Dedicated to .....

My teachers

Who taught me all that I learnt

and made me what I am today

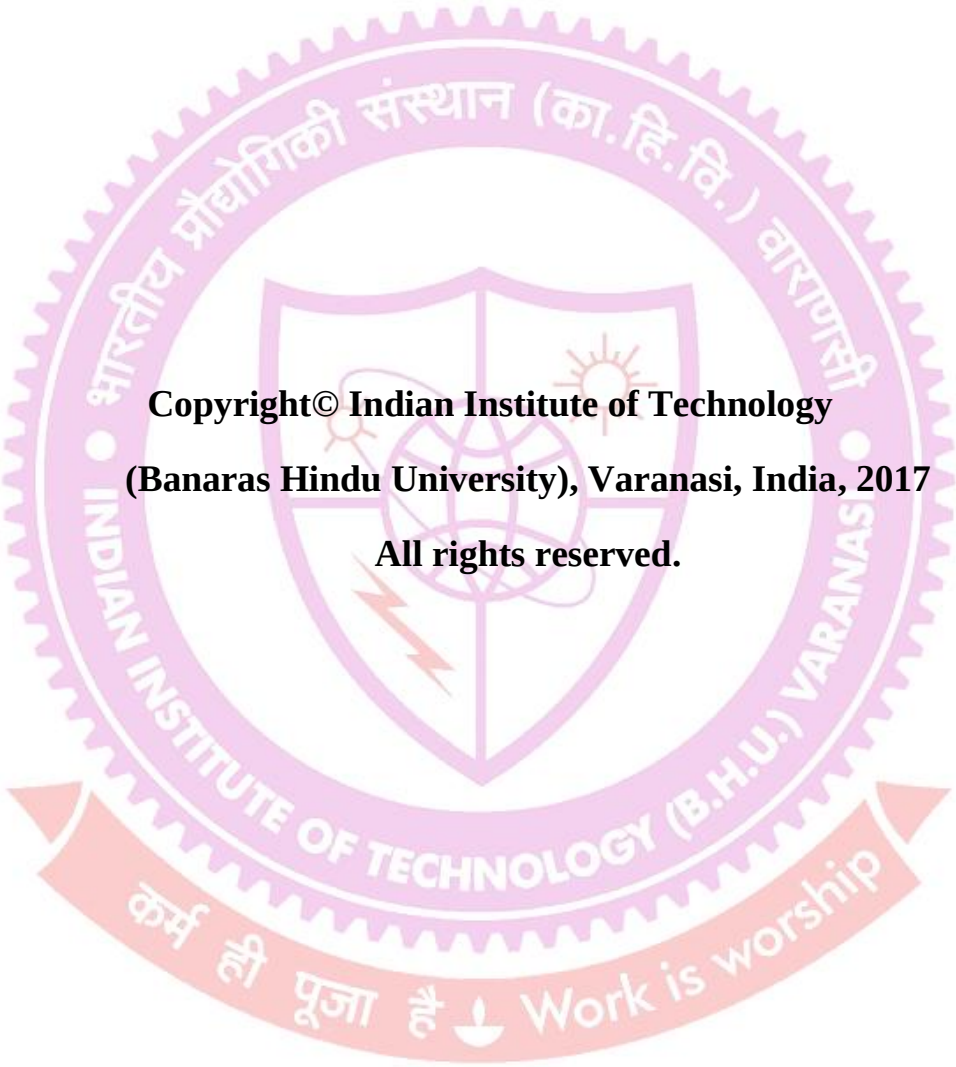
&

My Parents

Who sacrificed their today

for my better tomorrow

Contents



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I, **Anuranjeeta,** declare that the work embodied in this Ph.D. thesis is my own bonafide work carried out under the supervision of **Dr. Shiru Sharma and the co-supervision of Prof. K.K. Shukla** for a period of about **6 years and 4 months from March 2011 to June 2017** at the **School of Biomedical Engineering, Indian Institute of Technology (Banaras Hindu University), Varanasi**. The matter embodied in this thesis has not been submitted for the any other degree/diploma.

Date:

Place: Varanasi (**Anuranjeeta)**

CANDIDATE'S DECLARATION

I, **Anuranjeeta**, certify that the work embodied in this Ph. D. thesis is my own bonafide work carried out by me under the supervision of **Dr. Shiru Sharma** and the co-supervision of **Prof. K.K. Shukla** for a period of **6 years** and **4 months from March 2011 to June 2017** at **School of Biomedical Engineering, Indian Institute of Technology (Banaras Hindu University), Varanasi.** The matter embodied in this Ph.D. thesis has not been submitted for the award of any other degree/diploma.

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Supervisor Signature	Co-Supervisor Signature
Dr. Shiru Sharma	Prof. K. K. Shukla
(Assistant Professor)	(Professor)

(Signature of the Coordinator of the School with seal)
School of Biomedical Engineering
IIT (B.H.U.), VARANASI.

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Anuranjeeta

List of Figures

List of Tables

Preface

Cancer has turned out to be the leading causes of mortality in the world thereby creating the need for more awareness globally. The onset of cancer development is due to the unrestrained growth of cells and these cancer cells have the capability to migrate to other parts of the body causing metastasis. Cancer detection has always been a major issue for the pathologists and medical practitioners for diagnosis and treatment planning. The chances of curing of cancer are primarily in its detection and diagnosis. However, its correct diagnosis and treatment is an important factor for the better survival rates of the patients.

Currently, several imaging techniques such as X-Ray, Mammography, Positron Emission Tomography (PET), Computer Aided Tomography (CAT), Magnetic Resonance Imaging (MRI), and Ultrasound Imaging have been used for the screening and detection of cancer. Various biochemical tests such as blood test, serum tumour marker test, and Lipid peroxidation test (LPO) are also used for cancer diagnosis.

The above mentioned techniques are helpful in diagnosing the cancer. However, all these techniques have shortcomings in determining their respective malignancy levels. For this reason, these techniques are not considered as gold standards in pathological domains and biopsy examination is still necessary to reach the final decision. Screening histopathological imaging of the cancer is currently the most effective tool for detection of cancer.

The histopathological techniques are used for the study of structure, function, and interpretations of the tissue and cells. Histopathology gives information about abnormalities present in the cellular structure of the tissue and cells. The images provide complete information about the tissue at a cellular level. Currently, scrutiny of histopathological images is the routinely used method to examine biopsy sample for the diagnosis of cancer.

Firstly, pathologists observe and analyze the biopsy sample images for specific abnormalities or for some of the important signs of cancer such as appearance of cells, distribution of cells in tissues, regularities of cell shapes, sizes, cluster of cells and architectural distortions under the light microscope and compare all the features of the sample with healthy cells to interpret the result. The manual evaluation of cancer detection from histopathological images is subjective in nature, time consuming and varies with perception level of expert pathologists. Due to the limitation of manual observation, it's difficult for the pathologists to provide both accurate and uniform evaluation for the enormous number of histopathological images generated in widespread screening in shorter time.

To overcome this problem, there is a need of computer image analysis. Therefore, CAD techniques are being introduced for fast, reliable and accurate diagnosis of cancer. The CAD provides a quantitative result of each particular cell in the image to classify it into normal and abnormal categories e.g. benign and malignant ones with higher sensitivity. The basic steps involved in the CAD tool are pre processing, segmentation of abnormalities in cells, feature extraction, and classification from selected features. A CAD system for cancer detection and diagnosis can also be used as the second opinion by the pathologist.

The automated identification of cancerous cells by histopathological images helps in alleviating the above mentioned issues and provides better results if the important feature based approaches are used for the identification of disease. Therefore, improvement in CAD performance increases the diagnostic options and the cure is more likely to be selective. Also, to help the pathologist in screening a large number of images, use of a CAD system may be helpful in exact prognosis free from human error.

In the thesis, the efficient approaches for the design and development of CAD system for cancer detection from images have been proposed. Hence, the present thesis aims at increasing the accuracy of diagnosis by the design of CAD tool for analysis of images so that early, accurate and faster screening of cancer can be achieved.

CAD system has been proposed for analysis and quantitatively measuring from haematoxylin and eosin stained breast cancer histopathology. With the proposed solutions for different problems in automated cancer detection that are presented in this thesis, we believe that it will provide the pathologists with useful tools for assisting them with the cancer diagnosis task.

The entire thesis is divided into eight chapters as follows:

Chapter-1: This chapter describes a brief introduction on the present scenario regarding the examination of the tissue structure by the pathologists for the detection of the abnormalities leading to cancer. The essential need for automation of the procedure through a CAD system is addressed. In perspective of addressing the requirements for this necessity, the present chapter briefly represents the problem statement and motivation, aims and objectives and research contributions of the present thesis work. At the end of this chapter, the thesis organization section concisely highlights all the chapters present in this thesis.

Chapter-2: This chapter includes a detailed literature survey of the background research work done in the area of cancer detection from histopathological images using CAD system. It starts with an explanation of preprocessing techniques in histopathology image modalities. Segmentation methods are then discussed. The chapter continues with an explanation of feature extraction based on the various attributes including morphological, textural and intensity based features. A discussion of the classification methods and disease identification is also represented in this chapter. Finally, the existing researches on different cancer using image analysis of histopathological images are discussed.

Chapter-3: This chapter deals with the histopathological procedures for the obtaining images from the samples and then image acquisition techniques are discussed. After that, brief description of the image pre-processing and enhancement techniques required to process the acquired images. Further, Otsu's thresholding, k-means, fuzzy c-means and proposed DSR based approach has been discussed for the segmentation of histopathological images. Segmentation performance matrices in terms of correlation, GCE, NPR, and VI have also been explained. The performance of the proposed segmentation approach has been compared with the other commonly used segmentation methods such as Otsu's thresholding, k-mean and fuzzy c- mean.

Chapter-4: This chapter provides the CAD system for the quantitative measurement of features of haematoxylin and eosin stained breast cancer histopathological images. A brief introduction about breast cancer dataset available online University of California, Santabarbara (UCSB) that used in this research for feature extraction of single and group cells dataset. After that, image pre-processing, segmentation and feature extraction steps have been carried out. The definitions and mathematical descriptions of various morphological, intensity and texture based features have been described which are used throughout the thesis.

Chapter-5: This chapter explains the requirements of classification steps in CAD system, types of classification and training and validation steps have been discussed. Further, definitions and mathematical descriptions of various performance evaluation methods used throughout the thesis for examining the efficacy and suitability of the proposed approaches associated with the existing CAD systems have been investigated. In the present investigation three classifiers (1) Artificial Neural Network (ANN), (2) k-Nearest Neighbour (k-NN) and (3) Support Vector Machine (SVM) has been trained using breast cancer single cells and group cells datasets. The performance was evaluated in terms of classifier's performance measures such as accuracy, sensitivity, and specificity. Finally, a brief description and working of Graphical User Interface (GUI), named as CELL CHECK (v1.0) has been explained for identification of a benign and malignant cell in breast cancer histopathological images.

Chapter-6: This chapter presents the comparative study of different classifiers for histopathological image of breast cancer classification and detection using morphological features based on all cells present in the image. A computer aided diagnosis approach consisting of various steps, viz. pre-processing, segmentation, features extraction and classification has been proposed. Contrast Limited Adapted Histogram Equalization (CHALE) approach is used for pre-processing and Trainable Weka Segmentation (TWS) approach is used for segmentation purpose. Ranking of the features is accomplished using Relief-F algorithms.

Chapter-7: This chapter evaluates the changes in patterns of morphological, intensity and texture based features of malignant cells and the comparative features of benign cells in ovarian and breast cancer of histopathological images and its correlation with the several biochemical parameters. Further, morphological observation of these features disclose an improved a difference in area, perimeter, major axis length, circularity and max intensity values between benign and malignant cells. Further, it presents an overview of the biochemical tests such as RBC count, WBC count, Haemoglobin level, platelets count, CA-125, and malondialdehyde (MDA) of normal, breast and ovarian cancerous patients.

Chapter-8: This chapter describes the outcomes of the major findings of this research work with brief conclusions and suggestions for the future work.

References: This includes the references as a source of information to carry out the entire research work.