Chapter 6

Detection and Grading of Exudative Maculopathy

6.1 Introduction

Diabetic maculopathy is one of the complications of diabetes mellitus that is considered as the major cause of vision loss among people around the world. It results from the leakage of fluid rich in fat and cholesterol from damaged retinal vasculature. Accumulation of these fluids called exudates near the center of the retina, i.e., macula as indicated in the Figure 6.1 leads to distortion of the central vision.

Fig. 6.1: Diabetic maculopathy condition in colour retinal image; (a) Hard exudates in the macular region; (b) Enlarged exudates.
Progression of diabetic maculopathy is slow and silent, very often without any symptoms in the early stages. If maculopathy is not detected in the early stage then the damage of the macula or visual field is irreversible and can lead to blindness. Therefore, compulsory regular screening of diabetic eye will help to identify the maculopathy at initial stage and reduce the risk of severe vision loss. Digital screening of maculopathy results in generation of large number of retinal images to be manually analyzed by an expert. This often leads to observer fatigue and increase in the time taken for diagnosis. In this chapter a computer based system for automatic detection and grading of diabetic maculopathy severity level without manual intervention is presented as shown in Figure 6.2. The automatic detection of optic disc and macula are described in the Chapter 5. Optic disc is masked during the detection of exudates. Diameter of the disc and position of macula are used to mark the macular region. Hard exudates are detected using clustering and mathematical morphological techniques. Based on the location of hard exudates in marked macular region the severity level of maculopathy is classified into mild, moderate and severe. Following sections of the Chapter describes these methods in detail. Also, a graphical user interface has been developed for the use of clinicians during the mass screening is explained.

Fig. 6.2: Automatic diabetic maculopathy severity grading system.
6.2 Detection of Hard Exudates

Hard exudates are abnormal lesions caused by diabetic retinopathy in a diabetic’s eye. They are associated with patches of retinal vascular damage with leakage. They are considered to be one of the bright intensity regions in the retinal images and appear as random yellowish patches. The size and distribution of exudates may vary during the progress of the disease. The segmentation of hard exudates is achieved in two steps. First, candidate exudate regions are detected using a K-Means clustering method. After this, morphological reconstruction method is applied to find the exact exudate regions. The optic disc which has almost the same intensity as exudates is masked during the exudate detection process to avoid false positives.

6.2.1 Coarse Segmentation of Hard Exudates

Even though hard exudates are considered as bright regions in a retinal image, there are various factors that affect the segmentation of exudates using a single global threshold. For instance, the contrast enhancement algorithm not only enhances the brightness of lesions but also increases the brightness of some pixels. These pixels will be wrongly recognized as lesion pixels. There is also a possibility that segmented image may contain lesions like cotton wools, drusen and pixels surrounding the optic disc. Therefore to classify the segmented region into exudates or non exudates, K-Means clustering method is employed. In a colour retinal image, bright structures like exudates and optic disc appear more contrasted in green channel image as described in Chapter 5. Therefore, only green channel of the original RGB image is used for exudeate detection. Initially, a median filter of size $15 \times 15$ is applied to reduce the uneven illumination in the green channel image.
Then, intensity difference image required for the clustering operation is obtained by subtracting the median filtered image from the green channel image as shown in Figure 6.3. This isolates the bright lesions and optic disc regions from the dark background.

![Fig. 6.3](image)

Fig. 6.3: Creation of intensity difference image for clustering in image space; (a) Colour retinal image; (b) Green channel image; (c) Intensity difference image.

The clustering method separates a set of data points into clusters according to the attributes of data. The important measurement of similarity for data is distance between cluster centers and between points inside one cluster. In intensity difference retinal image, the distance measure is the difference in the intensity values between two pixels. Here, the number of cluster required will be two, i.e., dark
background cluster and bright lesion cluster. Exudates cluster will be located in the higher intensity range along with optic disc and other bright lesions and background cluster in the lower intensity range. Initial cluster centroid of exudate cluster \( C_E \) is set to \( \text{max} \), the maximum intensity level in the intensity difference image. And initial cluster centroid of background cluster \( C_B \) is set to \( \text{min} \), the minimum intensity level in the intensity difference image. The clustering performed in the image space is as follows:

1. At step \( k = 1 \), \( C_E (k) = \text{max}, C_B (k) = \text{min} \).

2. for \( i = 1,2, \ldots, m \times n \)
   
   \( X_i \) is the intensity level of pixel \( i \)
   
   \( D1 = \text{distance} (X_i, C_E (k)) \)
   
   \( D2 = \text{distance} (X_i, C_B (k)) \)

   if \( D1 < D2 \)
   
   Pixel \( i \) belongs to exudates cluster

   else

   Pixel \( i \) belongs to background cluster

3. Update cluster centers \( C_E (k+1) \) and \( C_B (k+1) \)

4. \( k = k+1 \), repeat steps 2 to 4 until stopping conditions is met.

The stopping condition can be that the distance between the two successive cluster centers is not more than user specified value. In this case it was found that maximum of three iterations are enough to separate the candidate lesion regions from the background. Therefore number of iterations was limited not more than three. Figure 6.4 shows the result of clustering in the image space. The optic disc that is part of bright regions is removed from further processing as it may result in false positive. Chapter 5 describes the detection of optic disc region.
6.2.2 Fine Segmentation of Exudates

The segmentation of image by clustering results in number of candidate exudate regions. In order to correctly classify the exudate pixels from the non exudate pixels, morphological image reconstruction is used. This is an iterative method that extracts regions of interest from an image by repeated dilation on two images, a marker and a mask. Let $I_f$ be the marker image and $I_v$ be the mask image such that $I_f \leq I_v$. Then the conditional dilation operation $R_i(I_f, I_v)$ is given as follows:

$$R_i(I_f, I_v) = (I_f \oplus B)^* I_v$$

(6.1)

The marker $I_f$ is allowed to grow in the region by a structuring element $B$ that is restricted by mask $I_v$. This process is repeated until the condition $R_i(I_f, I_v) = R_{i-1}(I_f, I_v)$ is met. The rough exudate regions obtained from the coarse segmentation are overlaid on the green channel image to get marker image and the original green channel image is used as a mask. The morphological reconstruction by dilation is then applied on the overlaid image. The dilations of marker image
under mask image are repeated until the contour of marker image fits under the mask image to get reconstructed image. Figure 6.5 shows the difference image obtained by subtracting the morphological reconstructed image from the original image.

![Images](a) Marker image; (b) Mask image; (c) Morphological reconstructed image; (d) Difference image.

Fig. 6.5: Morphological reconstruction operation for the segmentation of exudates; (a) Marker image; (b) Mask image; (c) Morphological reconstructed image; (d) Difference image.

A fundus boundary mask is generated for each image as described in the chapter 3. Only those pixels that are inside the fundus mask are considered as exudate pixels. Finally exudate pixels in an image are obtained by thresholding the difference image. The threshold
value varies from one retinal image to another. Therefore, a local entropic threshold for each image is calculated as described in the chapter 4. Figure 6.6 shows the final thresholded image and overlapping of detected exudate pixels on the colour retinal image. In the Figure 6.6(d) it can be seen that the cotton wool spot is not detected as exudate region. But, the image variance method (Walter et al., 2002) results in detection of cotton spot as part of exudate region.

Fig. 6.6: Fine segmentation of hard exudates; (a) Thresholded exudate pixels; (b) Exudates overlaid on original image; (c) Another example of colour retinal image; (d) Segmented exudates; (e) Enlarged view of detected exudates.
6.3 Automatic Severity Level Grading of Diabetic Maculopathy

Diabetic maculopathy is the condition of retinopathy where exudates are present within the macular region. Severity of the maculopathy depends on how close exudates are to the center of macula. In the CSME stage, most of the retinal blood vessels are damaged and the leakage area becomes bigger. The exudates leak out and this liquid concentrates very close to the fovea. The visibility is greatly affected as the image cannot be focused on the macula properly. The condition where the locations of exudates are far away from the center and outside the macular region is sometimes called clinically non significant macular edema. Here the patient will not realize that he is affected as there are no visible symptoms.

The severity level in CSME is classified as mild, moderate and severe based on the international grading standard. In an attempt to improve the communication worldwide between ophthalmologists and primary care physicians caring for patients with diabetes, an international clinical disease severity scale was recently developed as shown in Table 6.1. In this work, automatic grading of diabetic maculopathy is done according to this standard diabetic macular edema disease severity scale. This scale is based on the Early Treatment of Diabetic Retinopathy Study (ETDRS) classification of diabetic retinopathy. ETDRS has been set to assign a severity level based on evaluation of stereo retinal images of people suffering from diabetic retinopathy, and is described as the gold standard for early detection and treatment.
Table 6.1: International clinical diabetic macular edema severity scale

<table>
<thead>
<tr>
<th>Proposed Disease Severity Level</th>
<th>Findings Observable upon Dilated Ophthalmoscope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic macular edema apparently absent</td>
<td>No hard exudates in posterior pole</td>
</tr>
<tr>
<td>Diabetic macular edema apparently present</td>
<td>Some exudates in posterior pole</td>
</tr>
</tbody>
</table>

If diabetic macular edema is present, it can be categorized as follows:

<table>
<thead>
<tr>
<th>Proposed disease severity level</th>
<th>Findings observable upon dilate ophthalmoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic macular edema present</td>
<td>・Mild diabetic macular edema: some hard exudates in posterior pole but distant from the center of the macula (&gt;1DD and &lt;2DD)</td>
</tr>
<tr>
<td></td>
<td>・Moderate diabetic macular edema: Hard exudates approaching the center of the macula but not involving the center (&gt;1DD and &gt;1/3 DD)</td>
</tr>
<tr>
<td></td>
<td>・Severe diabetic macular edema: Hard exudates involving the center of macula (less than 1/3 DD)</td>
</tr>
</tbody>
</table>

After the detection of hard exudates, the macula is located based on its relative position from the optic disc as described in the chapter 5. The macular region is then divided into three marker regions using three circles with radii 1/3 of optic Disc Diameter (DD), 1 DD and 2 DD centered at macula. In any given image if the exudates are absent, then it is classified as normal without any maculopathy (Figure 6.7(a)). If exudates are present and are outside the 2DD region then it is classified as clinically non-significant macular edema. Presence of exudates within the 2DD is classified as clinically significant macular edema and it has to be treated by laser. In case of CSME, the presence of exudates outside the 1DD region is termed as mild (Figure 6.7(b)). The moderate case is one with presence of exudates within the 1DD region not involving the center of the macula called foveola, i.e., outside the circle of 1/3 DD (Figure 6.7(c)). In severe case, the exudates are present inside the 1/3 DD region obscuring the center of macula (Figure...
6.7(d)). This is the most sight threatening stage of maculopathy where vision is significantly reduced. Figure 6.7 shows the results of the automatic maculopathy detection and grading system without any manual intervention. It can be seen that the results provide a valuable aid for the clinician in identifying severity level of the disease.

Fig. 6.7: Exudative maculopathy severity grading; (a) Normal; (b) Mild stage; (c) Moderate stage; (d) Severe stage of maculopathy.
6.4 Graphical User Interface for Automatic Detection of Retinal Features

A graphical user interface has been implemented in Matlab 7.0 using Graphical User Interface Development Environment (GUIDE). It can be initialized through its main window (Figure 6.7). The interface currently comprehends:

- Selecting and opening the retinal images from three different databases. Namely, KMC, DRIVE and STARE retinal databases. The DRIVE and STARE databases are mainly used for the detection and evaluation of retinal vessel extraction method.

- Option to find the location and diameter of optic disc. Also its exact boundary can be detected.

- Option to find the macula and to automatically draw macular region is provided.

- Retinal blood vessels can be segmented using the gabor filter based method as described in the Chapter 4. The performance of vessel extraction method can be observed using sensitivity and specificity as evaluation parameters.

- Hard exudates detection method is provided.

- Option for automatic detection and severity level grading of diabetic maculopathy is provided.

- Option to save the result images for further analysis is provided.

Some of the snapshots of the GUI are as follows.
Fig. 6.8: Snapshots of GUI for the automatic identification of features in colour retinal images.
6.5 Results and Discussion

For the evaluation of automatic grading of diabetic maculopathy, 148 digital colour retinal images were used from KMC dataset. Among these, 52 are normal retinal images without any signs of maculopathy and 96 images are identified as clinically significant macular edema images by an ophthalmologist. Another dataset called Diaretdb1 was used for evaluating the hard exudate detection method. This dataset provided 88 colour retinal image along with information of presence or absence of exudates in image. Image based sensitivity and specificity is used to evaluate the performance of the exudate detection method and it is summarized as shown in Table 6.2. In KMC database, the hard exudates were detected correctly in 94 images with sensitivity of 97.9%. Out of 52 normal images two were classified as diseased with the specificity of 96.1%. The wrong classification was a result of high brightness in an image due to over exposure of the retina during the imaging.

Table 6.2: Performance of hard exudates detection method

<table>
<thead>
<tr>
<th>Database</th>
<th>No. of images</th>
<th>No. of normal images</th>
<th>No. of images with exudates</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KMC</td>
<td>148</td>
<td>52</td>
<td>96</td>
<td>97.9%</td>
<td>96.1%</td>
</tr>
<tr>
<td>Diaretdb1</td>
<td>88</td>
<td>45</td>
<td>43</td>
<td>93%</td>
<td>97.7%</td>
</tr>
</tbody>
</table>

Center of macular region was not detected properly in five images due to the poor contrast in the image and these were not considered to evaluate the automatic grading of maculopathy. The exudates detection method was tested on Pentium PC with 1.66 GHz and 1.5GB memory using Matlab 7.0. Each image took less than a minute to find the exudate regions. The result of the exudates detection
was superimposed on the original image and it was found that the previously unclear exudate regions were visibly highlighted and aided clinicians to identify pathology in less time. The overall performance of the system to automatically detect the maculopathy stages is given in the Table 6.3. Total of 143 images were considered from the database. Five images were not considered as the macula center was not detected properly due to the poor image quality. 91 images with different level of Exudative maculopathy and 52 normal images were considered for the evaluation. The overall sensitivity of 95.6% and specificity of 96.15% was achieved.

Table 6.3: Performance the maculopathy severity grading

<table>
<thead>
<tr>
<th>No. of images</th>
<th>True positive</th>
<th>True negative</th>
<th>False positive</th>
<th>False negative</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>143</td>
<td>87</td>
<td>50</td>
<td>2</td>
<td>4</td>
<td>95.6%</td>
<td>96.15%</td>
</tr>
</tbody>
</table>

For the statistical significance analysis of maculopathy severity level detection method, the area covered by the exudates in three circular regions R1, R2 and R3 centered at macula as in Figure 6.9 is considered.

Fig. 6.9: Illustration of macular regions
Based on the presence of hard exudates in the marked macular regions, Table 6.4 gives the distribution of exudates in the macular regions for the classification of maculopathy severity level.

Table 6.4: Classification of maculopathy severity level

<table>
<thead>
<tr>
<th>Severity level</th>
<th>Hard exudates</th>
<th>R2</th>
<th>R3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Moderate</td>
<td>Present/Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Severe</td>
<td>Present/Absent</td>
<td>Present/Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

Total area of the hard exudates in region R1, R2 and R3 are found for different severity levels. This data is subjected to ANOVA (Analysis of Variance between the three groups) to test the statistical significance. But for the data presented for the test in this case, the normality assumption is violated. That is, data is not normally distributed; this is due to large variations in the pixel values within the groups. Therefore, Kruskal-Wallis rank test, a non-parametric procedure has been used for testing clinical significance as follows.

Kruskal-Wallis test is an alternative to the one-way ANOVA F test. Instead of comparing each of the group means against grand mean, the Kruskal-Wallis test compares the mean rank in each of the groups against the overall mean rank. If there is a significant difference among the different groups, the mean rank differs considerably from group to group. In process of squaring these differences, the test statistic $H$ becomes large. If there are no differences present, the test statistic $H$ is small because the mean of the ranks assigned in each group should be very similar from group to group. The equation 1, defines the Kruskal-Wallis test statistic, $H$.

$$H = \left[ \frac{12}{n(n+1)} \sum_{j=1}^{c} \frac{T_j^2}{n_j} \right] - 3(n+1) \quad (6.2)$$
where

\[ n = \text{total number of values over the combined samples} \]
\[ n_j = \text{number of values in the } j^{\text{th}} \text{ sample} \]
\[ T_j = \text{sum of the ranks assigned to the } j^{\text{th}} \text{ sample} \]
\[ T_j^2 = \text{square of the sum of the ranks assigned to the } j^{\text{th}} \text{ sample} \]
\[ C = \text{number of groups} \]

To illustrate the Kruskal-Wallis test for differences among 3 medians, we consider the following data for severe maculopathy as in Table 6.5. Similarly data for mild and moderate maculopathy are also prepared.

Table 6.5: Exudates area in three regions of severe maculopathy

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>160</td>
<td>759</td>
<td>816</td>
</tr>
<tr>
<td></td>
<td>153</td>
<td>552</td>
<td>723</td>
</tr>
<tr>
<td></td>
<td>3324</td>
<td>546</td>
<td>212</td>
</tr>
<tr>
<td></td>
<td>1467</td>
<td>827</td>
<td>711</td>
</tr>
<tr>
<td></td>
<td>856</td>
<td>1927</td>
<td>394</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>151</td>
<td>276</td>
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Define Null hypothesis \( H_0 \) and Alternate hypothesis \( H_1 \) to start the test.

\( H_0 : \text{There is no difference between the regions} \)

\( H_1 : \text{There is a difference between the regions (at least one of the region differs from others)} \)

The Alpha value at start is considered to be \( \alpha = 0.05 \), and the degrees of freedom is 2. The test statistic, \( H \), is approximated by chi-square distribution. It is found that for a given alpha value 0.05 and degrees of freedom 2, the critical value \( \chi^2 \) is 5.99147. Therefore, the decision rule is

Reject \( H_0 \) if \( H > \chi^2 \)
Otherwise do not reject $H_0$

The statistic $H$ approximately follows a chi-square distribution with $C-1$ degrees of freedom. Using a 0.05 level of significance, $\chi^2$, the critical value of the chi-square distribution with $C-1 = 2$ degrees of freedom is 5.99147.

Table 6.6: Kruskal-Wallis Rank test for statistical significance of maculopathy severity levels

<table>
<thead>
<tr>
<th>Severity level</th>
<th>Average Rank</th>
<th>Test Statistic</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
</tr>
</tbody>
</table>
| Mild           | 38 | 15.5 | 15.5 | 29.34 | $p<0.05$
| Moderate       | 71 | 50 | 15.5 | 69.03 | $p<0.05$
| Severe         | 36 | 33 | 22 | 7.162 | $p<0.05$

Because the computed value of the test statistic $H = 7.162$ is greater than the critical value, the null hypothesis is rejected and conclude that there is a difference between the regions with respect to number of exudate pixels. The same conclusion is reached by using the $p$-value approach. Here, the $p$-value = 0.0278 < 0.05, indicating that it is clinically significant. The Table 6.6 shows the Kruskal-Wallis test performed on the mild, moderate and severe level of exudative maculopathy. Based on the result it is seen that there is significance difference between at least two regions.

The results obtained from the methods are also in accordance with the standard given in Mead et al., 2001. It states that a minimum standard of 80% sensitivity and 95% specificity is to be achieved by any automatic method for the detection of diabetic related eye disease. The result obtained from the work has met the requirement. The graphical user interface developed can be used by clinicians during the mass screening of diabetic retinopathy.
6.6 Summary

In this Chapter, the development of automatic retinal image processing system for detection and grading of maculopathy has been described. For the automatic detection of maculopathy two features in retinal image are needed. One is the macula, based on its position and optic disc diameter, macular region has been drawn. Another feature is hard exudates. The coarse segmentation of exudates, which was achieved using K-Means clustering provided a better initial coarse segmentation when compared with the variance based method proposed in the literature. In variance based segmentation cotton wools were considered as part of exudates. This resulted in classifying cotton wool spots as exudates in the end result. Also automatic threshold calculation after morphological reconstruction was important, and it was achieved with entropic thresholding. The existing models of retinal screening are expensive, time consuming and require trained ophthalmologists. The developed automatic system was able to detect diabetic maculopathy and its severity level in less time. The sample image data used to validate this software was comparable across manual graders with regard to the distribution of severity of the disease. It also provides a user interface for speedy analysis of large number of retinal images during the mass screening of diabetic related eye diseases. It is hoped that this system can assist the ophthalmologists to detect the signs of diabetic retinopathy in the early stage, in disease monitoring and for a better treatment plan.