DIGIMAMMOCAD: A NEW DEEP LEARNING BASED CAD SYSTEM FOR MAMMOGRAM BREAST CANCER DIAGNOSIS WITH MASS IDENTIFICATION

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I dedicate this work to my parent and almighty god.

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ABSTRACT

Worldwide Breast Cancer (BC) is the most severe cancer in women. There are no outward symptoms at an early stage and the survival rate decreases with the increasing stage. So, only regular screening can save a life. Mammography is the gold standard imaging modality used for regular BC screening due to its fast acquisition and cost-effectiveness. The available Computer-Aided Detection (CAD) systems based on traditional Machine Learning (ML) systems are unable to reduce the number of undetected and false-positive breast cancer cases because of their dependency on external feature extractors that provides an inferior abstraction of feature representations. Whereas Deeper Convolutional Neural Networks (DCNNs) can automatically extract features from their inputs, and hence, a remarkable change has been observed in medical image screening. A DCNN-based CAD system suffers overfitting due to the scarcity of the annotated data and the inconsistency was reported in their performance when they were validated with external datasets. So, an effective CAD system, DIGIMAMMOCAD, was developed in this study for digital mammogram screening to diagnose BC to reduce the number of false-positive and undetected cases. It was developed using a pre-trained Residual Network of 50 layers (Resnet50) and You Only Look Once (YOLO) V2 detector where only Full Field Digital Mammograms (FFDMs) were considered. The novelty of the work lies in the increased image input layer size of the Resnet50, 2 extracted feature maps for mass identification, and the use of a small dataset. The DIGIMAMMOCAD achieved the classification accuracy, sensitivity, and specificity of 98.33 %, 0.97, and 1, respectively, along with the Average Precision (AP) of 0.91 for mass identification with the INbreast dataset. It outperformed the state-of-the-art DCNN-based systems proposed by other authors. It also achieved high performance with external datasets of different image quality after minimum adaptation in the system and reduced the false-positive and undetected cases remarkably. So, the DIGIMAMMOCAD can have a significant contribution to clinical use, and can also serve the medical fraternity as well as patients in a better way.

ABSTRAK

Kanser Payudara (*BC*) di Seluruh Dunia adalah barah yang paling teruk pada wanita. Tidak ada gejala luar pada tahap awal dan kadar kelangsungan hidup menurun dengan meningkatnya tahap kanser. Jadi, hanya pemeriksaan biasa yang dapat menyelamatkan nyawa. Mamografi adalah modaliti pengimejan yang biasa digunakan untuk pemeriksaan *BC* kerana pemerolehan yang pantas dan keberkesanan kosnya. Sistem Pengesanan Berbantu Komputer (*CAD*) yang tersedia berdasarkan sistem Pembelajaran Mesin tradisional (*ML*) tidak dapat mengurangkan bilangan kes barah payudara yang tidak dapat dikesan dan kes positif palsu kerana ketergantungan mereka pada pengekstrak ciri luaran yang berkesan. Sedangkan Jaringan Neural Konvolusif yang Lebih Dalam (*DCNN*) dapat mengekstrak ciri dari imej inputnya secara automatik Oleh itu, perubahan yang luar biasa telah diperhatikan dalam pemeriksaan gambar perubatan. Sistem *CAD* berasaskan *DCNN* mengalami overfitting kerana kekurangan data yang dianotasi dan ketidakkonsistenan dilaporkan dalam prestasi mereka ketika mereka disahkan dengan set data luaran. Oleh itu, sistem *CAD* yang berkesan, DIGIMAMMOCAD, dibangunkan dalam kajian ini untuk pemeriksaan mamogram digital demi mendiagnosis *BC* untuk mengurangkan bilangan kes positif palsu dan kes tidak dapat dikesan. Ia dibangunkan menggunakan Jaringan Residual pre-terlatih yang mempunyai 50 lapisan (*Resnet50*) dan pengesan V2 You Only Look Once (*YOLO*) di mana hanya Mammogram Digital Medan Penuh (*FFDM*) yang dipertimbangkan. Kebaharuan karya ini ialah peningkatan ukuran lapisan input gambar dari *Resnet50*, 2 peta ciri yang diekstrak untuk pengenalan jisim, dan penggunaan set data input yang kecil. DIGIMAMMOCAD mencapai 98.33% ketepatan, 0.97 kepekaan, dan 1 kekhususan klasifikasi, dan 0.91 Ketepatan Rata-rata (*AP*) untuk pengenalan jisim dengan set data INbreast. Ia berfungsi dengan lebih baik jika dibandingkan dengan sistem berasaskan *DCNN* canggih yang dicadangkan oleh penulis lain. Ia juga memperoleh prestasi tinggi dengan set data luaran yang mempuntai kualiti gambar yang berbeza setelah penyesuaian minimum dalam sistem, mengurangkan kes positif palsu dan kes tidak dapat

dikesan. Oleh itu, DIGIMAMMOCAD dapat memberikan sumbangan yang signifikan terhadap penggunaan klinikal, membantu pegawai perubatan dan juga pesakit dengan cara yang lebih baik.

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LIST OF SYMBOLS AND ABBREVIATIONS

AI	–	Artificial intelligence
AP	–	Average precision
AUC	–	Area under curve
ANN	–	Artificial neural network
BC	–	Breast cancer
BCDR	–	Breast cancer digital repository
BIRADS	–	Breast imaging reporting and data system
CAD	–	Computer-aided detection
CBIS-DDSM	–	Curated breast imaging subset of DDSM
CC	–	Cranio caudal
CMMD	–	The Chinese mammography database
CNN	–	Convolutional neural network
CT	–	Computed tomography
DCNN	–	Deep convolutional neural network
DDSM	–	Digital database for screening mammography
DICOM	–	Digital imaging and communications in medicine
DL	–	Deep learning
FFDM	–	Full-field digital mammogram
FPR	–	False positive rate
GPU	–	Graphical processing unit
GUI	–	Graphical user interface
Hz	–	Hertz
IOU	–	Intersection over union
L	–	Local threshold value
mAP	–	Mean average precision

MG	–	Mammography
MHz	–	Megahertz
MIAS	–	Mammographic image analysis society
ML	–	Machine learning
MLO	–	Medio-lateral oblique
mm	–	Millimeter
MRI	–	Magnetic resonance imaging
m	–	Meter
NAF	–	Nipple aspirate fluid
PET	–	Positron emission tomography
PNG	–	Portable network graphics
RESNET	–	Residual Network
ROC	–	Receiver operating characteristic
ROI	–	Region of interest
R-CNN	–	Region-based CNN
T	–	Threshold value
TIF	–	Tagged image file
TNR	–	True negative rate
TPR	–	True positive rate
µm	–	Micrometer
YOLO	–	You only look once

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CHAPTER 1

INTRODUCTION

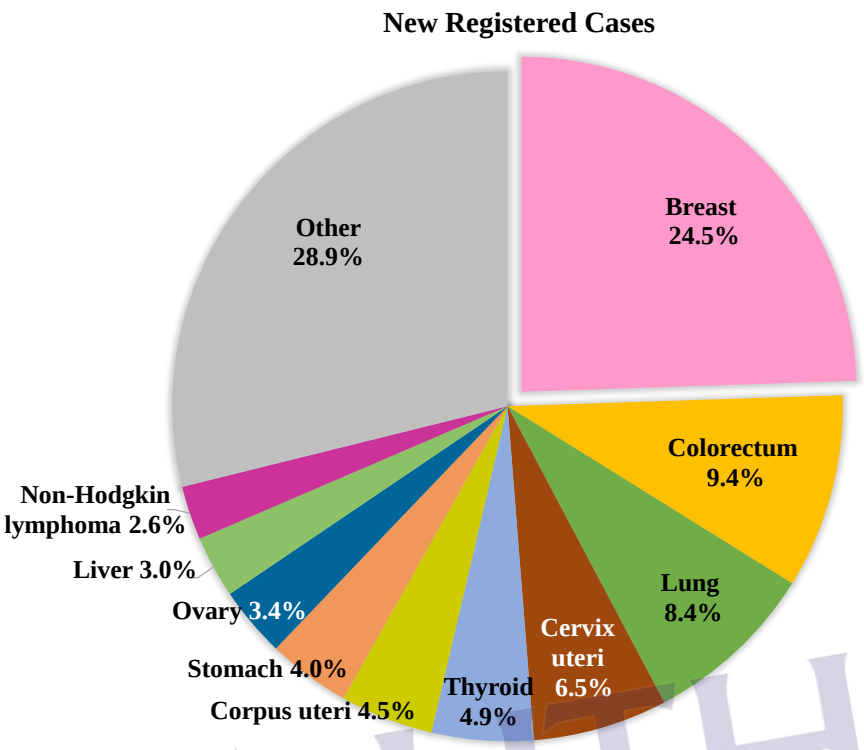
Cancer is a major health concern over the last few decades. This thesis concentrates on breast cancer diagnosis by a newly developed computer-aided detection (CAD) system named DIGIMAMMOCAD by analyzing digital mammograms. Chapter 1 introduces the background of the thesis and problem statement. Then the research objectives and scope of the research are elaborated by highlighting the main contributions of this study and lastly, the organization of this thesis is outlined.

1.1 Background of the problem

Breast cancer counts 1 in 4 among all cancer cases in women [1] and it is the most common cancer among Malaysian women [2]. The severity can be expressed with the help of the 2020 GLOBOCAN report [1], which reveals that breast cancer was estimated at 24.5 % among 9.2 million all new cancer cases and 15.5 % deaths out of a total of 4.4 million deaths due to all types of cancers, as shown in Figure 1.1 [1]. In Malaysia itself, more than 21,000 breast cancer cases were diagnosed between 2012 to 2016 which is higher than that reported in between 2007-2011 and the most vulnerable age group is 60-64 [2]. This disease not only raises concern for women, but it can happen to men also, although the number is limited [3].

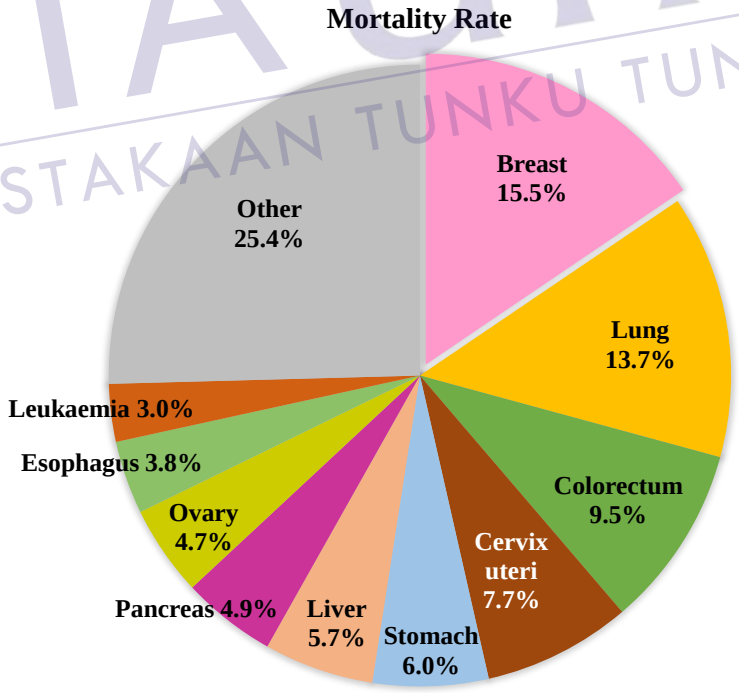
The uncontrollable growth of breast tissues causes cancer [4]. If any abnormality, i.e., tumor or lump, is found in the breast without any malignant/cancerous tissue, it is

(a)



Total 9.2 million new cancer cases

(b)



Total 4.4 million deaths due to cancer

Figure 1.1: Worldwide 10 most prevalent cancers in women
for (a) the registered new cancer cases and (b) deaths as reported in 2020 [1]

termed benign. The chances of life risk of a breast cancer patient can be minimized by early detection [5] and a regular breast cancer screening program can help in this regard [6]. It is evident from Figure 1.2 that early detection has more chances of survival for a breast cancer patient. However, the cost associated with breast cancer detection, starting from medical image screening to clinical examination, is always a concern throughout the world [6]–[8].

Figure 1.2: The survival rate of a breast cancer patient [9]

There are two ways of breast cancer detection, namely via image screening and clinical laboratory evaluation. Imaging diagnosis is hypothetical, and it includes interpretation of different medical images by radiologists and using Computer-Aided Detection (CAD) systems. Whereas, laboratory tests involve nipple aspirate fluid (NAF) analysis, breast biopsy, and genetic tests. These biological tests are costly, invasive, risky, and can contribute to patients' discomfort during the procedure and hence, image screening is performed to find out the presence of carcinoma in breast tissues before an individual is referred for invasive means of biological diagnosis [10].

The rate of mortality due to breast cancer can be reduced through randomized trials only by using Mammography [11] (special X-ray for breast tissues) that is the preliminary method to diagnose breast cancer; an individual with a suspected cancerous cell is referred for a biopsy to confirm the diagnosis. A mammogram is of two types, namely film mammography and digital mammography. This study considers only digital mammograms due to the ease of image manipulation and fast screening time. There are two types of tissues in mammography on which radiologists rely during breast cancer diagnosis such as microcalcifications and masses [12]. Cranio Caudal (CC) and Medio-Lateral Oblique (MLO) are two views generally captured for each breast of a patient to have a better mammogram screening outcome.

There are two objectives in image screening, object/lesion identification and its classification [13]. It is required to combine various signals from the raw image data to recognize the object [13], in this case, tumor/mass. When object detection helps in identifying the location of several objects in an image, then its classification provides the information contained in that image.

Digital mammograms are considered as one of the highly complicated medical images amongst all since there are several kinds of breast tissues to be studied. Initial signs of masses and microcalcification clusters are important visual clues for breast cancer detection. Unfortunately, all these indications are very elusive and appeared differently at primitive stages and hence, even for the specialists, the diagnosis becomes harder [14]. It is a tough job to separate a benign tumor from the malignant one since it is dependent on the experience of the radiologist. Statistics reveal that cancerous cases are within 20–30 % of all breast biopsies and 10-30 % of breast cancer cases were unable to detect during mammogram screening [15]. Better accuracy can be achieved in detecting the cancerous tumor if more than one radiologist is recruited to perform mammogram screening, but this can be time-consuming and costly. Hence, as an effort to minimize the number of avoidable breast biopsies and the overall cost of mammography screening [16], CAD systems were evolved to facilitate the radiologists with a single reading. The lack of expert radiologists, failure to complete the required work on time, and the unintentional human errors increased the use of CAD systems for mammogram screening from 5 % to 83 %

between 2003 and 2012 [17]. John D. Keen *et al.* [18] reported that up to 2016 the mean of using CAD system in the USA was expanded to 91.8 %.

Several researches were already done on different CAD systems for breast cancer diagnosis. These CAD systems were solely based on the hand-picked image features that were fed to the traditional Machine Learning (ML) techniques. But the report says [19] that the false-positive rate of mammographic screening has been increased substantially than in past years which in turn raises the over-diagnosis rate for breast cancer. Moreover, it was also revealed [17] that the results obtained after screening the mammogram with and without CAD systems for both sensitivity and specificity were nearly similar and the non-accurate breast cancer diagnosis by a CAD system increases the false-negative cases [17]. Altogether, a huge amount of money is being wasted per year [20] although the recent CAD systems are more sensitive towards breast cancer diagnosis. Therefore, further research is required to propose an improved CAD system for mammogram screening.

In this study, a new CAD system is developed to diagnose breast cancer using a deep neural network. It is expected that the diagnosed result will only refer to actual breast cancer cases for biopsy to minimize the cost and it will serve a patient in a better way.

1.2 Problem statement

The mammography screening by the radiologists faces over-diagnosis, overtreatment and increased false-positive rates and they all lead to negative psychological impact and unnecessary costs due to biopsies [21]. Interpretation of mammograms varies with experience, is subjective, and is an error-prone method due to the complexity of mammogram image to be interpreted, heterogeneous presentation of breast cancer, and the elusive nature of the masses/tumors particularly with dense breast tissues [21]. Although less than 1 minute is required to read a two-dimensional (2D) mammogram, however, manpower and resource problems are there due to the huge volumes of mammograms to be screened and double-reading of each mammogram [21].

Computer-Aided Detection (CAD) systems gained attention to automate the screening procedure and aid the radiologists [16], [17]. In past decades, researchers developed several CAD systems based on the traditional Machine Learning (ML) systems to classify breast tumors as normal, benign, and malignant. These CAD systems pre-process an image; then segment the Region of Interest (ROI); extract the features from ROI; and finally, feed the hand-picked features to the machine learning system to classify the breast abnormalities. In recent time, the performance of some radiologists was adversely affected due to the dependency on CAD and recalls were increased without any improvement in cancer detection rates [21]. This can be attributed to the dependency on handcrafted features in these CAD systems that makes feature mapping approximation inferior [22].

A significant change has been observed in medical image screening paradigms, particularly in CAD systems after the revolutionary emerging applications of deep learning with Convolutional Neural Network (CNN) for image classification and object detection [23]. A deep network consisting of multiple layers in between input and output layers is a supervised neural network in which feature selection and classification are done by itself via the correct selection of parameters for the neural networks and hence, no external feature selector is required. The deep network can diagnose breast cancer with similar expertise as radiologists [23]. Researcher proved in [24] that artificial intelligence (AI) based CAD system marked 56 % reduction in identifying masses/tumors compared to the conventional CAD systems.

A DCNN-based CAD system for breast cancer analysis faces the main challenge during the system training because of the scarcity of the available labelled and annotated data [25] that should be of high quality, and different population, including distribution of pathology, demographics, and breast density [26] because as per the general concept, bigger datasets are required to achieve good performance in a DCNN-based CAD system [25]. So, it is tough to compare the clinical efficacy of the developed DCNN-based CAD systems if datasets of different image quality are combined [26]. Moreover, there is a chance of overfitting during the training after several epochs with a smaller dataset [27]. It is also reported in [28] that the DCNN-based models, even the already published DCNN-based systems by other authors had inconsistency in their performances when

those systems were validated with external datasets although high performances were achieved with one dataset with which it was trained. Although the optimal clinical use of DCNN-based CAD systems remain to be determined, however, it was proved in [26] that the tumor localization performance by DCNN-based CAD system seems to be promising for early flagging of suspicious regions and their reviewing by experts. EPV. Le *et al.* [21] also suggested further studies are needed to make the DCNN-based CAD systems more cost effective that is now restricted due to the high cost of computing storage and use of GPUs.

1.3 Objectives

The proposed CAD system, DIGIMAMMOCAD, is a new non-invasive method for the diagnosis of breast cancer by analyzing digital mammograms. The DIGIMAMMOCAD is based on the deep learning technology that not only focuses on improving the accuracy but also enhances the specificity with proper mass identification within a mammogram, if present any. The feasibility of the developed algorithm was investigated on the collected online data. A small dataset was used to counter the general concept of the requirement of a bigger dataset and the developed system was validated with two external datasets from different populations and image quality to prove its efficacy.

The assessments are based on the objectives as follows:

1. To propose and develop a new technique for mass identification from digital mammograms.
2. To propose and develop a new method for the classification of digital mammograms into benign and malignant categories.
3. To validate the developed system, DIGIMAMMOCAD, with a new external Full Field Digital Mammogram (FFDM) dataset.

1.4 Scope of research

The scope of the research is focused to attain the objectives of this study. DIGIMAMMOCAD is a computer-based software simulation system that has been developed and executed on a 64-bit computational system with Intel Core™ i7-9750H 2.6 GHz CPU, 8 GB RAM, 500 GB hard disk, and NVIDIA GeForce RTX 2060 GPU using MATLAB R2020b software. No customized hardware has been developed in this study. It is developed for breast cancer diagnosis by screening only FFDMs where only masses were identified. Instead of patches, whole mammograms of both the CC and MLO views were fed for classification and mass identification.

A small two dimensional (2D) dataset INbreast [26] was used that contains only 410 FFDM images in DICOM format for the system development. External FFDM datasets, the Breast Cancer Digital Repository (BCDR) [27] and The Chinese Mammography Database (CMMD) [28]–[30] were used along with INbreast to validate the DIGIMAMMOCAD system. The CMMD as used only to validate the classification system. The pre-trained Residual Network of 50 layers, i.e., Resnet50 was used to develop the classification network. It was also used as the base network of mass identification system from which features were extracted and fed to the YOLO V2 network.

A GUI has been developed as a tool of DIGIMAMMOCAD for digital mammogram pre-processing and mass identification along with its classification into benign and malignant categories providing the processing time to make the system user-friendly. If the mammogram does not contain any mass, it will be classified as normal. GUI can accept only 2D images of any known format such as DICOM, TIF, and PNG.

1.5 Significance of this research

The research presented in this thesis aims to develop and evaluate a novel digital mammogram screening tool named DIGIMAMMOCAD that can analyze digital mammogram images intelligently with minimum interpretation time and human intervention. Efficient methodologies followed by heuristic approaches were applied to

develop the CAD system for breast cancer screening so that the number of undetected and false-positive cases can be reduced. It was also aimed that the developed system can perform well even with unknown FFDM images with minimum alteration in the system so that the DIGIMAMMOCAD can prove its potentiality for clinical use. The Residual Network of 50 layers (Resnet50) was chosen to classify the mammograms with an increased image input layer size to retain the fine details of the image. 2 feature maps from different layers were extracted from the modified Resnet50 and fed to the YOLO V2 detector for mass identification. Different feature representations helped in identifying the critical details of masses and provided higher precision and confidence score. Moreover, it was required to find out the suitable base network and detector that could work on a computing system of limited memory and storage capacity. The whole mammograms of both CC and MLO views were fed to the system. The used dataset to develop the system was small and hence, it was really challenging to make the system effective.

1.6 Thesis outline

This chapter is an overview of the research. The complete thesis consists of five chapters as described below:

Chapter 1: Introduction illustrates the background of the study, problem statement, research objectives, and its scope, and gives an outline of the thesis.

Chapter 2: Literature Review gives an idea about breast cancer, its stages, different diagnosis methods of breast cancer, available breast imaging modalities, working procedure of a CAD system, and a comparative study of earlier work on breast cancer using different CAD systems.

Chapter 3: Research Methodology illustrates the path that was taken, and all the techniques used to complete the experiment. The investigation was started with pre-processing followed by the classification, mass identification, Graphical User Interface (GUI) creation, and ultimately, the validation of the developed system.

Chapter 4: The obtained results for all the development stages are elaborated in this chapter with a thorough discussion to analyze how the obtained results helped in accomplishing the objectives of this study.

Chapter 5: This chapter concludes the complete thesis highlighting the contributions of this work and finally, some recommendations for future work are discussed.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview

This chapter gives a deeper insight into construction elements of breast, breast cancer, different breast cancer diagnosis methods, and medical images. Then, various CAD systems are elaborated along with the comparative studies of past works using several methods. Ultimately, this chapter is summarized with the research gap.

2.2 Construction elements of breast and breast cancer

Lobules, ducts, and connecting tissues are the main constructing elements of the breast as shown in Figure 2.1 [29]. Milk is produced in lobules, which are generally known as milk glands, and it is carried up to the nipple through ducts which are tiny tubes. Different fibrous and fatty tissues are responsible for the size and shape of the breast and keep other tissues in place. In most cases, cancer initiates either in ductal or lobular tissues of women's breasts due to the uncontrollable growth of breast cells which ultimately generate tumors or lumps [4]. Two types of breast tissues can be identified during the diagnosis namely normal, and abnormal. Benign and malignant are two types of tumors among abnormal tissues. While the normal tissues do not possess any tumor, the presence of malignant cells differentiates the benign from the cancerous tumors [30]. A lump at any point of the breast is the main indication of breast cancer. Other symptoms such as

swelling at any part of the breast, discharge from the nipple, redness of the nipple, and pain in the breast or nipple may also be accounted for breast cancer. The risk factors associated with breast cancer are breast density, age, personal history, family history, first menstrual cycle, pregnancy history, being overweight, and the habit of alcohol consumption. In addition, the use of combined hormone therapy, oral contraceptives, and previous chest radiation exposure would also increase the chance of having breast cancer. However, the mechanism of these factors in the development of breast cancer remains unknown [4].

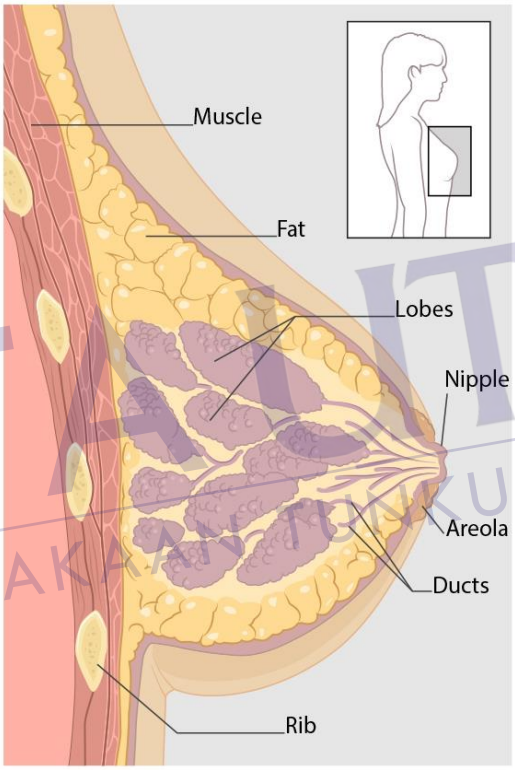


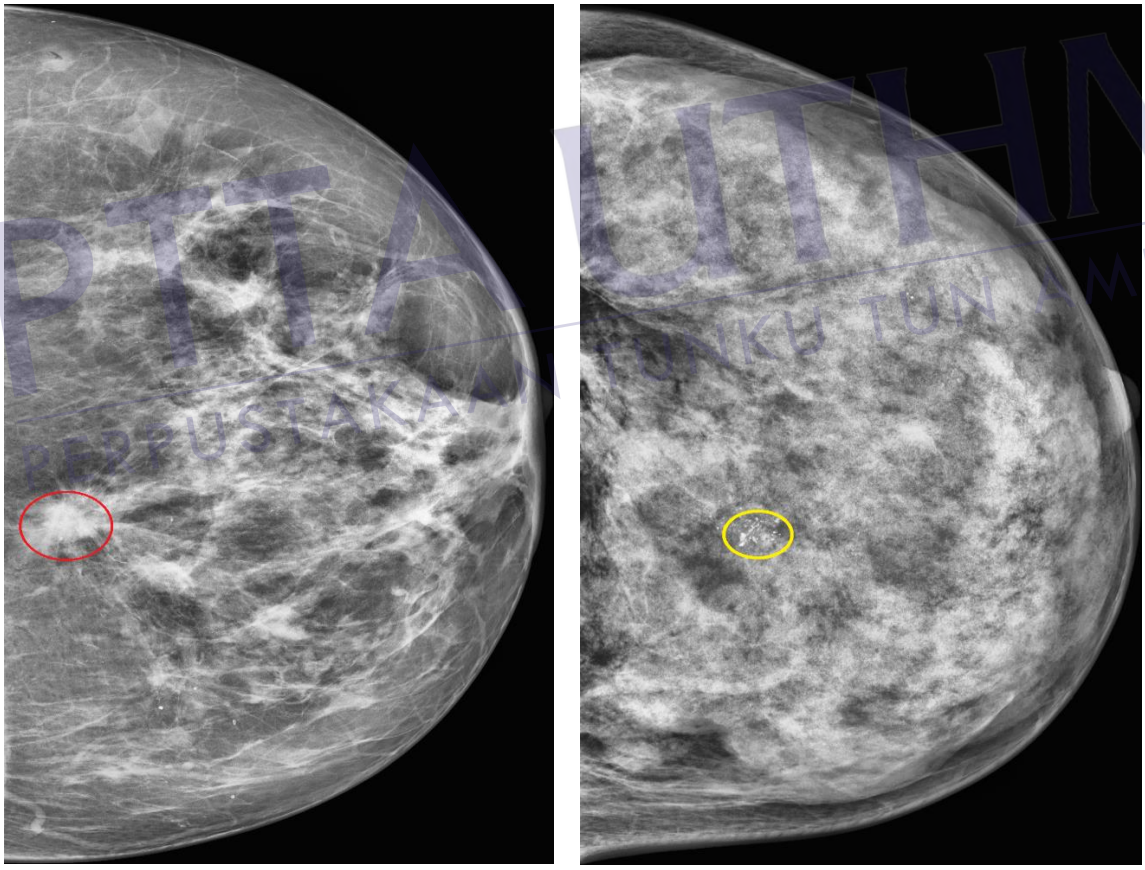
Figure 2.1: Breast anatomy [29]

2.3 Different breast tumors

Calcifications and masses are identified as two types of breast tumors [12] and they can be seen in Figure 2.2. A mass is a space-occupying lesion with features such as location, density, and margin. Benign masses are generally round-shaped with smoother and well-defined margins having a low density. The high-density masses of stellate or spiculated

shape with improper margins are usually found as malignant. Architectural distortion and bilateral asymmetry are other aspects of cancerous masses.

Minute calcium depositions in the breast are found as tiny bright spots in mammograms and they are known as Calcifications. Depending on size, it is classified as macro and microcalcification. The main concern is with the latter one as the probability of malignancy is high. Around 0.3 mm is the size of microcalcification in general and its possession of mass is not necessary. Benign calcifications are usually identical, large (diameter around 1–4 mm), coarse, round, or oval-shaped, and dispersed or diffused. Microscopic, stellate-shaped, clustered in branches, innumerable (more than 5 in numbers) microcalcifications of different sizes and shapes are found to be malignant [12].



(a) (b)

Figure 2.2: Different breast tumors

(a) Spiculated mass (b) Microcalcifications as referred from INbreast dataset [31].

Detection of masses is far complicated than that for microcalcifications as the traits of masses are hard to perceive, mainly in dense breasts and sometimes they appear like normal breast tissues [32]. Calcifications are bright spots to be identified in mammograms and biopsy is not required to check microcalcifications in most cases until they look suspicious [33]. Therefore, only masses were considered in this study for identification.

2.4 Medical images used for breast cancer

Detection of abnormal tissues in medical images is the sign on which non-invasive imaging diagnosis is based. There are several available methods for imaging of the breast, such as mammography, ultrasound, Magnetic Resonance Imaging (MRI), Computed Tomography (CT), Positron Emission Tomography (PET), and microwave imaging as illustrated in Figure 2.3 [10].

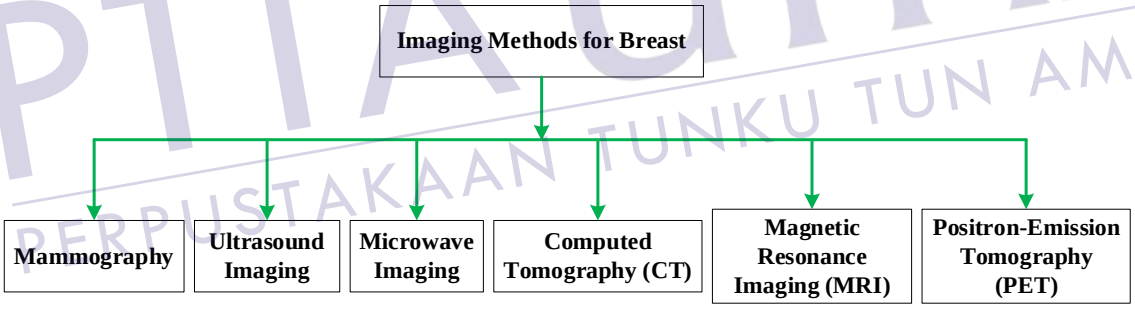


Figure 2.3: Different imaging methods for breast

All the medical images contain information about the human body and its composition or characteristics. They are formed by the signals due to their different penetration level through the tissues or by the re-emission of energy from the tissues, wherein these signals may not be of the same type. The information depicted by an image varies due to the changing contrast between different types of tissues. The target location of these images may be inside the body, even several centimeters below the accessible surface. Electromagnetic signals of frequency ranging between a few hertz to exahertz have the capabilities of penetration and accordingly, they are used in medical imaging

systems. Two key objectives are mainly considered in the previous studies in developing these imaging modalities; they are location specificity and lesion detection. Different techniques for breast imaging are discussed below.

A mammogram is a special type of X-ray for breast tissues. A lower dose X-ray of frequencies ranging from 30 petahertz to 30 exahertz is utilized to obtain two or three-dimensional (2D or 3D) mammography images [34]. Film and digital are two types of mammograms. Film mammography was considered a powerful tool for breast cancer screening for a longer time [35]. But it has drawbacks, such as lower sensitivity towards the dense breast, limited contrast characteristics, longer processing time, and grain effect. Moreover, a film mammogram needs 25 % more radiation than a digital mammogram [36]. The contrast can be manipulated in digital mammography and thus, the presence of the lesion can be visible. Moreover, the processing time is lesser and better sensitivity can be obtained for dense breasts in digital mammography. Another limitation of mammography is that the patients are exposed to X-ray ionizing radiation. Cranio Caudal (CC) and Medio-Lateral Oblique (MLO) are two standard views of each breast captured for each patient's mammogram screening [37]. CC is a view from above to depict the whole breast and nipple clearly as semi-circle in the mammogram where fat tissues closest to the breast muscle appear as a dark strip [38]. MLO view is captured at a 90 degree projection to portray more of the breast in the upper-outer quadrant along with the armpit area/pectoral muscle [38]. Figure 2.1 is the example of MLO view where pectoral muscle is visible and Figure 2.2 represents the CC view.

Sound waves ranging from 2-20 MHz [34] are used in ultrasound imaging to produce images of a single plane. This technique provides a better result for lesion detection in dense breasts and can be used in real-time. On top of that, tissue elasticity can also be determined as was elaborated in [35] for classification purposes. Nevertheless, it mostly depends on the expertise of the operator since real-time tuning of gain, pressure, focal zones, patient positioning, dynamic range are required along with the recognition of the peculiarity of the lesion.

Magnetic resonance imaging (MRI) system is built with RF coils along with a big size magnet (3-5 Tesla). An intravenous injection of gadolinium is given to the patients before capturing 3D images through MRI. It can detect minute abnormalities of breast

tissues and also the ductal carcinoma in situ in the dense breast along with its spread to the chest wall [35]; this is largely because it has better temporal and spatial resolution [34]. Nonetheless, MRI cannot be used for those with a medical history of kidney disease as the injection can cause nephrogenic systemic fibrosis [34]. Moreover, the patients with a pacemaker and any metal implant are also not suitable for MRI due to its magnetic effect. Additionally, it is time-consuming and generates blur images [34]. Therefore, incorrect reading of MRI images may require a patient to go through the same process several times.

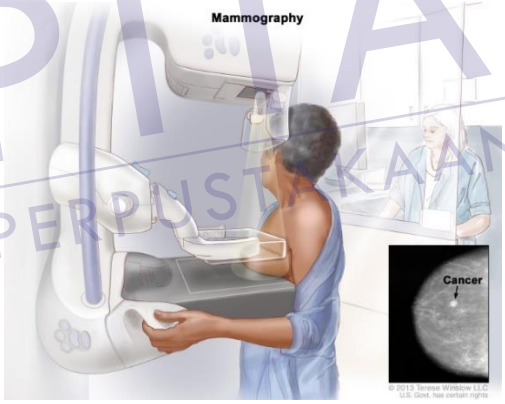
Computed tomography (CT) uses high-dose X-ray radiation to generate detailed scans or images of the inside body. In most cases, CT machines generate continuous pictures in a helical (or spiral) fashion rather than producing a series of pictures of individual slices of the body. Helical CT has several advantages such as it is fast, it produces better 3-D images and it has better sensitivity in detecting small abnormalities [39]. The newest CT scanners, called multislice CT or multidetector CT scanners, allow more slices to be imaged in a shorter time. Sometimes, contrast agents like Iodine and Barium are injected into the blood or given by mouth or enema as a way to do the CT scan. However, its high exposure to relatively large amounts of ionizing radiation than standard X-ray procedure makes it least favorable as a regular screening method.

In a Positron Emission Tomography (PET) imaging system, a radioactive substance is injected into the blood to identify the most active body cells, especially the cancerous tissues. PET scan can be added with computed tomography (CT) so that both anatomical and functional views of the suspected cells can be observed. PET is not restricted to breast density and is useful in identifying axillary nodes and distant metastasis [35]. However, it has poor sensitivity in detecting small tumors because of their small size.

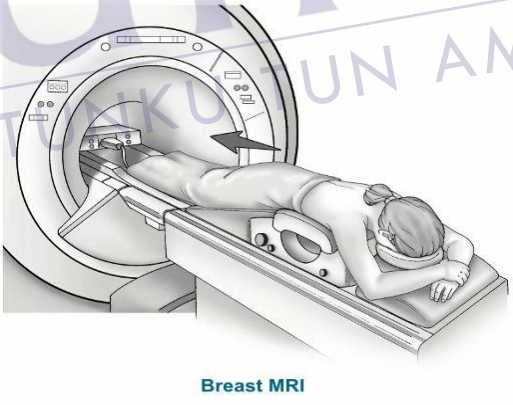
The wavelengths ranging from a millimeter to a meter can penetrate many optically opaque mediums like living tissues based on the presence of ionized molecules due to a variety of dissolved substances, such as sugar, and the permittivity of any tissue is strongly dependent on its water content [40]. This theory is utilized in microwave imaging either by using a contrast agent or by utilizing radar [41] and this technique is quite new to biomedical engineering. Microwave signals scatter significantly from malignant breast tissues due to their water content and these scattered signals are captured

in a microwave imaging system [42]. Time requirement is considerably less in microwave imaging, but the heavy computational load is the main drawback of this system [41].

Ultrasound imaging and MRI are used along with mammography to increase the screening specificity [34]. Other than mammography, ultrasound, and microwave imaging, the rest of the imaging systems discussed above are costly for regular screening. It is also observed that the use of microwave imaging as a regular screening tool is still subjected to further study and is also under trial. Whereas the accuracy of ultrasound imaging is fully dependent on the expertise of the operator. Moreover, despite all its limitations, to date mammography is the widely accepted imaging method. Radiation is 25 % less in digital mammograms than film mammograms and this issue can also be controlled by increasing the gap between two consecutive screenings. Therefore, the following subsections are devoted only to digital mammograms mainly due to their easy availability, ease of image manipulation, and fast screening time. Different breast imaging modalities are shown in Figure 2.4(a)-(f).

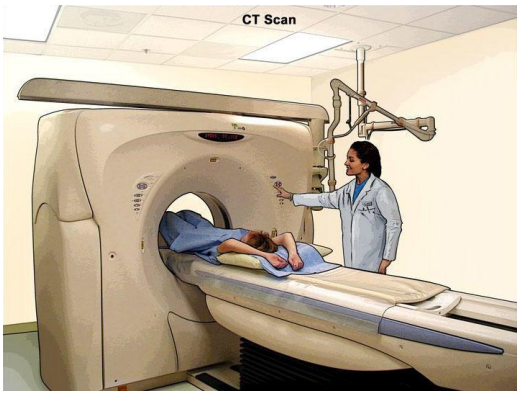


(a)



(b)

(c)



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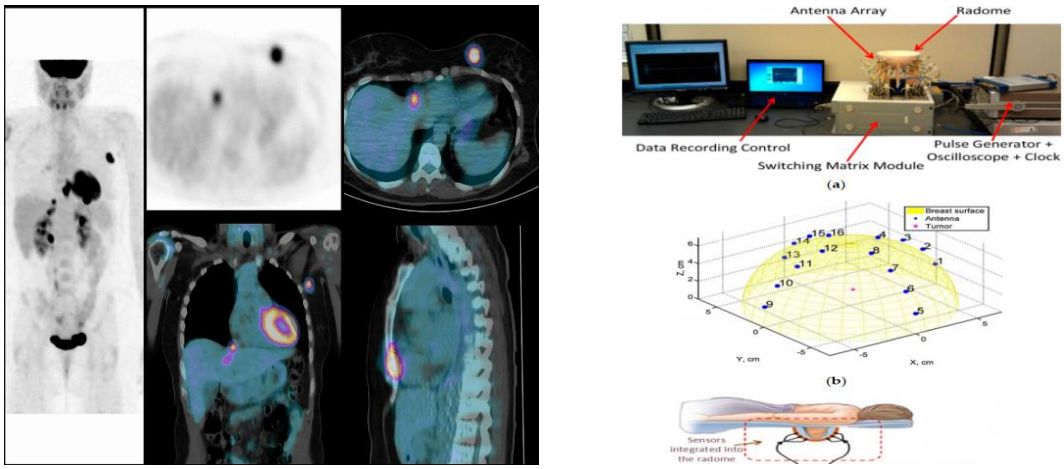

(e) (f)

Figure 2.4: Different breast imaging modalities

(a) Mammography [43] (b) Breast MRI [44] (c) Breast Ultrasound [45] (d) Breast CT scan [46] (e) Breast PET-CT scan [47] (f) Breast microwave imaging [48]

2.5 Categorization of breast imaging

Standardized terminology for the breast imaging findings was required by the radiologists for proper report organization and assessment structures so that these reports can be communicated properly with physicians. So, the American College of Radiology standardized the breast image reporting by proposing Breast Imaging Reporting and Data System (BI-RADS) as a quality assurance tool in 1993 [49], and the latest and improved BI-RADS fifth edition [50] was released in 2014 including the important changes for mammography. BIRADS assesses the mammograms into 7 categories starting from 0 to 6 and they are described in Table 2.1. It also provides clear information about the breast density (e.g., fatty, fibroglandular, heterogeneously dense, and extremely dense) and abnormality findings (e.g., mass, calcifications, architectural distortion, Asymmetries, etc.). In category 1, no abnormality is found and termed as normal. For categories 2 and 3, abnormal findings are there, but they are not likely to be cancerous or malignant. From category 4, it is suspicious to be malignant, and chances increased with increasing category.

Table 2.1: BIRADS category assessment for mammography

Category	Assessment	Likelihood of malignancy
0	Incomplete and need an additional imaging evaluation	Not applicable
1	Normal – no abnormality findings	0 %
2	Benign – one or more abnormal findings	0 %
3	Probably benign – instead of biopsy, periodic imaging surveillance preferred	> 0% but ≤ 2%
4	Suspicious – chances of malignancy have a wide range	> 2% but < 95%
5	Highly suggestive of malignancy and tissue sampling suggested	≥ 95%
6	Biopsy-proven malignancy	Not applicable

The available mammogram datasets are either categorized following BIRADS such as INbreast (only 1-6 categories) or just benign and malignant like BCDR and CMMD. Authors [28], [51]–[53] considered BIRADS category 1 as normal, 2 and 3 as benign, and the rest of 4, 5, and 6 as malignant to develop their proposed CAD system.

2.6 CAD systems for breast cancer diagnosis

A CAD system first reads a digital mammogram and performs the activities on it in sequence to classify it as normal, benign, and malignant. The working procedure of mammogram screening through a CAD system is depicted in Figure 2.5 [10].

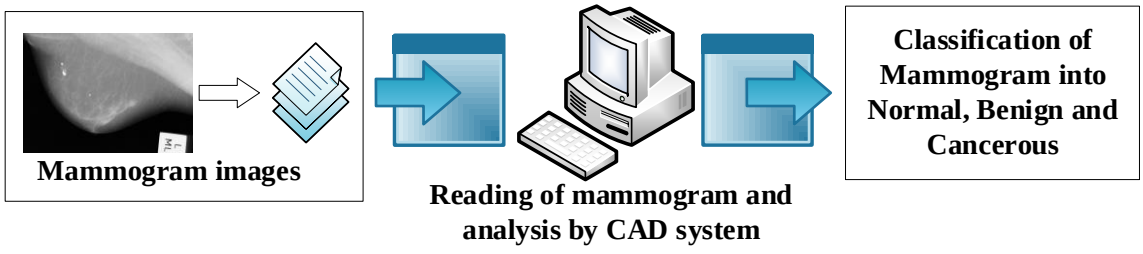

Figure 2.5: Working procedure of a CAD system

The CAD systems are of two types – traditional Machine Learning (ML) based and Deep Learning (DL) based. For the traditional ML-based CAD systems, the

mammograms are analyzed through pre-processing, segmentation, feature extraction, and classification. Whereas, DL-based CAD systems can classify the mammograms directly after preprocessing as illustrated in Figure 2.6.

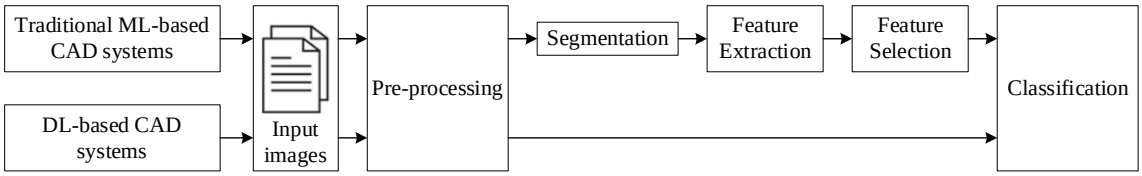

Figure 2.6: The difference in working methods of traditional ML-based and DL-based CAD systems

2.7 Traditional ML-based CAD systems for mammogram

The traditional ML-based CAD systems analyze a mammogram following a few stages in sequence to attain the required outcomes. They first preprocess an image; then segment the Region of Interest (ROI); extract the features from ROI; and finally, feed the hand-picked features to the machine learning system to classify the breast abnormalities [10]. The stages and all the involved methods of each stage followed by this system are illustrated in Figure 2.7. In this section, all the stages of traditional ML-based CAD systems used to analyze mammograms are discussed briefly. In section 2.8, DL-based CAD systems for mammogram screening are discussed.

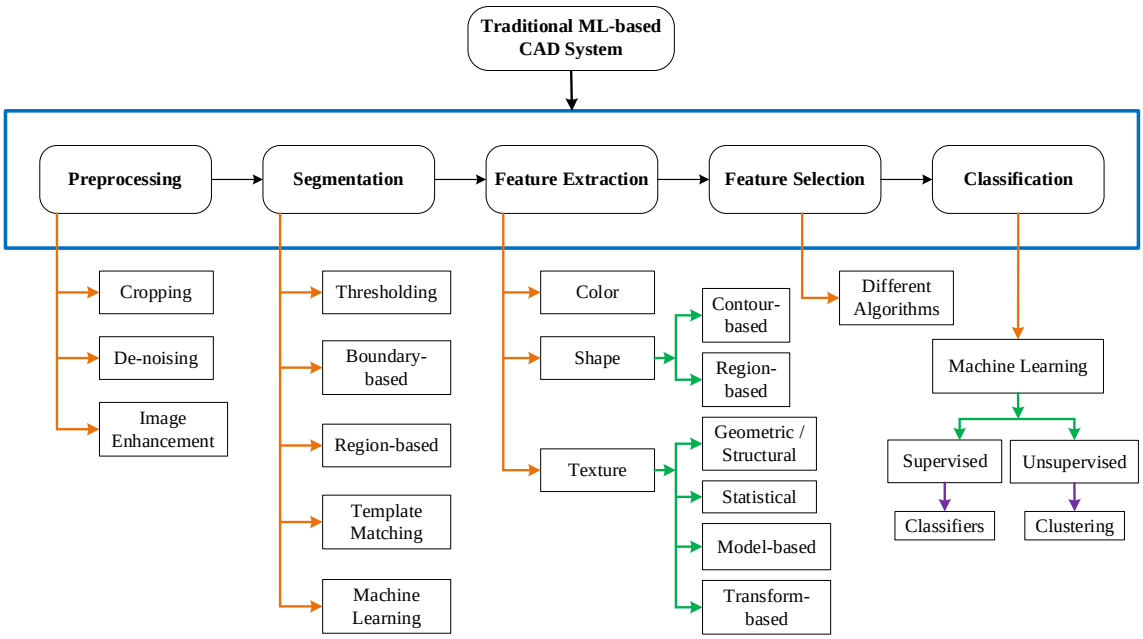

Figure 2.7: Stages of a traditional ML-based CAD system including different methods of each stage

2.7.1 Pre-processing

Noise, uneven illumination, and low contrast are the main drawbacks of the mammogram and thus, ROI identification and feature extraction are tough in this case. To negate the effects of these defects, cropping, de-noising, and enhancement of images are performed at the pre-processing stage before performing segmentation and feature extraction. The unwanted labels, artifacts, and the image portion without information can be removed by cropping.

The enhancement procedure improves the contrast level of an image based on the histogram of that image and hence, the features are more identifiable. Detection of masses is far complicated than that for microcalcifications as the traits of masses are hard to perceive and sometimes, they appear like normal breast tissues [32]. Since the microcalcifications have higher contrast than the rest of the region, and they correspond to high-frequency components, they may be easily detected through image enhancement and de-noising as it was done in [54] by using dyadic wavelet processing. Meanwhile,

masses have low contrast, varying densities, spiculated structures, and have low-frequency components. The implementation of Contrast Limited Adaptive Histogram equalization (CLAHE) along with Median filtering provided the sensitivity and specificity of 96.2 % and 94.4 %, respectively, for the detection of masses in the work [55].

2.7.2 Segmentation

The removal of the image background and the selection of ROI are vital tasks in image segmentation because the extracted features from these segmented regions are fed for classification, and hence, the outcome of the traditional CAD system is majorly dependent on this stage. The conventional procedures used in image segmentation include thresholding [56]–[59], boundary-based segmentation [60]–[62], region-based segmentation [63]–[67], and template matching [68], [69] as illustrated in Figure 2.8 [10]. However, these conventional segmentation methods are not fully automated.

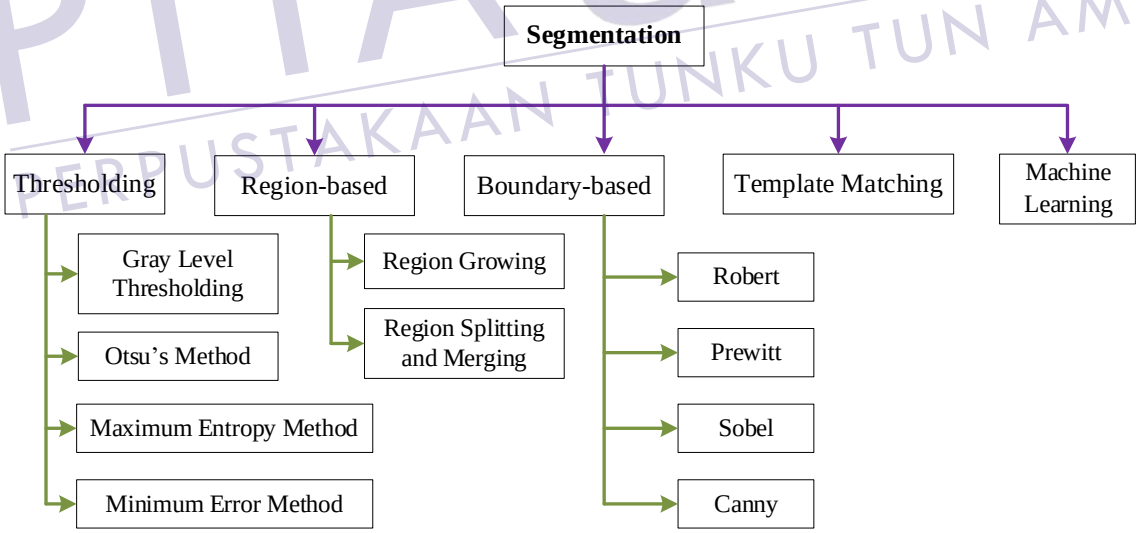

Figure 2.8: Different techniques of segmentation

2.7.3 Feature extraction and selection

An image feature may include color, shape, and texture [70]. The contour-based and

region-based representations are two types of techniques to provide shape features [71]. The texture features are geometric or structural, statistical, model-based, and transform-based and they were widely used in several earlier studies [5], [72]–[75]. The presence of redundant and irrelevant features may significantly degrade the precision of the CAD system. If the features are not properly selected, it may also reduce the learning speed of the appointed algorithm [76]. Therefore, the accuracy of classification depends largely on feature selection from a large set of data.

2.7.4 Classification

Classification is the last stage of image analysis to distinguish firstly, the normal and abnormal tissues and then, to segregate the benign and malignant tumors from abnormal cases. This is viable with pattern recognition [77] and machine learning techniques. Selected features can be classified either by supervised or by unsupervised methods. In the supervised method, it is required to train the system first and then the rest of the data can be tested by the trained system. However, an unsupervised method is dependent on machine learning to describe the hidden structure of unlabeled data.

A feature space is the whole range of a defined function of an image. The classifier is a supervised method to divide a feature space that is done by using labeled data [78] for training purposes to segment a new set of data automatically. The functions, which are already defined in feature space, are responsible to divide this feature space further into several regions [77]. Classifiers are computationally fast and can be implemented in multichannel images [78]. There are several methods to train a classifier namely Parzen window, nearest neighbor, k-nearest-neighbor, maximum likelihood/Bayes classifier, and decision tree. The computational burden of these methods is quite high, particularly with a large data set.

Clustering is an unsupervised method to classify an image; this technique can be described as a classifier without using training data, but it needs initial parameters or a segmentation process [78]. The self-training is done by iteratively dividing an image through segmentation and train itself with the existing data. K-means, Expectation

Maximization (EM), and Fuzzy c-means are considered clustering methods. Since it does not require initial spatial modeling, it may be sensitive to intensity, inhomogeneities, and noise. Clustering is mainly applied in segmenting MRI and in the cases where pixel intensity distributions are detached [77].

ANN is an information processing technique that is inspired by the way human brains process information. It is through a set of interconnecting nodes, usually known as neurons, which deliver the output through a computer model. Each node is associated with gain or weight that can be adjusted to get the required output from the given input. Learning, and recall are the two working phases [12]. Weight adaptation of the nodes is done to train the ANN about the task during the learning phase either through supervised or unsupervised methods [77], [78]. The recall is for validation and resolving an issue. Feedforward and backpropagation are two ways of learning procedures. ANN can also select features for which the weights or gains of the nodes should be adjusted and trained accordingly. The main advantage of ANN is that it has parallel processing capability and can predict the output even with insufficient training data although the accuracy is dependent on a large dataset. Its computational cost highly depends on the hidden layers and connected neurons.

The main drawback of the traditional machine learning systems is their dependency on the handcrafted features that are fed to the ML systems for classification for which the feature mapping is inferior and the optimality cannot be guaranteed [22].

2.8 Deep neural networks (DNNs)

Deep Learning (DL), also known as Deep Neural Network (DNN), is a subset of machine learning (ML) and belongs to the family of ANN, where a set of algorithms are implemented to learn patterns from its input using the functions that work in a nonlinear decision-making process. It has been applied in various medical imaging tasks as a powerful method for function approximation [79] that helped in attaining the required outcomes. The main advantage of DL lies in its automatic learning of feature representation abstraction in a hierarchical manner for which no external feature extractor

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