Wavelet Based Determination of Malignancy of the Pathological Images of the Prostate

REZA FARJAM, 1 HAMID SOLTANIAN-ZADEH, 1&2 REZA A. ZOROOFI 1
1Control and Intelligent Processing Center of Excellence, Department of Electrical and Computer Engineering, University of Tehran, Tehran 14395-515 IRAN
2 Image Analysis Lab., Radiology Department, Henry Ford Health System, Detroit, MI 48202, USA

Abstract—Malignancy determination of the pathological images of the prostate (PIoP) is very important for treatment planning of prostate cancer. When a cancer is suspected by clinical tests, biopsy specimens of prostate tissue are examined by pathologists for any evidence of cancer, and in the case of cancer, the specimens are used to determine its malignancy. Pathologists do this according to the architecture of the prostate glands. The aim of this paper is to automatically determine the malignancy of the PIoP. A texture based feature extraction method is applied to the image for the segmentation of glandular regions. Wavelet transform (WT) is employed to extract these features. The $K$-means clustering algorithm is then used in the segmentation process. The segmented glandular regions are labeled, and some features related to size and roundness of these regions are computed. These features are combined, and an index is computed which is proportional to the malignancy of cancer. By applying a linear classifier, the malignancy of each specimen is finally determined. To evaluate the performance of the glandular features and the proposed index, we use 161 PIoP. These images are of different magnifications and illuminations. The leave-one-out technique is used to evaluate the accuracy of these features and the index. The maximum accuracy of the features related to the size of the glands, roundness of the glands and the combination of these two, are 86%, 88%, and 92%, respectively. Also, the results show that the proposed method is robust to variations in magnification and illumination.

Key-Words: - Prostate Cancer, Malignancy, Texture Analysis, Wavelet, Linear Classifier.

1 Introduction

Cancer is the second common cause of death after cardiovascular diseases [1]. Prostate cancer is the most prevalent cancer among the men over the age of 50 with 25% of patients dying from the disease [2]. In prostate cancer diagnosis, the patient first undergoes some clinical tests like measuring prostate specific antigen (PSA), digital rectum examination (DRE), CT, MRI, and trans-rectal ultrasound (TRUS) scans [3]-[6]. If a cancer is suspected, biopsy specimens of prostate tissue are taken, stained and viewed by pathologists under a microscope with a fairly low magnification. Pathologists determine the malignancy of cancer according to the architecture of the glands. In benign cases, the glands are well differentiated and of approximately the same size. In malignant cases, the glands are erupted and have irregular shapes. Also, they are not as well differentiated as in benign cases. Malignancy determination of the PIoP is very important for treatment planning of prostate cancer. Furthermore, this is very subjective due to inter and intra observer differences among the pathologists. Also, it is a time-consuming and in some cases a difficult process. Hence, automatic determination of malignancy of PIoP is of interest.

So far, several attempts have been made towards analysis of pathological images [7]-[8]. In [7], an automatic method is proposed for classification of breast cancer in the digital mammography images. An application of gray level co-occurrence matrices and rough theory is investigated in this paper. In this area, a comparison is proposed in [8]. The effects of neural networks, fuzzy logic, genetic programming and combination of these techniques are examined and compared in this article for classification of breast cancer data.

Also, some attempts have been made for the analysis of PIoP [9]-[12]. Stotzka et al. [9] proposed a
method to distinguish the moderately and poorly differentiated samples. In this work, texture features describing the arrangement of nuclei in the image and a neural network are used to classify the images. The nuclear roundness factor analysis (NRF) is proposed in [10] to predict the behavior of the low-grade samples. Since this technique requires manual nuclear contour tracing, it is a time-consuming and tedious method. Furthermore, the NRF analysis can not be applied to any grade because the monotonic relationship between NRF and grade is lost in high grades. Application of gray level co-occurrence matrix is investigated in [11]. In this work, the prostate cancer lesions are interpreted and some features corresponding to the color images are provided. In [12], features related to energy and entropy of the multi-wavelet coefficients of the image are computed and optimally selected using simulated annealing. By using the K-nearest neighbor (K-NN) classifier, the grading process is finally done. In this work, it is assumed that the images have similar illuminations and magnifications.

In our proposed method, we mimic the pathologist to determine the malignancy of cancer. We segment the glandular regions in the image and consider the architecture of them. We extract some features related to size and roundness of the segmented glands. We then combine these features and compute an index corresponding to the malignancy of the cancerous tissues. By applying a linear classifier, we finally determine the malignancy of cancer. We also classify the images using multi-wavelet features proposed in [12]. Experimental results show the efficiency of the proposed method.

The rest of this paper is organized as follows. In Section 2, we briefly discuss clinical aspects of PloP. In Section 3, we present the glandular regions segmentation method. Extracting the glandular features are explained in Section 4. We present the experimental results in Section 5. We conclude in Section 6.

2 Clinical Aspects of PloP
Malignancy of the pathological images of prostate is determined according to the architecture of the glands in the image. Fig. 1(a) illustrates a typical gland. As shown, each gland consists of three main parts, nucleus, stroma and lumina. Regions containing nuclei are those dark areas with low homogeneity and high variance while stroma and lumina are bright regions with high homogeneity and low variance. In a normal gland, the lumina is located at the center and usually has an irregular shape. Also, it is the most bright region in the gland. Stroma, surrounds the lumina with nuclei floating in it. In a normal gland, these regions are arranged such that the gland is a round mass.

3 Glandular Regions Segmentation
To segment the glandular regions in the image, we propose the following wavelet based feature set.

3.1 Wavelet Transform (WT)
By WT, we mean the decomposition of signal with the family of orthogonal bases obtained through translation and dilation of a kernel function $\psi(t)$ known as the mother wavelet. To construct the mother wavelet, we first determine a scaling function $\phi(t)$ which satisfies the following difference equation [16].

$$\phi(t) = \sqrt{2} \sum_{k} h(k).\phi(2t - k), \forall k \in \mathbb{Z} \quad (1)$$

The mother wavelet $\psi(t)$ is related to the scaling function via:
In the above equations, \( h(k) \) and \( g(k) \) are low-pass and high-pass filters, respectively [16]. Applying WT to the image \( I \) in the first level of decomposition creates four images with the half length of the original image (\( I_{LL}, I_{LH}, I_{HL}, I_{HH} \)).

### 3.2 Texture Features

We extract the roughness information of the image via:

\[
f(x, y, s) = \exp\left[ -\frac{x^2 + y^2}{2s^2} \right].
\]

The first derivative of function \( f \) in direction \( \theta \) is computed as [17]:

\[
f'_0(x, y, s) = f'_x \cos(\theta) + f'_y \sin(\theta)
\]

where \( f'_x, f'_y \) are the first derivatives of \( f \) with respect to \( x, \) and \( y, \) respectively. To compute an informative feature set, the following procedure is done.

- Convolve \( f'_0 \) with each of the four components of the original image in different directions (\( f'_0 \ast (I_{LL}, I_{LH}, I_{HL}, I_{HH}) \)), for each pixel of these components, consider a symmetric neighborhood and convolve \( f'_0 \) with this window.
- Compute the power of each convolution. Call the resulting values \( F_{0w}(LL), F_{0w}(LH), F_{0w}(HL), \) and \( F_{0w}(HL) \), respectively (\( F_{0w}(.) \) is a matrix with the half length of the original image).
- Compute the average of \( F_{0w}(.) \) with respect to \( \theta \) (\( F_w(LL), F_w(LH), F_w(HL), F_w(HL) \)).
- Apply the inverse WT to each of the above components assuming the other components are zero (\( F(LL), F(LH), F(HL), F(HL) \)).
- Employ the following operators to obtain the feature set:
  \[
  F_1 = F(LL),
  F_2 = \sqrt{F(LL) \cdot F(LH) \cdot F(HL) \cdot F(HH)},
  F_3 = F(LL) + F(LH) + F(HL) + F(HH),
  F_4 = \sqrt{\frac{F(LL)}{F(LH) + F(HL) + F(HH)}},
  F_5 = F(HH).
  \]

In the above, \( w \) refers to wavelet space. We consider feature \( F_1 \) for highly structural patterns (in these patterns high frequency components are less important), features \( F_2, F_3, \) and \( F_4 \) for fairly structural or statistical patterns, and feature \( F_5 \) for highly statistical patterns (in these patterns, high frequency components are very important). We compute these features in scales \( s = 1, 2, 3 \) (see (3)). Thus, we obtain a feature set containing 15 elements for each pixel.

### 3.3 Applying Variance Filter

In practice, the biopsy samples are stained by solvents with their own illuminations and colors. The differences between solvents characteristics may affect the segmentation process. To avoid this problem, we first make the image \( I \) gray scale \( I_{gs} \), and then apply a variance filter to the gray scale image \( I_v \). This filter assigns each pixel, the variance of the corresponding neighborhood intensities. Since the regions containing nuclei have higher variance than the regions containing stroma and lumina, applying variance filter to the gray scale image, makes these regions brighter than the others. Fig. 2 shows an example of the above process.

![Fig. 2. Applying variance filter to a prostate biopsy image. (a) Original image, (b) gray scale image, (c) the resultant image after applying variance filter.](image)

### 3.4 K-means Clustering Algorithm

For the segmentation of glandular regions, we employ the K-means clustering algorithm [18] as follows.

- Take the WT of the images \( I_{gs} \) and \( I_v \) in the first level of decomposition.
- Apply the feature extraction method explained in section 3.2 to the resulting images.
- Apply the K-means clustering to the resulting feature space of the image \( I_{gs} \) for the segmentation of stroma and lumina. Assume the feature space is of two clusters. One, is the regions containing stroma and lumina and the other is nuclei.
- Apply the K-means clustering to the resulting feature space of the image \( I_v \) for the segmentation of nuclei with the same assumption.
- Obtain the glandular regions by excluding the regions containing nuclei from the regions containing stroma and lumina.

In Fig. 3, an example of the glandular regions segmentation is shown.
4 Glandular Features

4.1 Labeling Segmented Regions

To extract the glandular features we need to label the segmented glands. We consider the connectivity of each pixel in the segmentation map with respect to the others. We put all connected pixels into a category and assign each category a label (color). Fig. 4 shows a typical labeled segmented image.

![Fig. 4. Labeling segmented regions. (a) A malignant sample, (b) labeled glandular regions, (c) overlaying the boundaries of (b) on (a).](image)

4.2 Variance Feature

The glands in benign specimens are approximately of the same size, while in malignant cases they are merged and have different sizes. Furthermore, in benign cases the glands are morphologically similar and are approximately of the same illumination. In malignant cases, not only the glands are not similar but also are of different illumination. We consider this point in the definition of the first feature. Assume \( L_i \) is the label of the \( i \)th gland. \( SB(i) \), size of the mentioned gland including its illumination is obtained by:

\[
SB(i) = \sum_{k=1}^{N} \delta(L(k) - L_i) \cdot I_{gs}(k), \quad i = 1, 2, ..., M
\]

where \( \delta \) is a discrete delta function, \( N \) is the number of pixels in the image, \( k \) represents the \( k \)th pixel, \( I_{gs}(k) \) is the intensity of the \( k \)th pixel in the gray scale image, \( L(k) \) is the label of \( k \)th pixel, and \( M \) is the number of the glands in the segmentation map. The first feature, \( MF_1 \), is obtained as (7). The higher the \( MF_1 \), the higher the malignancy of the specimen.

\[
MF_1 = \frac{\text{variance}(SB)}{[\text{mean}(SB)]^2}.
\]

4.3 Roundness Factor

The glands in benign specimens are approximately round, while in malignant specimens, they are erupted and have irregular patterns. We consider the roundness of the glands as the second and the most important feature. Assuming \( S(i) \) is the area of the \( i \)th gland, \( r(i) \) is the radius of a circle with area of \( S(i) \), and \( SR(i) \) is the periphery of the \( i \)th gland, the roundness factor of a gland is computed via:

\[
R_n(i) = \frac{SR(i)}{S(i) \cdot 2} \cdot r(i)
\]

where \( p \) is the pixel size, and \( R_n \) is the roundness factor of the \( i \)th gland. For a circle \( R_n \) is 1. The higher the roundness of a gland, the closer the \( R_n \) to 1. To consider this point in the system, we calculate the following parameter for each gland.

\[
S_{Rn}(i) = S(i) \cdot \exp(-|1 - R_n(i)|)
\]

the closer the \( R_n \) to 1 the closer the \( SRn(i) \) to \( S \). We compute sum of the \( S \)’s and \( SRn \)’s of all glands.

\[
S_t = \frac{1}{N} \cdot M \sum_{i=1}^{M} S(i)
\]

\[
S_{tRn} = \frac{1}{N} \cdot M \sum_{i=1}^{M} S_{Rn}(i)
\]

Ultimately, the second feature is computed as follows:

\[
MF_2 = \frac{S_t - S_{tRn}}{S_t}
\]

In benign specimens with the round glands, \( MF_2 \) is small. In malignant cases which the glands have irregular patterns, \( MF_2 \) is large. We normalize \( MF_1 \) and \( MF_2 \) such that they have values between 0 and 1. We then combine them to compute an index which is proportional to the malignancy of each specimen:

\[
CI = MF_1^2 + MF_2^2
\]

In (12), \( CI \) is a cancer index and has low values for benign cases and high values for malignant cases. In Fig. 5, a block diagram of overall system is shown.

![Fig. 3. Segmentation of the glandular regions in a prostate biopsy image. (a) A benign sample, (b) resultant image after applying variance filter, (c) segmentation of stroma and lumina, (d) segmentation of nuclei, (e) excluding nuclei from stroma and lumina, (f) overlaying the boundaries of (e) on (a).](image)
5 Experimental Results

To evaluate the performance of the proposed method, we used a dataset containing 161 pathological images which includes Gleason grades #1, #2, #4, and #5 (we exclude grade #3, because this is a transition grade and its malignancy is highly dependent on clinical tests). These images have different sizes, illuminations, and magnifications. This dataset contains 41 benign and 120 malignant cases. The malignancy of each case is determined by pathologists.

To evaluate the accuracy of the glandular features and the proposed index, we used the leave-one-out technique [18]. Tables 1 shows the accuracy of $MF_1$, $MF_2$, and $CI$ for classification of the images obtained using different wavelet bases. As noted, the best results correspond to db3. Also, the results show that $MF_2$ is stronger than $MF_1$ and determine the malignancy of the specimens with an accuracy of about 88%. Also, the results show that $CI$ is better than each of them and determine the malignancy of the samples with an accuracy of about 92%.

We also applied the proposed method to 46 images of grade #3. Our proposed system considers these samples as malignant cases with an accuracy of about 83% obtained for db3. Furthermore, We classified the images using multi-wavelet features proposed in [12]. We computed energy and entropy of the multi-wavelet coefficients of the images in the first and second levels of decomposition. We extracted these features for either repeated row or critically sampled preprocessing. To evaluate the error rate of the features, we used a $k$-NN classifier and simulated annealing (SA) algorithm like [12]. Table 2 shows the results.

Table 1. Accuracy percentage of $MF_1$, $MF_2$, and $CI$ for classification of the images obtained using different Wavelet bases (W.B). Ave. Acc = Average Accuracy.

<table>
<thead>
<tr>
<th>W.B</th>
<th>Haar</th>
<th>Db3</th>
<th>Sym1</th>
<th>Coif1</th>
<th>Bior1.1</th>
<th>Bior3.3</th>
<th>Ave. Acc</th>
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<tbody>
<tr>
<td>$MF_1$</td>
<td>81</td>
<td>86</td>
<td>84</td>
<td>84</td>
<td>83</td>
<td>80</td>
<td>83</td>
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<tr>
<td>$MF_2$</td>
<td>83</td>
<td>88</td>
<td>86</td>
<td>87</td>
<td>86</td>
<td>85</td>
<td>85.8</td>
</tr>
<tr>
<td>$CI$</td>
<td>88</td>
<td>92</td>
<td>90</td>
<td>91</td>
<td>89</td>
<td>89</td>
<td>89.8</td>
</tr>
</tbody>
</table>

Table 2. Accuracy results of energy and entropy features proposed in [12] for either repeated low or critically sampled preprocessing. The results obtained in first and second levels of decomposition. r.r = repeated row, c.s = critically sampled.

<table>
<thead>
<tr>
<th>Level of Decomposition</th>
<th>1st level</th>
<th>2nd level</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k$</td>
<td>1 3 5 7</td>
<td>1 3 5 7</td>
</tr>
<tr>
<td>$L_T$</td>
<td>GHM 82</td>
<td>80 79 77</td>
</tr>
<tr>
<td></td>
<td>CL 83</td>
<td>81 80 78</td>
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<tr>
<td></td>
<td>SA4 84</td>
<td>82 80 79</td>
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<tr>
<td></td>
<td>BiGHM2 83</td>
<td>81 80 78</td>
</tr>
<tr>
<td></td>
<td>BiH32 83</td>
<td>81 79 79</td>
</tr>
<tr>
<td></td>
<td>CardBal2 77</td>
<td>75 73 73</td>
</tr>
<tr>
<td>$L_S$</td>
<td>GHM 84</td>
<td>80 79 78</td>
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<tr>
<td></td>
<td>CL 83</td>
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<td></td>
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<tr>
<td></td>
<td>BiGHM2 80</td>
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<td></td>
<td>BiH32 84</td>
<td>83 81 81</td>
</tr>
<tr>
<td></td>
<td>CardBal2 81</td>
<td>80 79 77</td>
</tr>
</tbody>
</table>

Tables 1 and 2 show that the proposed method outperforms the method of [12]. In fact, the difference of illumination of the images changes level of the energy. Hence, when we decompose the samples and compute the energy of different sub-bands, this produces an error. Also in benign cases, when the images are captured using low magnifications, the glands are seen more uniformly than when they are captured using high magnifications (see Figs. 6-b and 6-c). This also affects the level of the entropy of the images. In Fig. 6, six pathological images and the labeled segmented glandular regions are shown. These samples are of different magnifications and illuminations. As shown, the proposed method is robust to variations in magnification and illumination. The values of features $MF_1$ and $MF_2$ are also noted.
Fig. 6. Examples of prostate biopsy images and their glandular regions segmented by db3. They have different illuminations and magnifications. (a-c) Three benign samples with \( MF_1 = 0.22, 0.27, 0.24 \), and \( MF_2 = 0.28, 0.20, 0.16 \), respectively. (d-f) Three malignant samples with \( MF_1 = 0.78, 0.71, 0.75 \) and \( MF_2 = 0.66, 0.74, 0.74 \), respectively.

6 Conclusion

In this paper, we have proposed and evaluated an automatic method for malignancy determination of the pathological images of the prostate. In the proposed approach, a wavelet-based technique is used to segment the glandular regions in the image. Features related to size and roundness of these regions are then extracted and combined to determine the malignancy of the images. The proposed method has been evaluated using a dataset containing 161 pathological samples. A maximum accuracy of about 92% has been achieved in our experience.

References