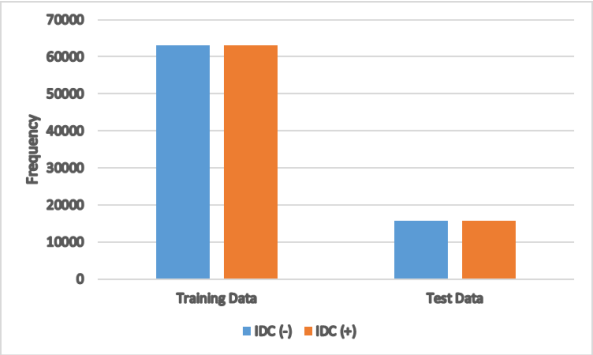

Fig. 5: Balanced dataset for IDC (+) and IDC (-)

IV-B. Model Architecture and Training

The implemented architecture consists of six convolution layers where max pooling layer was inserted after two consecutive convolution layers which is depicted in figure 6. The number of 64, 128 and 256 filters of size 3x3 were used in both convolution 1,2; 3,4 and 5,6 respectively. In each convolution layer, ReLU nonlinearity was used. One hidden dense layer was used in the fully connected layer and the final fully connected layer consists of two neurons that apply softmax non-linearity to produce the class scores. A dropout of probability 0.5 was used in both convolution and fully connected layers. The weights of the network are initialized with Xavier initialization method [32]. The network is trained all over using Adadelta optimizer [33] with initial standard parameters (learning rate=1.0, rho=0.95). We trained the model using mini batches of size 128. The learning rate is decayed [4] by a factor of 0.5 every time when the validation loss doesn't improve after consecutive three epochs and chosen the model with the lowest validation loss. A method of early stopping [34] was introduced (patience = 5) so that the training will be stopped if consecutive five epochs don't improve the validation loss. Data augmentation techniques such as random 10-degree rotation, zooming, shifting and flipping horizontally and vertically were imposed in training set. Thus it reduces overfitting and produces a robust prediction system that has more generalization power.

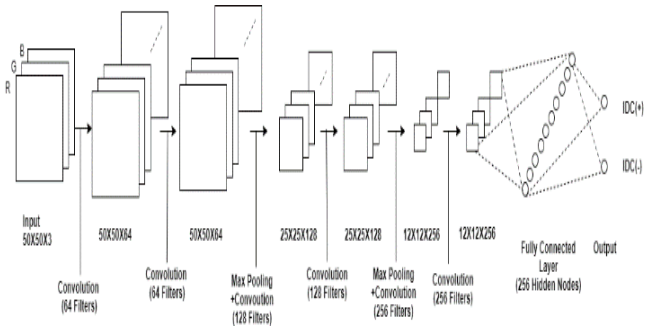

Fig. 6: An illustration of the architecture of the implemented convolutional neural network

126064 training images of size 50x50x3 (RGB) were loaded into the input layer. The output shape of convolution 1 and 2 layers was 50x50x64 as the convolution operation used the same padding technique. Later max pooling operation was used to down sample the input shape of 50x50x64 into 25x25x64. The rest of the output shapes are shown in table 1. The total trainable parameters were 3,505,474.

TABLE I. Model Summary

Layer (Type)	Output Shape	Parameter Number
Input	(50, 50, 3)	0
Convolution1	(50, 50, 64)	1792
Convolution2	(50, 50, 64)	36928
Max Pooling	(25, 25, 64)	0
Dropout (0.5)	(25, 25, 64)	0
Convolution3	(25, 25, 128)	73856
Convolution4	(25, 25, 128)	147584
Max Pooling	(12, 12, 128)	0
Dropout (0.5)	(12, 12, 128)	0
Convolution5	(12, 12, 256)	295168
Convolution6	(12, 12, 256)	590080
Max Pooling	(6, 6, 256)	0
Dropout (0.5)	(6, 6, 256)	0
Fully Connected	(256,1)	2359552
Dropout (0.5)	(256,1)	0
Softmax	(2)	514

The IDC detection is a binary classification task, where the input is WSI histopathology slides X and the output is a binary label, $y \in \{0,1\}$; representing the absence or presence of IDC respectively. In the training set, weighted binary cross entropy loss is optimized for an example:

$$L(X;\ y) = -w_+ \cdot y \log p(Y\ =\ 1|X)$$
$$-w_- \cdot (1-y) log p(Y = 0|X) \quad (4)$$

where $p(Y\ =\ i|X)$ is the probability of the label i, $w_+ = |N|/(|P| + |N|)$, and $w_- = |P|/(|P| + |N|)$ with $|P|$ and $|N|$ represent the number of IDC(+) and IDC(-) in the training set respectively.

V. Experimental Analysis

The balanced data set has been divided into training (80%) and testing (20%) set randomly. The dataset is split into these two sections to ensure that the same patient used for training cannot be used again for testing. This guarantees that the classifier is generalized to unseen specimens. The CNN model was trained on an NVIDIA GeForce GTX 1080 Ti (11GB DDR5 memory), CPU RAM 32GB using keras API on top of TensorFlow (CUDA toolkit 9.0, cuDNN SDK v7 and python 3.6) [35]. The training took about 202 seconds per epoch and it converges comparatively faster in only 21 epochs.

The results presented in this work is based on accuracy and f1 score [36] which are described by the following equations:

$$accuracy = \frac{tp+tn}{tp+tn+fp+fn} \quad (5)$$

$$f1\ score = 2 * \frac{precision*recall}{precision+recall} \quad (6)$$

Where tp, tn, fp, fn represent true positive, true negative, false positive and false negative respectively. Recall is defined as

the fraction of the relevant instances in a dataset that is successfully retrieved and precision expresses the proportion of the data points the model says is relevant actually are relevant.

CNN has the advantage of learning features automatically instead of manual feature extraction techniques. The self-learning ability of CNN model makes it more convenient than the traditional learning system. We can visualize the generated output for convolution, activation and pooling operation for an input image displayed in Figure 7 from left to right.

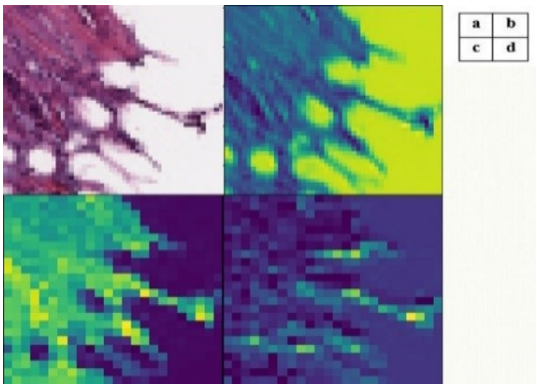

Fig. 7: Understanding CNN: a) input image, b) convoluted image, c) activation output, d) pooling layer output

The accuracy curve for training set (126064 images) and test set (31508 images) is showed in figure 8 and the classification matrix is showed in figure 9.

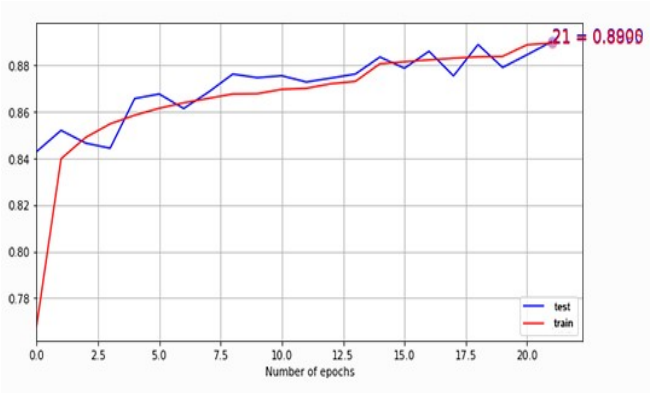

Fig. 8: Accuracy curve for training and testing

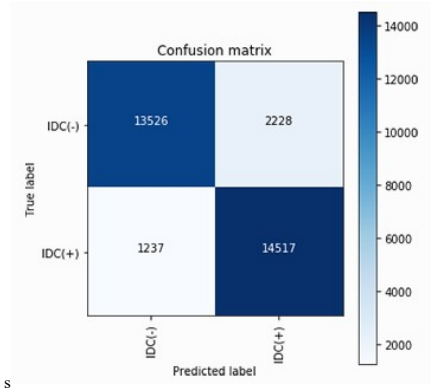

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Fig. 9: The classification matrix

Using equations (5) and (6), the proposed system achieved 89% accuracy and 89.34% f1 score which outperformed the previous state of the art. In comparison with [9] and [11], a quite significant improvement in f1 score can be seen in our proposed system. From f1 scores of 71.80% and 76.48% respectively, it has improved to 89.34%. A more recent research [10] had an accuracy of 85.6% which was also overcome by a good margin of 3.4%.

VI. Conclusion

Accurately detecting Invasive Ductal Carcinoma is the first step in breast cancer diagnosis and treatment. Even a little mistake in this task can causes grave danger. In this paper, an automated system for detecting IDC using convolutional neural network was proposed. The proposed system was successful in detecting if a patient has IDC or not by analyzing histopathology images of the patients. It outperformed the previous state of the art. We hope that this automated system will help the pathologists in decision making and improve healthcare system regarding breast cancer. Future work can explore different architectures using optimized hyperparameters and data augmentation to improve the system accuracy.

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