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Introduction

Fundus is an eye area that includes inner parts of the retina: optical disc, blood vessels, and macula. A digital image of this area, typically acquired using a fundus camera, is called a fundus image. A sample of fundus image containing labels of its different parts is shown in Fig. 1.1. Such images provide various pathological signatures indicating diseases like glaucoma [Joshi *et al.*, 2011], diabetic retinopathy (DR) [Mookiah *et al.*, 2013], cataract [Guo *et al.*, 2015] etc. Diagnosis through fundus images is done via inspection of morphological changes in the optical disc, macula, and blood vessels. Fundus images are also very effective in the diagnosis of various systemic diseases like cerebral diseases, kidney diseases, brain tumors, etc. Among all ocular diseases, DR is one of the primary causes of vision loss worldwide. This ophthalmic complication is developed due to uncontrolled Diabetes Mellitus. According to World Health Organization, there are a total of 422 million people already diagnosed with Diabetes [WHO, 2020]. Also, it is expected that the number of patients diagnosed with diabetes will get double around the world by 2030. Here, almost one-third of the people already diagnosed with diabetes, are on their way to develop DR. Similarly, a large proportion of the world population is affected by other ocular diseases.

For effective medical assistance to such a large number of patients, there is an inadequacy of the required number of ophthalmologists, specially in developing countries. According to a report [ICO, 2020] published by the international council of ophthalmology, there are only 11 ophthalmologists available per million population in India. Also, the distribution of the number of ophthalmologists in developing countries like India is not equitable, higher concentration in metros than in rural areas. This makes Telemedicine and computer-aided diagnosis (CAD) systems very important.

CAD systems are very effective in diminishing the diagnostic oversights and consequently the false negative rates of ophthalmologists [Sinthanayothin *et al.*, 2002]. The indicative significance of a fundus image relies on its visual quality perceived by an ophthalmologist. Regardless of whether it is manual or mechanized, to guarantee a dependable conclusion, the quality of the fundus images must be guaranteed. However, in a real-time scenario, many factors affect the quality of a fundus image. A study [MacGillivray *et al.*, 2015] at UK BioBank indicates that more than 25% fundus images do not fall into the category of good quality. Advancement in optics, computerized sensors, and picture handling led to the invention of sophisticated imaging devices like smartphone-based retinal imaging system D-EYE and the panoptic ophthalmoscope, shown in Fig. 1.2 (a) and (b). It allows an affordable way to capture, store and share the fundus images with minimum effort. However, due to ease of use, fundus images acquired using such devices are more susceptible to various types of distortions than by devices in controlled set-up. Therefore such images demands strict quality assessment and enhancement if required before using the same in CAD system-based diagnosis.

Next in this Chapter, a brief introduction to the image quality assessment and image enhancement/denoising is provided in Section 1.1; Section 1.2 explains the mathematical reasoning behind need of separate quality assessment and enhancement methods for fundus images; finally, Section 1.3 discusses the commonly appearing distortions and the factors affecting the quality of fundus images.

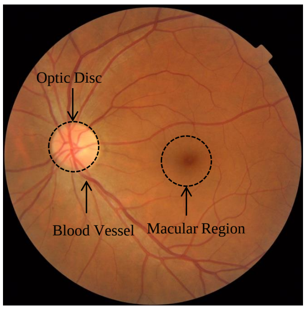

Figure 1.1 : Sample fundus image indicating different structures in a fundus image: (i) Optic disc, (ii) Macula, and (iii) Blood vessels.

(a) D-EYE (b) Panoptic Ophthalmoscope

Figure 1.2 : Advanced fundus image acquisition devices: (a) D-EYE, (b) Panoptic Ophthalmoscope. Image Credits: D-EYE [HOSPEQ, 2020], and Panoptic Ophthalmoscope [EYEWIRE.News, 2020]

1.1 BRIEF INTRODUCTION TO IMAGE QUALITY ASSESSMENT AND IMAGE ENHANCEMENT

1.1.1 Image Quality Assessment (IQA)

It is the process of analyzing the quality of an image. The subjective and objective IQA are the two types of methods that are used for the IQA process. Subjective IQA is performed by the human observers and it is assumed to be the most reliable method as humans are the end users in most of the multimedia applications. The types of subjective quality assessment methods and their guidelines are provided by the International Telecommunication Union (ITU) in recommendation BT.500-13 [Union, 2012] (although the focus of this one is television pictures) and ITU-T P.912 [Union, 2015], addressing video quality assessment methods for recognition tasks. For medical images, a standard recommendation is still missing. For a review on the IQA methods used in the medical imaging area, the reader can refer to [Lévêque *et al.*, 2018].

Subjective IQA is a very costly and tedious process that makes it unsuitable to implement in real time. To overcome these limitations, objective IQA is being used. It is a process of predicting the quality of an image by means of mathematical models with an intention to produce results similar to subjective IQA process. In order to facilitate the challenges of developing an efficient IQA method, many IQA data-sets [Le Callet and Autrusseau, 2005; Sheikh *et al.*, 2006; Ponomarenko *et al.*, 2009] have been created. These data-sets contain distorted images with their subjective ratings provided by human subjects. These subjective quality ratings have been used to evaluate the performance of IQA methods.

Types of objective IQA methods: Objective IQA methods can be categorized into three categories: (i) Full-Reference (FR) IQA methods, (ii) Reduced-Reference (RR) IQA methods, and (iii) No-Reference (NR) IQA methods.

FR-IQA: Under this category, the unprocessed reference image is available and it is assumed to be of best quality. FR-IQA methods are intended to evaluate the statistical dissimilarities between the pixel values of the input image (i.e., distorted) and the reference image. Such methods evaluate a number of parameters and finally combine all the evaluated results into a single scalar value indicating the overall image quality. Peak signal-to-noise ratio (PSNR) is one of the most commonly used metrics in different type of domains in multimedia (i.e., audio, image, and video). Some of the popular FR-IQA methods are Structural Similarity Index (SSIM) [Zhou Wang *et al.*, 2004], Visual Information Fidelity (VIF) [Sheikh and Bovik, 2005], Most Apparent Distortion (MAD) [Larson and Chandler, 2010], FSIM [Zhang *et al.*, 2011], and GMSD [Xue *et al.*, 2014], etc.

Next, the **RR-IQA** methods are designed to predict the quality of an image with little information about the reference image. RR-IQA methods are useful in evaluating the quality of multimedia transmitted over a communication channel. Some RR-IQA methods are WNISM [Wang and Simoncelli, 2005], EPM [Min Zhang, 2011], RIQMC [Gu *et al.*, 2016], DNT-RR [Li and Wang, 2009], SIRR [Min *et al.*, 2018], SDM [Gu *et al.*, 2013], and FTB [Narwaria *et al.*, 2012].

In contrast to FR-IQA and RR-IQA, the **NR-IQA** methods assess the image quality without any information about the reference image. Most of the NR-IQA methods are designed to predict the quality in presence of a specific distortion, such as compression, blur, etc. BLIINDS-II [Saad *et al.*, 2012], DIIVINE [Moorthy and Bovik, 2011], BRISQUE [Mittal *et al.*, 2012], NIQE [Mittal *et al.*, 2013], and CORNIA [Ye *et al.*, 2012] are a few popular and highly cited NR-IQA methods. In addition, recently many convolutional neural network (CNN) based FR and NR IQA methods [Bosse *et al.*, 2016; Kim and Lee, 2017; Kim *et al.*, 2018; Kang *et al.*, 2014a; Bosse *et al.*, 2018; Kang *et al.*, 2014b; Gu *et al.*, 2014; Hou *et al.*, 2015; Guan *et al.*, 2017] have been published, which have shown standout performances over the data-sets mentioned above. The detailed information about the state-of-the-art in IQA research can be found in the following references [Mohammadi *et al.*, 2014; Chandler, 2013; Kim *et al.*, 2017].

Applications of IQA: Objectively assessing the visual quality of an image has been a research field of significant interest for the researchers over the years. It is growing exponentially due to its usefulness over a wide range of applications like performance evaluation and standardization of image acquisition devices, and various image processing algorithms like image restoration and image enhancement for various type of images. Different IQA algorithms are developed over a variety of images like natural [Yue *et al.*, 2018a,d], screen-content [Yang *et al.*, 2015], document [Kang *et al.*, 2014c], tone-mapped [Yue *et al.*, 2018b], 3D stereoscopic [Yue *et al.*, 2018c], Depth-image-based-rendering (DIBR) synthesized [Yue *et al.*, 2019], medical [Cosman *et al.*, 1994] images, etc.

Among all, ensuring the quality of medical images is one of the most important application areas. The evolution of digital medical imaging enables an easier and more reliable diagnosis process. At the same time, it raises challenges like the selection of the required display device, the compression level, the accuracy level, and the reliability of computer-aided diagnosis. The overall focus of analyzing the entire medical imaging system is to ensure that the image quality enables diagnostic reliability. It is done either subjectively or objectively, by analyzing the necessary pathological information present in the image. While in some cases IQA metrics developed for general purpose images and video have been applied to medical images [Razaak *et al.*, 2014], specific IQA algorithms have been developed so far for the different medical image modalities like magnetic resonance imaging (MRI), computed tomography (CT), ultrasound imaging, fundus images, etc. Fundus imaging is one of the important medical imaging techniques, that is used to monitor the health status of human eyes.

1.1.2 Image Enhancement

The image enhancement methods accentuate the specific image features to get an improved visual appearance of the image. Fundamentally, it maps one image to another image to make it easily perceivable by the human visual system. The principle objective of the image enhancement is to preserve the essential details and noise supression. Image enhancement methods can be broadly divided into following categories: (i) Pixel Operations, (ii) Local Operators, (iii) Frequency Domain.

Pixel operations based enhancement methods works on modifying the pixel intensity values. Such methods do not consider the image characteristics like pixel neighbourhood information. Intensity scaling and histogram equalization methods comes under this category. Intensity scaling methods emphasize specific intensity ranges in the image required by the observer. Although, information about the desired intensity bands is often not available. Such cases are addressed using histogram equalization methods. It maps the histogram of the input image into a maximal-flat histogram to convey the maximum possible information from the image to the user [Panetta *et al.*, 2011].

Local operators are also termed as kernels or filters. These methods enhance the images by assigning a new value to each pixel in the image. It is achieved by performing a convolution operation with a kernel over the entire image. These kernels can be linear or non-linear. Due to their mathematical simplicity, linear kernels were the most commonly used methods for image enhancement during the initial development of image processing methods. Linear filters perform the averaging operation in the neighborhood of the target pixel. It suppresses the noise by creating a smoothening or blurring effect. However, the linear filters do not perform well in the presence of noise that is not additive or follow non-linear characteristics and impulse noise. To address these limitations, non-linear filters are used. The non-linear filters also termed as order-static filters, uses a spatial mask to select pixels within a neighborhood and employ an ordering mechanism to compute the output pixel value. The weights in the spatial mask can be uniform or vary depending on the similarity between the neighborhood pixels. These filters are effective in the presence of impulse noise. Another method under this category is local histogram equalization. It applies the concept of histogram equalization to the local areas of the image. It is a non-linear operation that significantly enhances the features details around the area encompassed by the filter [Singh and Mittal, 2014].

Frequency domain methods achieves the enhancement in the frequency domain by multiplying each image pixel with an appropriate filter. Here, both the image and the filter are apriori transformed into the frequency domain using the Fourier transform method. The enhanced image is finally obtained by applying the inverse Fourier transform. Using such methods, noise removal and image smoothening can be achieved by removing the high-frequency components. In contrast, edge enhancement can be achieved by eliminating low-frequency components. The advantage of frequency domain methods is that it is simple compared to spatial filtering based enhancement methods. Here, the filtering is achieved using the multiplication operation that is easy compared to the convolution operation [Yang *et al.*, 2010].

1.2 NEED OF NEW IQA AND ENHANCEMENT METHODS FOR FUNDUS IMAGES

The only similarity between the fundus and natural images is that both are acquired from a digital camera. However, the statistical properties of fundus images vary largely from those of natural images. As mentioned in [Mittal *et al.*, 2013], the statistical behaviour of a digital image can be determined using its *naturalness property*. The *naturalness* of an image is derived in [Ruderman, 1994] by calculating naturalness value $\hat{I}(i,j)$ for pixel $I(i,j)$ of the image, as follows:

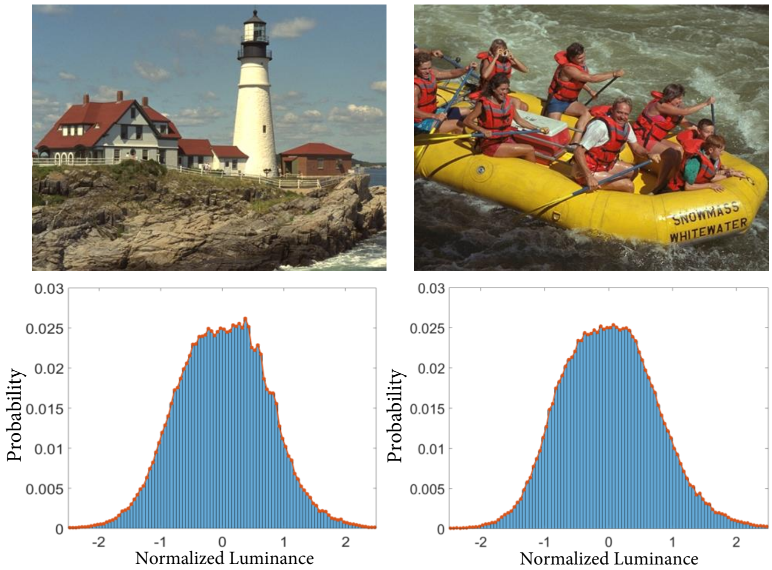

Figure 1.3 : Distribution of the naturalness values of the examples of natural images

$$\hat{I}(i,j) = \frac{I(i,j) - \mu(i,j)}{\sigma(i,j) + 1} \tag{1.1}$$

with $i \in \{1,2,...m\}$ and $j \in \{1,2,...n\}$, where m and n are the horizontal and vertical dimensions of the image I; $\mu(i,j)$ and $\sigma(i,j)$, estimating the local mean and contrast, are derived as follows:

$$\mu(i,j) = \sum_{k=-3}^{3}\sum_{l=-3}^{3} \omega_{k,l} I(i+k, j+l) \tag{1.2}$$

$$\sigma(i,j) = \sqrt{\sum_{k=-3}^{3}\sum_{l=-3}^{3} \omega_{k,l}[I(i+k, j+l) - \mu(i,j)]^2}. \tag{1.3}$$

Here $\omega_{k,l}$ is a circularly-symmetric 2D Gaussian weighting function. We have evaluated the *naturalness* property of various natural and fundus images. For illustration purpose, in Fig. 1.3 and Fig. 1.4, an example of natural and fundus image with their respective distribution of the naturalness values has been shown. It has been observed that the distribution of the naturalness values of natural images follows a Gaussian distribution. On the other hand, for fundus images the distribution curve is steep, indicating low naturalness. Therefore, the IQA and enhancement algorithms developed for natural images may not work adequately for the fundus images.

1.3 DISTORTIONS AND CAUSES AFFECTING THE QUALITY OF FUNDUS IMAGES

The quality of a medical image can be considered to be appropriate if all the required structures are clearly visible. As mentioned earlier, the primary structures visible in fundus images of a healthy eye are optic disc, macula, and blood vessels, as shown in Fig.1.1. A careful study of literature

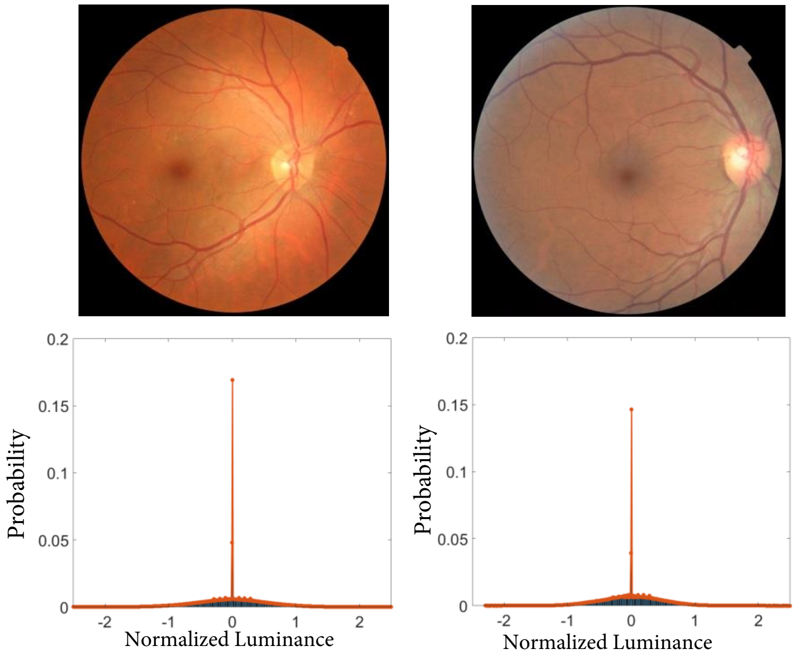

Figure 1.4 : Distribution of the naturalness values of the examples of fundus images

and observation of various fundus image data-sets led to infer that improper luminance, uneven illumination, and haze are the frequently occurred distortions in retinal images, as illustrated in Fig. 1.5. The improper luminance leads to highly bright or dark fundus images (Fig. 1.5 (a, b) while the uneven illumination mostly affects the border and macular area of such images (Fig. 1.5 (e, f)). Here, the primary reasons behind the occurrence of these artifacts are: (i) dust and dirt on camera lenses, (ii) improper light conditions, and (iii) haze event. In addition to this, eye blink and occlusion by eyelashes causes extremely poor quality fundus image, as shown in Fig. 1.5 (g).

Further, due to errors generated by light refraction, a red color print occurs throughout the fundus image, which is also referred to as "leopard print" fundus image, shown in Fig. 1.5 (d). A fundus image distorted with haze is shown in the Fig. 1.5 (c). Next, in few cases a circular rings of light in the center of the image occurs, as shown in Fig. 1.5 (h). It is important to mention that, although the visual appearance of both Fig. 1.5 (d, h) images indicates inadequate quality, experts consider it as an acceptable quality image. In order to acquire an appropriate quality fundus image, the following are the important constituents: Proper space between camera and eyes; Clean camera lenses; Appropriate gamma and flash adjustment; Quality of sensors; Compression; Image resolution; Color, contrast, and saturation. A proper setting or choice of the above-mentioned factors will be required for the desired quality of the image.

1.4 RESEARCH OBJECTIVES OF THE THESIS

The facts mentioned above indicate the importance of automated quality assessment and enhancement algorithms for retinal images. The major concern with the previous algorithms is their development approach and practical utility in real applications. The primary reason behind the limited applicability of these methods are: (i) less understanding of ophthalmologist's perception of fundus image quality, (ii) deficient use of subjective inputs on retinal image quality assessment data-sets, (iii) scoping off the requirement of enhancement by developing binary classification methods for assessing

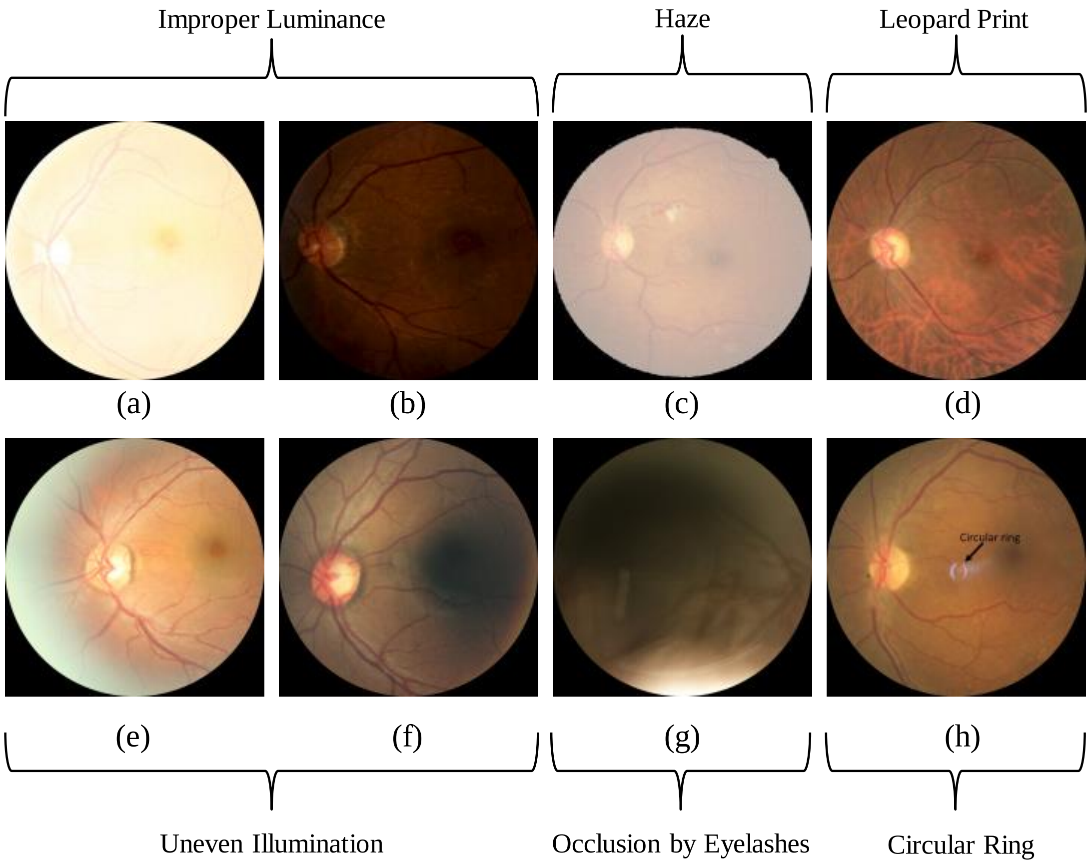

Figure 1.5 : Commonly occurred distortions in fundus images

the retinal image quality, (iv) enhancement work based on synthetic distortions that are least likely to appear on retinal images. This thesis aims to address these problems to fill the research gap in the existing works and develop novel mechanisms for efficient quality assessment and enhancement of fundus images. The main research objectives of the thesis are listed below.

- **To develop an effective and efficient fundus image quality assessment algorithm**: The research area has recently drawn the attention of researchers. However, compared to the methodological development of natural image quality assessment, this field still requires much development in the areas related to the above-mentioned limitations. To this end, our objective is to develop an efficient fundus image quality assessment method that follows the approach of an ophthalmologist. Here, the approach of an ophthalmologist indicates the following two important points:

  (i) The local and global quality parameters of a fundus image that an ophthalmologist considers while examining its diagnostic reliability.

  (ii) The minimum number of quality classes that ensures quality and the scope of enhancement of a fundus image.

- **To develop an effective and efficient fundus image enhancement algorithm**: Based on the above-mentioned limitations of the current work. Our objective is to develop a novel fundus image enhancement method that effectively works on the real degraded fundus images. In addition, this Thesis also aims to address the challenge of data unavailability for enhancement purposes.

1.5 CONTRIBUTIONS OF THE THESIS

- **A quality assessment data-set of fundus images with subjective inputs**: As mentioned earlier in this section, understanding the ophthalmologist's perception and approach in terms of quality parameters and classification is one of the crucial factors in developing an effective mechanism for fundus image quality. To this end, a fundus image quality assessment (FIQuA) data-set is prepared, with three categories of quality: Good, Fair, and Poor. In addition, for each image in the data-set, subjective ratings in the range of [0,10] have been collected for six quality parameters, both structural and generic. This study helps to get insights into the ophthalmologist's approach while assessing the quality.

- **A multivariate regression based neural network model for fundus image quality assessment**: The objective of this work is to develop one that mimics the ophthalmologists in terms of approach and perception. To achieve this, we propose a multivariate linear regression-based neural network model for the quality assessment of fundus images. The proposed model produces the output in two steps: first, it predicts the values for the six quality parameters, then based on these six predicted outputs, it classifies a fundus image into the three categories mentioned above of quality.

- **Method to model the distortions commonly appearing in fundus images**: On the enhancement part, one of the major roadblocks is the unavailability of an appropriate data set. In addition, state-of-the-art enhancement methods are tested over the distortions that are least likely to appear in fundus images. To address this issue, we proposed mathematical models to synthetically create distortions that are commonly seen in fundus images. Initially, we identified five common degradations that typically appear in fair quality fundus images: (i) Uneven-illumination over macula (MUI), (ii) uneven illumination over border region (BUI), (iii) bright, (iv) dark, and (v) haze. Thereafter, algorithms are proposed to manually create similar distortions in fundus images.

- **A RDC-UNet based model for fundus image enhancement**: A UNet-based architecture residual-densely connected UNet (RDC-UNet) is proposed for the task of fundus image enhancement. Using UNet as backbone architecture, we proposed exploiting the capabilities of residual and dense connections for the enhancement task. Here, compared to other UNet based works, our RDC-UNet effectively utilizes the virtues of bottleneck layer using RDC blocks. Another peculiarity of the proposed model is that it is trained over synthetically generated distortions and tested over naturally generated distortions.

1.6 THESIS OUTLINE

The remainder of this Thesis is organized as follows:

Chapter 2 surveys the related work in the field of fundus image quality assessment and enhancement and concludes with the challenges that are addressed in the Thesis.
Chapter 3 describes the peculiarities and specifications of the fundus image quality assessment (FIQuA) data-set.
Chapter 4 presents the proposed multivariate regression based fundus IQA algorithm.
Chapter 5 presents the proposed RDC-UNet based architecture for fundus image enhancement.
Chapter 6 concludes the Thesis and discusses important areas for future research work.

List of Publications

1. A. Raj, A. K. Tiwari and M. G. Martini, "Fundus image quality assessment: survey, challenges, and future scope", in IET Image Processing, vol. 13, no. 8, pp. 1211-1224, 20 6 2019, doi: 10.1049/iet-ipr.2018.6212.

2. A. Raj, N. A. Shah, A. K. Tiwari and M. G. Martini, "Multivariate Regression-Based Convolutional Neural Network Model for Fundus Image Quality Assessment", in IEEE Access, vol. 8, pp. 57810-57821, 2020, doi: 10.1109/ACCESS.2020.2982588.

3. A. Raj, N. A. Shah, A. K. Tiwari (2021). "A Novel Approach for Fundus Image Enhancement". Biomedical Signal Processing and Control, vol. 77, Part B, 2022, 103208, ISSN 1746-8094, doi.org/10.1016/j.bspc.2021.103208.

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