Department of Electronics and Electrical Engineering

IIT Guwahati

Bachelor Thesis Project Report (July-Nov 2015)

Classification and Segmentation of Prostate Gland Tissue

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OBJECTIVE

Given the biopsy slides of the prostate glands, segment the glands and classify them into malignant, grade 3, 4 or 5 tumors using Convolutional Neural Network.

WORK DONE IN THIS SEMESTER

- ✓ Got familiar with Python language and its libraries (Numpy,Scipy, Theano etc).
- ✓ Trained the Convolutional Neural Network on MNIST [9] and CIFAR-10 [10] dataset and obtained a test error rate of 0.92% and 28.51% respectively.
- ✓ Read the state-of-the art techniques used for segmentation and classification of prostate gland tissues.
- ✓ Trained the Convolutional Neural Network on the colon dataset for segmentation of the biopsy slide pixels into gland and non-gland.
- ✓ Experimented upon the values of different parameters to achieve minimum test and validation error for gland segmentation.

WORK TO BE DONE IN NEXT SEMESTER

- ➢ Test the proposed method on bigger datasets (CPCTR etc.) as well as with different classifiers.
- ➢ Devise a technique for classification of the glands into benign, grade 3, 4 or 5 tumors.
- ➢ Compare with the existing techniques of the same.

CONTENTS

***Abstract* - Automated system of segmentation and classification of prostate gland tissues has become a necessity of the hour provided the ever increasing rate of people suffering from cancer. In this work, we have proposed a novel technique of gland segmentation using deep learning. The scheme involves training the dataset using a convolutional neural network having two convolutional layers, one hidden layer and the final segmentation into gland or non-gland is done using logistic regression model. In contrast to the other techniques which are highly dependent on the gland structure such as presence of lumen or nuclei around the gland, our proposed method overcomes all these problems. The efficacy of the automated gland segmentation system has been evaluated by computing the validation and test error on the colon dataset from the gland segmentation challenge contest at MICCAI 2015.**

I. INTRODUCTION

Prostate cancer is a disease affecting men which is caused because of the growth of cancer cells in the prostate gland of the men reproductive system. Prostate cancer is the second most prevalent cancer among men after non-melanoma skin cancer [1]. In the US, 209,292 men are diagnosed with prostate cancer and 27,970 men die of it every year. If cancer is detected, it is necessary to know its stage or how far it has spread. The diagnosis is done by a radiologist or a pathologist using the biopsy sample of the patient. The grading is done using the Gleason grading method which grades a tumor with a score between 2 to 10. This method is the addition of two scores (the most and the second most prevalent pattern in the sample) each ranging from 1 to 5. A grade 1 pattern is very well differentiated whereas grade 5 is poorly differentiated. Fig. 1 shows the different carcinoma patterns. In grade 1 and 2 (benign patterns), the glands have large lumen with prominent nuclei. Grade 3 glands are more circular with smaller lumen and thin nuclei boundaries. The glands start to lose their architecture as we move to grade 4 whereas grade 5 glands have poorly defined units. The tumors are graded manually by the pathologists by observing the biopsies under a microscope. This method is both tedious as well as error prone. Moreover, it also depends on the skills of the person. Hence, an automated system for cancer detection and grading is the need of the hour. Such a system should not only grade the tumors in less time but also with great precision and accuracy.

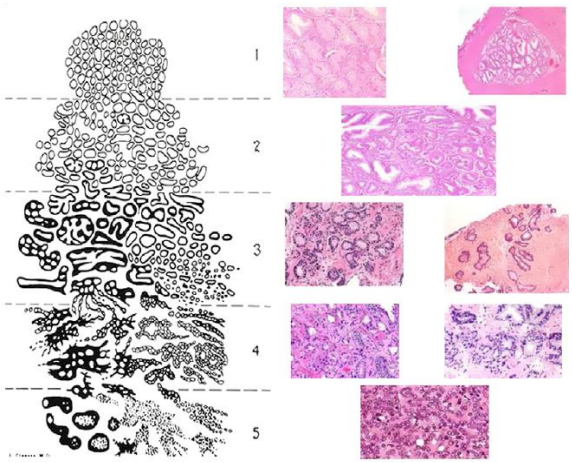


Figure 1 Five grades of the Gleason grading pattern applied to the prostate tissue.

II. LITERATURE REVIEW

Nguyen et al. [2] have presented a segmentation based classification method which is based on the structure of the glands. The pixels were first converted into Lab space from the RGB and then divided into 5 categories viz., stroma, nuclei, cytoplasm, lumen and mucin using the voronoi tessellations of the training points. They then created a binary image of nuclei and non-nuclei objects. The nuclei objects were enlarged by combining with the adjacent cytoplasm pixels. The enlarged nuclei objects which intersect were combined to construct the gland boundary segments. However, since the nuclei may not be densely packed everywhere on the boundary, so a complete gland boundary may not be obtained at this stage. The complete boundary was obtained by combining with the lumen. The authors created a lumen and non-lumen binary image and expanded the lumen boundary until either the boundary touches the stroma or exceeds a defined threshold and combined with the cytoplasm objects. After obtaining separate glands, fifteen features were extracted from the glands which included lumen features (area statistics, perimeter statistics, circularity statistics, percentage of the gland area to be lumen area, number of lumina in the gland), nucleus features (percentage of the gland area to be nuclei area, nucleus density), gland morphology features (average and variance of gland radius), mucin features (percentage of gland area to be mucin area). They used Adaboost, nearest neighbor, decision tree, bayes, svm and fnn to classify the glands into benign, grade 3 and 4 out of which svm and fnn produce the best results.

In [3], Gaussian filter was applied to the image which was then converted from RGB to grayscale. Thresholding was employed to separate out the lumen objects. The image was converted from RGB to Lab space and k-means clustering was applied to a* space of the image for initial segmentation of the glands. The number of clusters was two: cluster of lumen and cytoplasm pixels, and cluster of stroma and nuclei pixels. Closing operation was applied on the initially segmented glands so as to fill any holes or gaps. Size constraint was also applied to keep only true glands. Nine features were extracted from the segmented glands, namely, average lumen area, maximum lumen area, average lumen eccentricity, average gland area, maximum gland area, average gland diameter, average gland perimeter, average gland eccentricity and gland density. Classification of the glands was done using Bayes Classifier.

Naik et al. [4] proposed a method of gland and nuclei segmentation using low-level and high-level information. In low-level information, Bayes theorem was used to obtain pixel-wise likelihood for each pixel which in turn generated likelihood scenes giving the probability of the pixel to belong to lumen, cytoplasm or nucleus class. In the detection of lumen objects, the authors took the likelihood scenes of the lumen and computed the probability of the objects actually belonging to the lumen class. The false positives were removed depending on the area of the predicted lumen region. Moreover, the non-gland regions were removed by ensuring that the detected regions were surrounded by cytoplasm regions. After the detection of lumen objects, gland segmentation was carried out by high-level information using level sets. It made use of neighboring pixels during evolution to form the target boundary. Curve evolution was done by the likelihood scene of the nucleus and the initial contour was initialized to the detected lumen object. The curve was evolved outward from lumen object within the likelihood scene of nucleus and thus the gland and nuclei boundaries were extracted. Similar to gland segmentation, nuclear segmentation was done using low-level and high-level information. From the gland and nuclei boundaries, the authors calculated 16 morphological features. Further, 51 graph-based features were taken from Voronoi diagrams, minimum spanning tree and Delaunay triangulation using the centroids of nuclei. The feature set so obtained was reduced using graph embedding, a non-linear dimensionality reduction method and then support vector machine was used to classify the glands into benign or grade 3/4.

Nguyen et al. [5] proposed 3 different techniques for segmentation and classification of prostate glands. In the lumen based grading method, glands were segmented following which 22 structural contextual features were extracted from each gland. An svm classifier was trained to remove the noisy regions from the extracted glands and then the 22 dimensional vector was used in an svm to classify glands into benign, grade 3 or 4. In the nuclei-based method, the authors first detected the tissue components of the image that is, nuclei, lumen and stroma. As nuclei are mostly

circular and have small sizes, they used the radial-based symmetry to detect nuclei. Textural features were then computed in the neighborhood of nuclei and a svm was used to differentiate between epithelial and stromal nuclei. Stromal nuclei were then discarded. Lumen and stroma were detected using k-means. The nuclei-lumina graph which depicts the relationship between nuclei and nuclei, and nuclei and lumina was constructed using two algorithms: nuclei-nuclei link creation and nuclei-lumina link creation. Around every nucleus, a conical region was formed and the nucleus closest to the central nucleus in every conical region was marked. If the line joining the two nuclei did not intersect stroma, then nuclei-nuclei link was created. For the nucleus-lumen link creation, a conical region was made around a lumen pixel lying on the lumen boundary. All the nuclei falling in the region were considered for the nucleus-lumen link creation. All the links obtained so formed the edges of the nuclei-lumina graph. To remove bad links, normalized cut method was used. The authors also computed the gland score which measures the closeness to closed chain structure. In grade 3 glands, the nuclei tend to be form more closed chain structure leading to a high gland score. On the other hand, nuclei in grade 4 glands are randomly distributed because of which they have a low gland score. The authors then fused the above two methods that is, lumen based and nuclei based and observed a higher accuracy than obtained in the two methods independently.

Nguyen et al. in [6] used k-means clustering algorithm to segment the different components of the gland (lumen, cytoplasm, nuclei etc.). A connected component algorithm on nuclei pixels and lumen pixels generates nuclei objects and lumen objects, respectively, which are used for segmentation. Nuclei-lumen association (NLA) algorithm, associates appropriate nuclei with each lumen to create a gland segment. Nuclei are searched along the normal direction of the lumen boundary contour. For gland classification the differences in structures of the three classes (artefact, normal gland and cancer gland) are used to make four sets of structural features, including 19 features, for each gland which are as follows. Set 1 (8 nuclei features), Set 2 (6 cytoplasm features), Set 3 (3 lumen shape features) and Set 4 (2 global features). The following 3 features as Neighbourhood crowdedness, Shape similarity and Size similarity are also taken for each gland segment to capture the contextual information. Finally, each gland segment can be represented by a full feature vector of dimensionality 22 (19 + 3) and for the classification purpose a SVM classifier (linear kernel, C = 1) with this feature vector is used.

III. CONVOLUTIONAL NEURAL NETWORK

Convolutional Neural Network [8] is mainly used in the fields of image and video processing. CNNs consists of multiple convolutional layers which are collection of small filters that take only a small portion of the original image as input and process over it. The outputs of these filters of a convolutional layer are pooled to have a better representation of the given image and passed as input to the next convolutional layer.

The same set of weights of a filter is used over the entire image which reduces the training time and memory required. The function of a filter is to extract the different aspects of the input image. The complexity of the extracted features increases as the number of layers increase.

To reduce the possibility of overfitting and variances different techniques are applied:

- Pooling layer: Before the output of the convolutional layer is passed on to the next layer pooling is done wherein the maximum or the average value of the region is computed which replaces the other values of the region. This ensures that the result becomes translation invariant.
- Dropout: In this method at any stage some of the nodes are randomly dropped which results in a reduced network which is trained in that stage. The removed nodes are later added back to the network. Fully connected layers often result in overfitting, thus by reducing the network dropout decreases the chances of overfitting.

Now these learned features can be passed through a hidden layer with a linear or nonlinear activation function. The output is used as input to a logistic regression model, multi-layer perceptron or other classifiers to solve binary or multi-class classification problems.

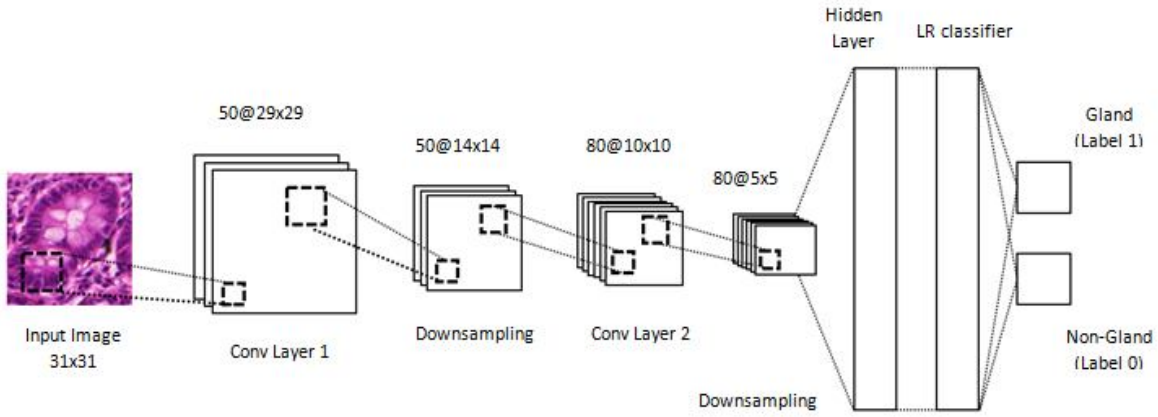
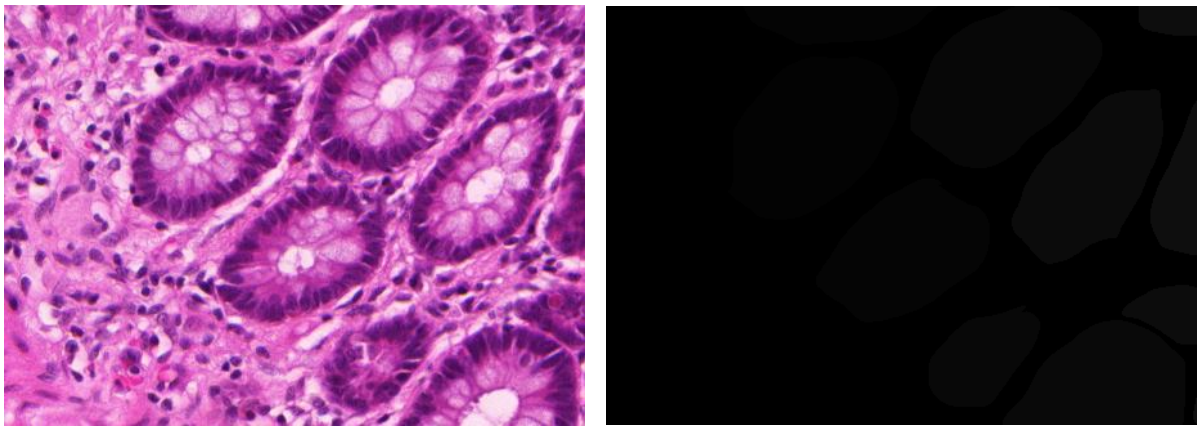


Figure 2 CNN Architecture

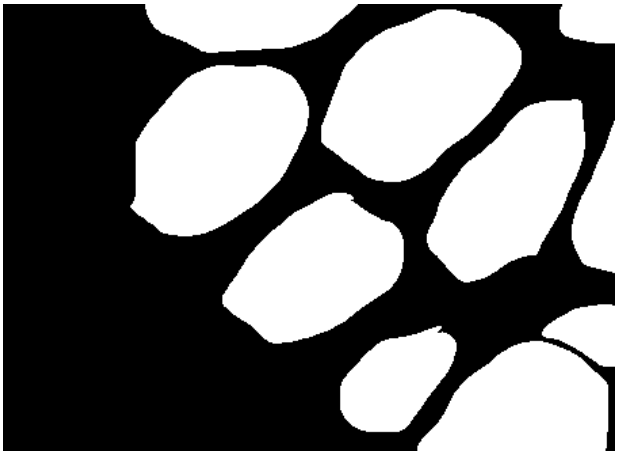
IV. PROPOSED METHODOLOGY

We used the colon dataset from the Gland Segmentation challenge contest (GlaS) at MICCAI 2015 [7] for conducting the experiments which had 37 benign and 48 malignant H&E stained biopsy slides of colon tissue. Each image was a RGB image of size 775x522. Along with these we also had the annotated images where the background was black while the different glands were marked with different grey values.

Fig. 3 (a) shows a sample image of the dataset. Pink portion of the image is the stroma which forms the background. The white portion in the centre of the gland is called the lumen which is surrounded by purple coloured cytoplasm. The gland boundary is marked by the round dark blue coloured epithelial nuclei. The other round objects in the stroma are called the stromal nuclei.



(a) (b)



(c)

Figure 3 (a) Sample image from the dataset (b) Annotated image (c) Binary image

To begin with we first generated the binary image (See Fig. 3(c)) using the annotated image (See Fig. 3(b)) where every pixel with intensity greater than zero was marked as 1. Thus all the glands were represented by white colour (label 1) while the background as black (label 0).

Out of the 37 benign images 30 were used for the training and validation and the rest 7 images were used for testing. For predicting the class of each pixel we require the local information to be passed in to the CNN. So a patch of size 31x31 is taken which is used to predict the class of the centre pixel of that patch. So we randomly selected a fixed number of patches from every image such that the ratio of gland vs non-gland centre pixels is 1:1. We extracted 117600 patches for the training set, 11760 patches each for the validation set and test set.

For prediction we used a CNN which had 2 convolutional layers, 1 hidden layer and a logistic regression layer. The size and the number of filters were experimented upon to achieve the minimum test and validation error. Pooling was done which reduced the output of the convolution layer by a factor of 2. Dropout was also added with probabilities 0.15 and 0.25.

For training and testing we used batch processing with a batch size of 420 and the number of epochs was set to 200. We used a dynamic learning rate initialized at 0.001 with a decrement value of (0.000025*current learning rate).

V. EXPERIMENTAL RESULTS

S.No.	Dataset size (Number of patches)			Convolutional Layer 1 Filters		Convolutional Layer 2 Filters		Learning Rate	Decrement in Learning Rate	Error (in %)	
	Training	Validation	Test	Number	Size	Number	Size			Validation	Test
1.	11760	2940	2940	20	5x5	50	5x5	0.001	-	15.07	25.54
2.	11760	2940	2940	30	5x5	50	5x5	0.001	-	15.34	25.00
3.	117600	2940	2940	30	3x3	50	5x5	0.001	0.25	12.99	16.83
4.	117600	29400	29400	30	3x3	50	5x5	0.001	0.25	21.50	30.80
5.	117600	11760	11760	30	5x5	80	5x5	0.001	0.25	13.66	14.44
6.	117600	11760	11760	30	3x3	80	5x5	0.001	0.25	12.67	14.78
7.	117600	11760	11760	20	3x3	50	5x5	0.001	0.25	14.47	14.51
8.	117600	11760	11760	20	5x5	50	5x5	0.001	0.25	14.37	15.51
9.	117600	11760	11760	100	3x3	80	5x5	0.001	0.25	11.26	14.50
10.	117600	11760	11760	120	3x3	80	5x5	0.001	0.25	11.82	14.97
11.	**117600**	**11760**	**11760**	**50**	**3x3**	**80**	**5x5**	**0.001**	**0.00025**	**11.07**	**13.62**

VI. CONCLUSION

In this work, we used a novel deep learning architecture using convolutional neural network to segment glands from the biopsy slides. We have used two convolutional layers, one hidden layer and a logistic regression classifier to do the final classification. From the experimental results, we can conclude that the errors obtained depend upon the parameters of the architecture of CNN. We were able to achieve a minimum validation set error of 11.07% and test set error of 13.62%. We plan to further reduce the error using different classifiers on large datasets. Also, an automated gland classification algorithm has to be designed to classify the tumors as benign, grade3, 4 or 5.

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