A MAMMOGRAM AND BREAST ULTRASOUND-BASED EXPERT SYSTEM WITH IMAGE PROCESSING FEATURES FOR BREAST DISEASES

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“Say: If the ocean were ink (wherewith to write out) the words of my Lord, sooner would the ocean be exhausted, than would the words of my Lord, even if we added another ocean like it, for its aid.”

~The Holy Quran: Al Kahfi (18): 109~

“I do not know what I may appear to the world; but to myself I seem to have been only like a boy playing on the seashore, and diverting myself in now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me."

~Sir Isaac Newton~

“If I had seen further, it is by standing on the standing on the shoulders of giants.”

~Sir Isaac Newton~

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by

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LIST OF ABBREVIATIONS

ACC	Accuracy
AI	Artificial Intelligence
ANN	Artificial Neural Networks
ANOVA	Analysis of Variance
AMSBRG	Automated Modified Seed-Based Region Growing
AUC	Area Under the Curve
BI-RADS	Breast Imaging Reporting And Data Systems
BN	Bayesian Network
BS	Bright Stretch
BSE	Breast Self Examination
CAD	Computer Aided Detection
CADx	Computer Aided Diagnosis
CBR	Case Based Reasoning
CC	Cranio-Caudal
CE	Contrast Enhancement
CF	Compression Factor
CS	Contrast Stretch
DICOM	Digital Imaging and Communications in Medicine
DM	Digital Mammography
DOE	Design of Experiments
ES	Expert Systems
DS	Dark Stretch
FCIP	Fuzzy-Count Image Processing
FDA	Food and Drug Administration
FFDM	Full Field Digital Mammography
FN	False Negative
FNA	Fine Needle Aspirates

FP	False Positive
GUI	Graphic User Interface
HE	Histogram Equalization
HRT	Hormone Replacement Therapy
HUSM	Hospital Universiti Sains Malaysia
KBS	Knowledge Based Systems
LC	Linear Contrast
MI	Medical Informatics
ML	Medio-lateral
MLO	Medio-lateral oblique
MRI	Magnetic Resonance Imaging
MSBRG	Modified Seed-Based Region Growing
NPV	Negative Predictive Value
PACS	Picture Archiving and Communication Systems
PET	Positron Emission Tomography
PPV	Positive Predictive Value
RG	Region Growing
ROC	Receiver Operator Characteristics
SENS	Sensitivity
SBRG	Seed-Based Region Growing
SF	Stretch factor
SFM	Screen Film Mammography
SPEC	Specificity
SS	Sum of Squares
TAHBSO	Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy
TN	True Negative
TP	True Positive
US	Ultrasound

GLOSSARY

areola	~	the area of dark-coloured skin on the breast that surrounds the nipple
aspirate	~	fluid drawn from a lump, often a cyst.
atypical hyperplasia	~	a benign or non-cancerous condition in which cells have abnormal features and are increase in number
axilla	~	armpit
benign	~	relatively harmless, in contrast with malignant
biopsy	~	sample of tissue removed from a patient
carcinoma	~	cancer
cyst	~	a sac or capsule filled with fluid
cytology	~	examination and interpretation of dispersed cells
duct	~	a tube though which body fluid pass
estrogens	~	A family of hormones that promote development and maintenance of female sex characteristics
hysterectomy	~	an operation in which the uterus is removed
lobule	~	a small lope or small division
lumpectomy	~	surgery to remove tumour and a small amount of normal tissue around it
lymph node	~	a rounded mass of lymphatic tissue surrounded by capsule of connective tissue.
malignant	~	cancerous
mastectomy	~	surgery to remove the breast
menarche	~	onset of first menstruation
menopause	~	time in life when a woman's menstrual period stops permanently
metastases	~	transfer of disease from one organ or part of the body to another not directly connected with it
morbidity	~	the sum of the effects of a disease upon patient
morbidity	~	sum of the effects of a disease upon patient
pathology	~	scientific study of diseases
prognosis	~	forecasts of the known or likely cause of the disease.
risk factor	~	anything that increases the chance of developing a disease

LIST OF APPENDICES

LIST OF PUBLICATIONS & SEMINARS

Chapter in Book

1. Ngah U.K., Chan C. P., Aziz S. A., (2004). Mammographic Image and Breast Ultrasound Based Expert System for Breast Diseases. *Lecture Notes in Computer Science*, Publisher-Springer Verlag Heidelberg, Volume 3213/2004.

International Journal

1. Ngah U. K., Aziz S. A., Aziz M. E., Murad M., Nik Mahdi N. M., Mat Shakaff A. Y., Mat Isa N. A., Mashor M. Y., Arshad M. R. (2007). A BI-RADS Based Expert Systems for the Diagnoses of Breast Diseases. American Journal of Applied Sciences. (In Press).

International Conferences

1. Ngah U.K., Ooi T.H., Venkatachalam P.A., Sulaiman S.N. (2002). Determination of Mammographic Calcification Clusters Using the Region Growing Technique. *6th World Multiconference On Systemics, Cybernetics ad Informatics* (SCI 2002) Orlando, Florida, USA, 14-18 July.
2. P. A.Venkatachalam, U. K. Ngah, A.H. Mohd Hani, A. Y. Md Shakaff (2002). Seed Based Region Growing Technique in Breast Cancer Detection and Embedded Expert System, the *International Conference on Artificial Intelligence And Technology* (ICAiET 2002), Kota Kinabalu, Sabah, Malaysia, 17-18 June.
3. Ngah U. K., Ooi T.H., Sulaiman S. N., Venkatachalam P. A. (2002). Embedded Enhancement Image Processing Techniques On A Demarcated Seed Based Grown Region. (*BIOMED 200*2), Kuala Lumpur, 6-8 June.
4. U. K. Ngah, L. S. Kim, C. C. Loon, (2003). The Breast Ultrasound Expert System. *Technical Journal*, School of Electrical And Electronic Engineering, USM, Engineering Campus, Volume 8, pp. 40-46.
5. U. K. Ngah, H. E. Ling, (2003) .Detection and Analysis of Mammographic Microcalcifications. *Technical Journal,* School of Electrical And Electronic Engineering, USM, Engineering Campus, Volume 8, pp. 35-39.
6. U. K. Ngah, N.A. Mat Isa, M. Mohd. Noor(2003), .Automated Seed-based Region Growing Using the Moving K-Means Clustering for the Detection of Mammographic Microcalcifications. CDROM Proceedings, paper no. 154, *the World Congress on Medical Physics and Biomedical Engineering* (WC 2003), 24-29 August, Sydney, Australia.
7. U. K. Ngah, C. C. Loon, N. Mat Shariff, L. S. Kim, S. A. Aziz, (2004), .The Image Incorporated Mammogram and Ultrasound Based Expert System for Breast Diseases. *the International Conference on Engineering of Intelligent Systems*(EIS'04), Island of Madeira, Portugal, February.
8. U. K. Ngah, C. C. Ping, S. A. Aziz, (2004). Mammographic Image and Breast Ultrasound Based Expert System for Breast Diseases. *the 8th. International Conference on Knowledge-Based Intelligent Information & Engineering Systems*(KES '04), 20-25th. September, Wellington, New Zealand.

SISTEM PAKAR BERDASARKAN MAMMOGRAM DAN ULTRABUNYI BERCIRIKAN PEMPROSESAN IMEJ UNTUK PENYAKIT-PENYAKIT PAYU DARA

ABSTRAK

Barah payu dara adalah penyakit yang paling banyak meragut nyawa kaum hawa. Kadar sembuh dari penyakit ini boleh ditingkaykan jika ia dapat dikesan secara awal. Pengesahan awal penyakit ini dapat dilakukan melalui ujian mamografi yang terbukti keberkesanannya. Begitu juga dengan ujian klinikal, fizikal secara terperinci dan ujian ultrabunyi yang disyorkan bagi mendapatkan gambaran lengkap semasa pemeriksaan. Pemeriksaan payu dara secara meluas akan menyebabkan timbunan kes terbeban pada pakar radiologi. Ini mengakibatkan kemungkinan berlakunya diagnos kurang tepat. Bilangan pakar radiologi berpengalaman pula adalah tidak mencukupi. Wujudnya satu sistem pakar akan dapat membantu mengatasi situasi ini dengan memungkinkan pembelajaran dan penerusan ilmu berbantukan komputer dan melahirkan lebih ramai pakar dalam bidang ini. Pengumpulan ilmu disertai dengan kes-kes pesakit akan membolehkan cara interpretasi yang lebih konsisten, di samping boleh dirujuk pada bila-bila masa. Kajian ini menjurus kepada pembinaan sistem pakar mamografi (MAMMEX) dan ultrabunyi (SOUNDEX) yang dapat digunakan untuk mengenalpasti pengkelasan kes-kes mengikut BI-RADS (‘***B**reast **I**maging **R**ecording and **D**ata **S**ystem*’) dengan mengambil kira butir latarbelakang sejarah pesakit, pemeriksaan fizikal dan klinikal, di samping imej mamograf dan ultrabunyi. Peningkatan digital yang dibina menerusi rutin-rutin pemprosesan imej akan dapat memperjelaskan lagi maklumat pada imej semasa penganalisaan. Pengembangan sistem pakar kepada bentuk yang membolehkan paparan imej dan manipulasi juga telah dilakukan. Ujian dengan sejumlah 179 kes retrospektif yang diperolehi dari Jabatan Radiologi, Hospital Universiti Sains Malaysia mencapai kejituan, sensitiviti dan spesifisiti bagi MAMMEX bernilai masing-masingnya 97%, 96% and 92% manakala

bagi SOUNDEX adalah 99%, 98% and 100%. Kawasan bawah lengkungan menggunakan analisa lengkungan *Receiver Operating Characteristic* (ROC) didapati bernilai 0.997(±0.003) bagi MAMMEX dan 0.996(±0.004) bagi SOUNDEX. Analisa statistik menggunakan *Randomized Complete Block Design* (RCBD) menerusi *Two Way Analysis of Variance* (ANOVA) membuktikan hasil MAMMEX dan SOUNDEX adalah selari dengan keputusan pakar radiologi. Dua pengembangan pada algoritma pemprosesan imej iaitu *Fuzzy-Count Image Processing* (FCIP) dan *Automated Modified Seed-Based Region Growing* (AMSBRG) untuk tujuan mengesan mikrokalsifikasi juga telah dapat dilbangunkan.

A MAMMOGRAM AND BREAST ULTRASOUND-BASED EXPERT SYSTEM WITH IMAGE PROCESSING FEATURES FOR BREAST DISEASES

ABSTRACT

Survival rates for breast cancer patients may be increased when the disease is detected in its earliest stage through mammography. A thorough assessment during breast screening would also include clinical, physical examination and ultrasound. The implementation of mass screening would result in increased caseloads for radiologists which would incur chances of improper diagnosis. Diagnosticians with the training and experience to interpret mammographic images and breast ultrasounds are scarce. The existence of an expert system would facilitate computer aided study and learning and produce more experts in the area and would also prove to be useful in the training of radiologists in the early part of their career. The archiving of knowledge gathered in this area with patient cases would also promote the interpretation of images in a more consistent manner and may be referred to from time to time. This study focuses on developing expert systems based on the interpretation of mammographic (MAMMEX) and ultrasound (SOUNDEX) images that may be used by expert and non-expert doctors to deduce cases (according to the BI-RADS '**B**reast **I**maging **R**ecording and **D**ata **S**ystem') based upon patients' history, physical and clinical assessment as well as mammograms and breast ultrasound images. Digital enhancement of mammograms and breast ultrasound through the existence of image processing routines may help to accentuate images in the process of analyzing procedures. Image based extension of the expert systems have also been built. A total of 179 retrospective cases from the Radiology Department, Hospital Universiti Sains Malaysia were tested, producing an accuracy, sensitivity and specificity of 97%, 96% and 92% respectively for MAMMEX and 99%, 98% and 100% for SOUNDEX. The Receiver Operating Characteristics (ROC) curve analysis produced an Area Under the Curve (AUC) with values of 0.997(±0.003) for MAMMEX and 0.996(±0.004) for SOUNDEX. The Randomized

Complete Block Design (RCBD) and the Two-Way Analysis of Variants (ANOVA) proved that the results of MAMMEX and SOUNDEX are consistent with the radiologists' opinion. Two extensions of image processing algorithms, namely the Fuzzy-Count Image Processing (FCIP) and the Automated Modified Seed-Based Region Growing (AMSBRG) techniques are also implemented to facilitate the detection of microcalcifications

CHAPTER 1

INTRODUCTION

1.0 The Evolution of Knowledge, Computers, Radiology and Decision-Making

Ever since man first learnt to communicate, knowledge that are to be shared and used by humans is most likely to be confined to what is stored in a person's head or what the person can learn from another (Swett, 1991).

Consider the following words by Sir William Osier (Wood, 1999):

“Medicine is a science of uncertainty and an art of probability”.

Important components of the art of medicine are skills in repeatedly making decisions, formulating appropriate judgments and being comfortable with risk and uncertainty. Medical training, with its heavy emphasis on factual learning, often assigns a lesser priority to the study of decision making.

Our own history of medicine contributes to dismissive attitudes about decision making. Before the later part of the 19^{th} century, medical treatment was largely a matter of tradition, spurred on by a physician’s need to do something for the patient.

1.1. The Relevance of Health Informatics and Training

The future of MI as a profession is thus very promising (Expresshealth, 2003). In other words, MI means managing medical and health care through information science and engineering technology. Like medicine, MI is also multidisciplinary. MI deals with the entire domain of medicine and health care, from computer-based patient records to applications of image processing and from primary care practices to hospitals and regions of health care.

A few years ago, only a handful doctors had even heard of the term "health informatics." Health informatics is a relatively new sub-speciality of medicine which uses information technology to manage clinical information. At a three-day eHealth Asia 2004 conference held at Kuala Lumpur in early April 2004, a local expert, Dr H.M. Goh, council secretary of the Malaysian Health Informatics Association (MHIA) stated that there is space for growth in the local health informatics scene since few public and private hospitals have significant health management systems in place. The extraordinary thing about eHealth Asia 2004 was that it was attended by 350 participants (compared to 250 participants in 2001) which featured 54 speakers from over 20 countries around the world. This indicates that the field of health informatics has made itself felt throughout the world. Globally, health informatics include change management, artificial intelligence, messaging, mobile technology and the like. Only 10 of the 120 government hospitals are computerized, and only the Putrajaya and Selayang hospitals have been fully-enabled with health informatics (The Star, 2004). With this upcoming awareness, the field of health informatics is very relevant to the Malaysian market. It is very strongly felt and believed that the research involvement in this study addresses a portion of and fits into this niche of health informatics.

1.2 Radiology and the Use of Technology

The rapid evolution of technology and clinical research makes it difficult even for the specialist to keep up. In the light of this 'information explosion', it has been demonstrated that physicians do not always make optimal decisions. It has been mentioned earlier in the introduction that immense knowledge needs to be dissipated amongst health providers through in-depth training. Specifically in radiology, this strategy has been fairly effective in large academic centers but realistically, much has to be done by radiologists to practice state-of-the-art radiology at the forefront of radiological practice, especially in Malaysia. Although computers have proven to be very efficient and helpful in carrying out mundane tasks and the processing of data into useful information, its potential as a powerful technology can be further exploited to assist radiologists in knowledge processing.

The utilization of computers in decision-making can be employed in many different forms. However, the basic understanding to be realized and engraved in each and everyone's mind is that these tools in decision-making have never been and are never intended in the first place to camouflage or belittle the decision makers in health care. Computers can be made as slaves to record huge amounts of detailed information. Simultaneously, these vast and abundant accumulated wealth of knowledge and information can be made available to radiologists at their disposal, put to use wherever or whenever abnormalities are encountered and ultimately arrive at a more consistent decision-making.

Some diagnoses can be made in a more quantitative, algebraic fashion although it cannot be denied that most radiological decision-making is very subjective. An expert is usually consulted for solving a difficult diagnostic problem. This situation and paradigm has served as a model for the birth of a class of computer systems that are known as expert systems. A KBS is designed to meet the knowledge gaps of the individual physician with specific patient problems. KBS and such other ES can be a boon to the rural health centres because even general medical practitioners can operate the systems. These are ideal examples of AI.

1.3 Expert Systems Evolution

Expert systems emerged as a branch of artificial intelligence - an amalgam of disciplines such as computer science, mathematics, engineering, philosophy and psychology. From the efforts of AI researchers, computer programs are developed that can reason as humans. ES are one of the most commercially viable branches of AI and although there have been reports of ES failures, surveys show that many parties have remained enthusiastic proponents of the technology and continue to develop important and successful applications in various fields (Duan *et al.*, 2005).

1.4 The Application Areas of Expert Systems

From its early days of infancy when MYCIN (Negnevitsky, 2005) was first pioneered, ES have been developed in broad walks of life, in various areas and disciplines ranging from geology, statistics, electronics to medicine. In fact, the sky has no limit! To emphasize on this matter, a kaleidoscope of the expert systems developed in their respective fields is mentioned here. Williams (1991) suggested a prototype expert system for the design of complex statistical experiments. GEOPLAY (GEOPLAY, 2003) is a knowledge based expert system developed by the U.S. Geological Survey that is available for explorations in the oil and gas industry.

Yang *et al.* (2005) developed an ES for vibration fault diagnosis of rotating machinery using decision tree and decision table and Duan *et al.* (2005) addressed the issues associated with the design, development and use of web-based ES from a standpoint of the benefits and challenges of developing and using them. Wagner *et al.* (2001) and Mak & Blanning (2003) applied ES to various problem domains and for the entry decisions of new products in business applications. The use of ES in business has grown steadily since their introduction. Pham & Chen (2002) used applications of fuzzy logic in rule-based expert systems involving the problem of autofocusing camera lens system and also another on a financial decision system. Tocatlidou *et al.* (2002) built an ES that was capable of diagnosing plant diseases and disorders while Park & Storch (2002) shared a representation of ES in the shipbuilding industry which was able to downsize sizable development costs.

Craker & Coenen (2006) proposed Knowledge Bazaar, the concept of which a paradigm for the development of ES and knowledge bases are created dynamically using knowledge supplied by self appointed internet communities. The philosophy underpinning the Knowledge Bazaar is the observation that knowledge can be accumulated, not from a limited number of experts or expert sources, but dynamically from internet users as they solve problems and offer advice. Mahmod *et al.* (2000) had shown the usage of neural networks combined with an expert system environment.

Perhaps, all the relevant studies are best encapsulated in the paper by Liao (2005) where ES methodologies in almost all applications have been reviewed by the author for a span of a decade beginning from the year 1995.

1.5 Expert Systems in Medicine and Medical Application Areas

Expert or knowledge-based systems are the most common type of artificial intelligence in medicine (AIM) system in routine clinical use. Indeed, it was in the medical area that expert systems have made their presence felt in the first place. AIMs contain medical knowledge, usually about a very specifically defined task and are able to reason with data from individual patients to eventually emerge with reasoned conclusions. Although there are many variations, the knowledge within an expert system is typically represented in the form of a set of rules (Keles & Keles, 2006).

Other areas of specific medical applications of expert systems are in Obstetrics and Gynaecology (Medical Decisions, 2003), for leukemia management (Chae *et al.*, 1998), for estimating the prognosis of head injured patients in intensive care unit (Sakellaropoulos & Nikiforidis, 2000), for heart valve diseases (Turkoglu *et al.*, 2002), applied to brain MRI (Zhang & Maeda, 2000), even as early as the 1980's to determine the irreversible cessation of all functions of the entire brain before any other organ transplantation (Pfurtscheller *et al*., 1988).

Alonso *et al.* (2002) developed a medical diagnosis system, obtained by combining the expertise of a physician specialized in isokinetic and data mining techniques where patients may exercise one of their knee joints using basically a physical support machine according to different ranges of movement and at a constant speed.

Lee *et al.* (1999), introduced a holistic system, which amalgamates case-based reasoning, rule-based reasoning, causal-based reasoning and an ontological knowledge base for managing clinical incidents in general practice enabling health professionals to share medical incident information, which has caused harm and may or can cause potential harm. The re-use of such information may prevent or mitigate human or medical errors. Morelli *et al.* (1987) and Solano *et al.* (2006) both described computational systems for automated diagnosis of depression and as an aid to clinical decision making in the mental health field. Verdaguer *et al.* (1992) investigated the application of ES in patients suffering from pneumonia, while Leong (1987) developed a system to detect irregularities by analyzing heart sounds through the interpretation and analysis of ausculatory findings.

Costly and sometimes deadly clinical incidents may occur during the provision of health care, such as errors in dispensing inappropriate drugs due to the similarity of medication names to a patient for example. Lee *et al.* (1999) developed a prototype for this situation. In the same year, Li (1999) proposed a system to diagnose AIDS risky patients. While Lee & Lee (1991) suggested that future medical E.S. be specifically developed having at least one, if not all of these three characteristics i.e. simulate the performance of group of human experts, deal with chronic diseases and deal with several diseases simultaneously, Lhotska *et al.* (2001) focused on efficiency enhancements on rule based systems.

1.6 Breast Cancer Scenario

Breast cancer is among the leading causes of deaths in women worldwide. Its incidences have been rising at an alarming rate. More and more women have been subjected to the misery, suffering and pain caused by the disease. In Malaysia alone, approximately one in 20 women will be afflicted with breast cancer by the age of seventy, and by the age of 85, women have a one in eight chance of developing breast tumour. In the year 2000, almost 4,000 newly diagnosed cases emerge in the country. Of these, nearly 45% result in deaths, making it the number one cause of cancer-related deaths among Malaysian women (Sunday Star, 2003).

In a technical report drafted by the Ministry of Health Malaysia in the year 2001, 20% of patients afflicted by all kinds of the 1392 cancer cases have died from breast cancer alone. In its first report, the National Cancer Registry stated that 26,089 people were diagnosed with cancer in Peninsular Malaysia in the year 2002, of which 14,274 (55%) cases were cancers among women and 30.4% of it, were cancer of the breast (Mat Sakim, 2004).

In Europe, 2004 estimates indicated 371,000 new cases with 129,900 breast cancer deaths. Mortality rates rose from 1951 until 1990 but fell noticeably in Western Europe, especially in the United Kingdom. However, this is not the case in Eastern and central Europe. Although rates in Hong Kong and Japan have been lower than those in Europe, they have also been increasing. Rates in North and South America are similar to Western Europe and so is Australia. The reasons for this decline in mortality rates in Western Europe, Australia and the Americas include the widespread practice of mammographic screening (Boyle *et al.*, 2005).

1.7 The Necessity for This Work

Looking at the previous facts, we are immersed in a war, where the latent 'enemies' that we are confronted with in the battle against this killer disease is lying dormant out there, lurking and striking from unexpected corners. Indeed, we find ourselves in a difficult situation. In formulating the strategy best taken in this 'war', certain points as in the following, are noteworthy.

Diagnosticians with the training and experience to interpret mammographic images are scarce. Therefore, there is an emphasis in training new radiologists to be able to interpret the mammographic images. The situation would be more crucial if mass screening were to be adopted as a national policy in this country as has been practiced in certain countries in the west.

In the early period of a doctor's professional activity, an expert system would prove valuable in minimizing the troubles that he or she might face due to inexperience. The existence of such facilities could be helpful especially for young radiologists or non-specialists. The existence of a diagnostic tool to aid in the interpretation process has been proven to be more useful for the junior than for the senior radiologists

(Baileyguier *et al.*, 2005). It is also a valuable teaching tool for the junior radiologists. Sensitivity also improved slightly for the senior radiologists. However, specificity remained unchanged in the study. An expert system for this application would make diagnostic expertise more widely and readily available in the clinical community.

Therefore, the success of medical imaging depends on subjective factors that influence the ability of the observer to ‘ interpret the information’. These factors can be summarized into two broad classifications:

1. Those factors that are image dependent and relate to the visual conspicuity of features relevant to the clinical problem; and
2. Those that are image independent; are primarily cognitive in nature and relate to what the observer knows about the visual information in front of him.

Variation between readers was greater than the differences between imaging techniques (Manning *et al.*, 2005). There are many image acquisition, display and processing parameters, and their effects on optimizing images for human interpretation are largely unknown. But we know less still, allowing the observer to structure the task of interpreting image features; perhaps a better understanding of these factors now deserves our research attention so that we can achieve a better match of image displays to cognitive/perceptual skills. The availability of Computer Aided Detection(CAD) and Computer Aided Diagnosis(CADx) should be employed with a word of caution. That is, it is important that the development and availability of such systems do not detract from quality and the need for radiological skills across the imaging workforce. In other words, the skill of radiologists using such CAD and CADx remains paramount. Maintaining high radiological skill levels whilst using technology efficiently and effectively to formulate correct diagnostic decisions quickly is a key issue for the future (Manning *et al.*, 2005).

Even though the Breast Imaging Reporting and Data System (BI-RADS) was introduced to help standardize feature analysis and final management of breast modality findings, there still exists variations in their interpretations. Continued efforts to educate radiologists to promote maximum consistency still need to be carried out (Lehman *et al.*, 2002). The risk of breast cancer increases with age. Considerable evidence indicates that older women frequently do not undergo mammography. Offering on-site mammography at community-based sites where older women gather is an effective method for increasing breast cancer screening rates among older women (Reuben *et al.,* 2002). It is hoped that this work may be useful in filtering only the abnormal cases to be further scrutinized by specialists.

Routine and repetitive use of computer-based systems developed for experiments would bring several benefits. Radiologists could be trained to evaluate the perceptual features appropriately (D'Orsi *et al.*, 1992). In clinical practice, only 15-30% of patient referred for biopsy are found to have a malignancy (Hadjiiski, 2004). Unnecessary biopsies increase health care costs and may cause patient anxiety and morbidity. It is therefore important to improve the accuracy of interpreting mammographic lesions (Hadjiiski, 2004), thereby improving the positive predictive values of detection modalities.

As the expert system contains specific rule base for the differentiation of breast diseases, it may be utilized both to help train physicians in breast cancer modalities and to promote a more consistent mammographic and ultrasound interpretation. The criterion for interpreting imagery is subjective and variable. With the help of an expert system, the diagnostic criteria can be made more explicit. This would serve as a basis for consistent and reproducible diagnoses. At the same time, it would also form the basis for discussion and further research to improve the validity of the diagnostic criteria. Expert systems would serve as models with intelligent behavior in cognitive and perceptual realms and skills to solve problems thought to require human intelligence. People are better at clarifying a problem, suggesting kinds of procedures to follow, judging the reliability of facts and deciding if a solution is reasonable. The problem solver must know how to use knowledge and see patterns in the signals presented.

To sum up, the following points are relevant:

- The human heuristic approach of combining evidence to reach a prognosis can deal successfully with a limited amount of evidence. The proliferation of large databases of patient findings, due to the increased use of computers in clinical settings, offers an abundance of available data, challenging the limited human capacity for indirect inference. Decision support systems that are able to model uncertainty and analyze diverse sources of information can therefore become a useful tool for medical experts (Sakellaropoulos & Nikiforidis, 2000).

- Some of the most successful applications have been for instruction e.g. use of a medical expert system to develop diagnostic skills thus encouraging students to structure knowledge and process it systematically in response to a problem or abnormality. Also, as precise analytical models of knowledge and through the ways in which they are used, expert systems can enhance our understanding of human decision-making processes.

- As clinical decision making inherently requires reasoning under uncertainty, expert systems will be suitable techniques for dealing with partial evidence and with uncertainty regarding the effects of proposed interventions (Shortliffe, 1987).

- Radiology is gradually developing a more systematic approach to training, replacing the traditional mixture of ad hoc apprenticeship and formal lectures with a combination of structured tuition and case-based experiential learning. This is intended to meet a long-recognized need for clinicians to encapsulate general medical knowledge within the development of skills through diagnostic practice. A structured approach to training can have the additional benefit of equipping learners with a coherent ‘conceptual framework’: an appropriately defined and organized notation that enables them to externalize, reflect on and share diagnostic knowledge (Structured Computer-based Training, 2005).

- Radiological expertise is based on two kinds of skills: the swift and accurate processing of normal appearance, and the ability to distinguish disease from normal variation in appearance. Thus, skill development in radiology requires exposure to, and reporting of a large range of images, so that recognition of varied normal anatomy are firmly etched in the minds of the skilled interpreters and cognitive resources can be devoted to the process of describing abnormal appearances (Structured Computer-based Training, 2005).

- Despite the wide applications of AI techniques to a range of clinical activities, few expert systems have been implemented in the field of medical imaging; its scarcity possibly due to the inherent difficulty in high-level vision. The data acquired from medical scanners can be noisy and ambiguous. Nevertheless, the potential benefits make it tempting to aim at designing expert systems using the digital images provided by the various modalities, especially with the advent of networking of medical images through PACS and the DICOM format. DICOM is an international standard, recognized by most hardware and software manufacturers for the storing and transmission of medical images acquired with all modalities (Chabat *et al.*, 2000).

This work is an attempt to fulfill or partially fulfill the dearth of imaging expert systems and with the inadvertent and inevitable emergence of digital mammography, radiologists would need to undergo pertinent retraining (Digital Imaging, 2004). Hence, this work will all the more be relevant.

1.8 Artificial Intelligence In Breast Cancer Research

The earliest study encountered was by Cook & Fox (1987), where mammographic image analysis was investigated using a decision table to represent all the parameters and possibilities in 41 rules that were created, all centred on masses and lesions. Wu *et al.* (1993) also applied ANN on mammography for decision making in the diagnosis of breast cancer. A network that used image features performed well in distinguishing between benign and malignant lesions. Floyd *et al.* (1994), predicted breast cancer malignancy using an ANN on a retrospective set of data of patients scheduled for biopsy, i.e. breast biopsy decisions. Results of biopsies were taken as the truth in diagnosis of the malignancies. Baker *et al.* (1995) did a study to determine if an ANN to categorize benign and malignant breast lesions can be standardized for use by all radiologists, using a subset of the database used by Floyd *et al*. (1994), using 10 BI-RADS descriptors and 8 input values from patient medical history as inputs.

Lo *et al*. (1999), evaluated whether an ANN can predict breast cancer invasion on the basis of readily available medical findings (i.e. BI-RADS mammographic findings and patient age). Chen *et al.* (1999) used neural network to increase the capabilities of ultrasonographic (US) technology for the differential diagnosis of solid breast tumors. The system differentiated solid breast nodule with relatively high accuracy. Mat Sakim *et al.* (1999) investigated the impact of ANN based on cytological features to solve breast cancer diagnosis and prognosis. Using the same sets of data as in their study in

1994, Floyd *et al.* (2000) used simplified parameters for creating a case-based reasoning computer algorithm which used mammographic findings for breast biopsy decisions.

Wells *et al.* (2000) developed a knowledge-based expert system for the purpose of improving radiotherapy planning efficiency for a standardized, tangential breast technique. Burnside *et al.* (2006) retrospectively wanted to determine whether a BN computer model can accurately predict the probability of breast cancer and to improve the PPV of image-guided breast biopsy. Most of the quite recent works that are found are based on ANN (except the one by Floyd *et al*., 2000) who used case-based reasoning). Few expert systems have been implemented in the field of medical imaging (Chabat *et al.*, 2000) and none of the past work fit quite exactly in what this study is intended to achieve. A comparison of the performances of the systems mentioned with the system developed in this study will be discussed in the last chapter.

1.9 The Objectives of the Study

This work has chosen expert systems to become its vehicle or medium of knowledge reasonings and development environment. In expert systems, knowledge may be divided into individual rules and the user can see and understand the piece of knowledge applied by the system. In contrast, with other AI techniques such as neural networks, one cannot select a single synaptic weight as a discrete piece of knowledge. Knowledge is embedded in the entire network; it cannot be broken into individual pieces, and any change of unpredictable results. It cannot reason out or give explanations for answers. A neural network is, in fact, a black-box for its user (Negnevitsky, 2005, pg.262). Therefore, radiologists are reduced to become mere spectators. And for this, some radiologists have expressed their concerns. The factors that govern decisions in breast assessments are too many, factors are multi-faceted and combinations are too numerous. Cases too are different and individualistic. It is difficult to find the same circumstances or situations. Therefore, to venture into case based reasoning, would require years of data gathering and archiving. To venture into fuzzy systems then time would be an unfavourable factor as all rules must be tested and tuned, which can be a prolonged and tedious process. It took Hitachi engineers several years to test and tune only 54 fuzzy rules to guide the Sendai Subway System (Negnevitsky, 2005).

Mammography remains the proven technique for early detection of breast cancer and the use of ultrasound may one day be made a complementary procedure as is the practice in other parts of the world. The demand for breast screening services is increasing because there are greater numbers of women older than 40 years in the population. These projections also mean there will be a need for greater numbers of interpreting physicians (Basset *et al.*, 2003). Radiologists, particularly those involved with mammography screening, believe intuitively that experience improves performance. At the same time, particularly in environments where the requirement for interpreting large volumes of screening mammograms leads to fatigue and distraction, there is a potential for misinterpretation and the implicit threat of litigation. Performance in screening is, of course, inextricably linked to personal skill, inherent visual and interpretative ability, as well as the degree of specialized training received (Burhenne *et al.*, 2001). Hence, to lessen the burden on the existing number of physicians who are faced with these extra tasks and to facilitate more expertise, training sufficient numbers of residents interpret mammograms in the future is one effort to solve the problem. Therefore, this work will be relevant for now and for future use.

The following are the objectives envisioned for this work:

- To build a system that emulates and simulates the radiologists' way of thinking and would be able to produce results that are consistent with that of the expertise.

- To evaluate the performance of the systems developed in terms of accuracies, sensitivities, specificities and related properties.

- To develop image processing modules and explore new techniques and algorithms in image processing (specifically to detect microcalcifications in mammograms, if possible, in mammograms with various densities) that may add to the richness of the current image processing methods available and then be integrated with the system developed and also to identify the usefulness of the appropriate techniques.

- To provide a systematic approach in interpreting mammograms and ultrasound where the workings are in a structured manner, hence more consistent decision-making as a computer evaluation is often more consistent and reproducible than a human decision maker (Chan *et al.*, 1999).

- To accumulate and gather most (if not all) relevant facts so that information are more explicit in the fountain of knowledge in this area by bridging the gap in the development of expert systems specifically for mammographic and ultrasound interpretation.

1.10 The Organization of the Thesis

This chapter has instigated the boom and evolution of knowledge and the importance of having a more documented form of these knowledge that are possessed by the few to be pooled and made available in a more discrete and explicit form. It also gives insights as to the relevance and necessity for this study to be embarked upon.

Chapter 2 gives an insight and understanding of the various factors and risk for breast cancer, the prevalent methods of detection of breast cancer, the modalities of diagnoses, the reasons for the necessity of the recent standards introduced (BI-RADS), the breast anatomy, the characteristics of features, certain definitions and the signs of abnormality associated with both the modalities which form the subject of this study.

Chapter 3 presents the various image processing modules incorporated to be used for digital manipulation of the acquired patients' images in this study. Extensions of the existing methods have also been explored and unveiled, namely the **R**egion **G**rowing with **E**mbedded **E**nhancement (RGEE) method, the **F**uzzy-**C**ount **I**mage **P**rocessing (FCIP) technique and the **A**utomated **M**odified **S**eed **B**ased **R**egion **G**rowing (AMSBRG) method.

Chapter 4 captures and details the entire development of the expert system in this work. Knowledge acquisition and knowledge representation are absolutely vital to the integrity of the rule-base for the expert system that would ultimately be constructed. The necessary steps that have to be undertaken to arrive at the ultimate knowledge base is also discussed in detail. An attempt to integrate the expert system developed that is integrated with imaging manipulations and facilities is also explained.

Chapter 5 explains the statistical analysis methods that are used to quantify the performance of the expert system developed in this study. These are some aspects of modifications to the Two-by-Two Table, the **R**eceiver **O**perating **C**haracteristic (ROC) curve analysis and the **D**esign **o**f **E**xperiment (DOE) technique, specifically the randomized block design (RBD) technique through the usage of the A Two-Way **AN**alysis **O**f **Va**riance (ANOVA) to verify the approach in the data collection and to justify that the results obtained from the execution of the expert systems are consistent with the doctors' opinions.

Chapter 6 tables the results of the whole study, an example of the Graphic User Interface of the Expert Systems, the results obtained from the execution of the expert systems, the significant implication of the statistical analyses concerning the performance of the system developed and the results obtained after digital image manipulations from the implementation of the image processing routines. This chapter also discusses the performances of the systems in comparison with other studies (which are nearly similar or close to the system developed. Feedback from users of the system (namely the radiologists) are also indicated.

Conclusions are drawn in Chapter 7 and the contributions of this research are highlighted. Finally, some recommendations for further extensions are included at the end of the last chapter.

CHAPTER 2

BREAST CANCER: METHODS OF DETECTION AND MODES OF DIAGNOSES

2.0 Introduction

Breast cancer ranks second to lung cancer and is the most common form of malignancy in women. There are about one million breast cancer cases in women coming into light each year worldwide. One out of every ten women is said to be subjected to this disease in her lifetime. It is a pernicious disease that is causing large numbers of deaths not only in developed countries like the United States of America, United Kingdom and Canada but also in the underdeveloped and developing countries including Malaysia. It occurs most commonly amongst women in the age group of 40 to 50 years of age. As the incidence of this disease is increasing all over the world, it is therefore an extremely important public health objective to be able to detect the disease at the earliest possible stage. With an alarming increase in the rate of deaths every year, there is an obvious cause for concern.

The steps that have to be taken to control breast cancer are

(i) prevention,

(ii) detection and

(iii) treatment

Prevention seems to be the most difficult line of defense. Moreover, the cause of the disease is not yet clearly understood. Considerable improvements in treatment have been observed. Even then, treatment is effective only when the disease is detected in its early phase. Therefore, the most sensible line of action to undertake would be in detection.

2.1 The Modes of Detection and Diagnosis for Breast Cancer

Early detection is the most successful method of dealing with breast cancer. Detection is the ability to find abnormalities for which a 'significant' case will prove to be malignant. Proper detection techniques will help to segregate the benign cases from the malignant ones.

At the present moment, detection of breast cancer is achieved through

(i) breast self examination (BSE),

(ii) clinical evaluation and physical examination,

(iii) mammographic screening and

(iv) other tests.

2.2. The Procedures In Diagnosing Breast Diseases

The procedures in diagnosing breast diseases are as shown in Figure 2.1.

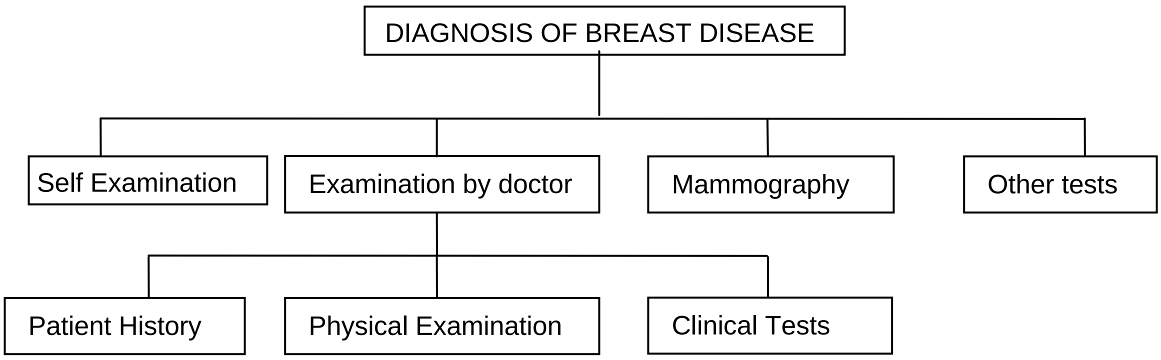

Figure 2.1. The procedures in diagnosing breast diseases.

The most valuable steps taken by the clinician in the diagnosis of breast disease are the clinical history and physical examination. When these two clinical activities have been completed even by the most experienced clinician, doubt as to the diagnosis may still be present which means that further diagnostic assistance will be needed in some patients. The aids currently available to the clinician for these difficult patients are a second professional opinion, X-ray imaging of the breast i.e. mammography, ultrasonic imaging, aspiration with or without cytology and other tests. More details pertaining to these will be available in the chapter. A brief explanation for each of the modes and procedures of breast diagnoses including self breast examination will be dwelled upon.

2.2.1 Breast Self Examination

In spite of advances in detection techniques, most breast cancers continue to be self detected. Women who practise regular self-examination will be aware of nodularity and they would be the best observers to appreciate or detect an alteration (Parsons, 1983). It is therefore necessary that every woman be made aware of the importance of breast self-examination (BSE). However, many women do not examine their breasts and some do not know what to feel for. The most important things to be aware of are signs and symptoms.

2.2.1.1. The Signs and Symptoms to Look Out For During Breast Self Examination

A woman should be wary of any of the signs or symptoms of:

- lump in the breast,
- an increase in the size of the breast,

- one breast unusually lower than the other,
- puckering of the breast skin,
- dimpling of the nipple,
- change in the skin of the nipple/areola, e.g. persistent scabbing,
- lumps in the armpit,
- swelling of the upper arm and
- bleeding from the nipple.

2.2.2. Examination by the Doctor

Careful medical history and physical examination are the first and most important steps in identifying patients' risk factors.

2.2.2.1. The Patient's History

The following factors are usually noted.

(a) The Patients Reproductive History

(i) **Age and reproductive status**: the patient's age and her reproductive status, whether at pre menopausal or post menopausal stage,

(ii) **Pregnancy:** age at first delivery and subsequent age at each nursing history,

(iii) **Menses**: the patient's age at first onset, frequency, duration and regularity,

(iv) **Menopause** (if applicable): the patient's age at onset and

(v) **Gynaecologic operative procedures**: abortion, hysterectomy, oophorectomy, etc.

(b) A History of Breast Disease

(i) **Family history**: whether any close relative has had breast cancer,

(ii) **Personal history**: fibrocystic disease or previous breast cancer and its location,

(iii) **History of trauma**: any past procedures like aspiration, biopsy, and mastectomy.

(c) Hormonal manipulation: drugs taken e.g. oral contraception or others, estrogen administration and side effects.

(d) Patients' own symptoms: Report on self examination by the patient**,** for example, the presence of lumps, retraction of skin or nipple, nipple discharge, pain or tenderness.

2.2.2.2 Physical Examination and Clinical Tests

A thorough and methodical examination of the breast by an experienced clinical staff is essential for the detection of breast abnormalities.

The steps that would be necessary are

(a) visual inspection and

(b) palpation

(a) Visual Inspection

Suspicion is aroused when there arises any one of the visual indications from the following:-

(i) marked increase or change in size and shape of one breast,

(ii) redness or edema (*peau 'd' orange*) over the skin,

(iii) changes in the nipple area,

(iv) dilated subcutaneous veins,

(v) retraction of the nipple especially if retraction is unilateral, recent and

(vi) nipple discharge: color (suspicion is aroused when discharge is blood).

These changes have to be noted with the patient sitting or standing. If there are any changes then these may be exaggerated when the patient is asked to elevate the arms or by placing the patient's hands on the hips.

(b) Palpation

The presence of a dominant mass will certainly trigger suspicions. The details of the mass that will be noted would be:-

(i) **size**: approximate measurements,

(ii) **mobility**: fixed or freely mobile,

(iii) **hardness**: soft, firm or hard,

(iv) **multiplicity**: single or multiple and indistinct and

(v) **bilateral**: on one side of the breast or on both sides.