Computational modeling of biopotential fields in the female breast with and without tumour

Ng, Wan Kee

2005

Ng, W. K. (2005). Computational modeling of biopotential fields in the female breast with and without tumour. Master's thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/6215>

<https://doi.org/10.32657/10356/6215>

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COMPUTATIONAL MODELING OF BIOPOTENTIAL FIELDS IN THE FEMALE BREAST WITH AND WITHOUT TUMOUR

NG WAN KEE

**SCHOOL OF MECHANICAL AND AEROSPACE ENGINEERING
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2005

Computational Modeling of Biopotential Fields in the Female Breast with and Without Tumour

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A thesis submitted to the Nanyang Technological University

In fulfilment of the requirements for the Degree of

Master of Engineering

2005

ABSTRACT

Most of us would agree that there is substantial room for the improvement of breast cancer detection, diagnostic and treatment. Preliminary analysis of the effects of mammographic screening suggests that early detection helps in achieving a real but small fall in overall mortality. Numerous sources suggest the efficacy of skin surface electrical potentials due to the underlying lesions. In the present studies, we presented a new approach; termed the Biofield Diagnostic System (BDS) might have the potential to augment the process of diagnosing breast cancer. A theoretical three-dimensional, simplified and yet realistic model of female breast was presented to investigate the feasibility and distinguishability of surface biopotential resulted from the presence of different types of breast abnormalities. An inhomogeneous female breast model was developed, which was close enough to the actual, by considering a breast as a hemisphere in supine condition the various layers were of unequal thickness. Isotropic homogeneous conductivity was assigned to each of these compartments and the volume conductor problem was solved using finite element method to determine the potential distribution developed.

For the optimisation part, the h2 Richardson Extrapolation was performed for grid invariance test to ensure the results are of reliable accuracy. From simulation results, tumour location influences the surface potential profoundly and is easier to be detected if it lies closer to the surface. It is suggested that detection probes to be placed as close to the predicted location of tumour as possible.

Finally, four important parameters were identified and analysis of variance (ANOVA, Yates' Method) was performed using 2^n design (n = number of parameters 4). The effect and importance of these parameters were analysed. The Taguchi method was further used to optimise the parameters in order to ensure the signal from the tumour is maximum as compared to the noise from the other factors. Taguchi methods used proved that probes' source strength, tumour size

and location of tumours have great effect on the surface potential field. For best results on the breast surface, the low amplitudes of current should be applied while having the biggest possible tumour size and nearest to the breast surface.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my supervisors, Dr. Eddie Ng Yin Kwee and Dr. Ang Whye Teong for their continuous guidance and fruitful discussions throughout the year.

Also, a note of thanks is also extended to Dr. Llewellyn Sim (Consultant Radiologist) of SGH for his support and collaboration in this research. Special note of thanks is extended to Dr. Sutthiphong Srigrarom and the technical support team of FEMLAB Comsol for their valuable discussions and help in troubleshooting the problems aroused from the PDE calculator.

I am very grateful to NTU for the research scholarship and conference financial support. Special thanks to Dr. Tony Chan Kai Yun, Director of CAMTech NTU, for allowing me to station and use all the facilities in CAMTech laboratory. I also owe my warm thanks to all of my friends there, without their cheers and laughter; research life would not have been so much fun.

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NOMENCLARURE

ϕ	Electric potential (mV)
σ	Tissue space variant conductivity tensor (Ωm) ⁻¹
I_v	Source term (mA)
∇	Laplacian operator
X, Y, Z	Cartesian coordinates (m)
n	Unit normal vector
J	Magnitude of applied current density (mA)
f	Discrete solution
h	Grid spacing
g	Functions defined in continuum and do not depend on any discretization
H.O.T	Higher order terms
r	Refinement ratio
p	Orders of the basic numerical method
E_1	estimated fractional error
ϵ	Error band
A_1	Actual fractional error of fine grid solution
GCI	grid convergence index
Ep	Asymptotic range of errors
SS	Sum of square
F	Variance effect
S/N	Signal-to-noise ratio
S_t	Total variation
S_m	Average variation
S_e	Error variation
V_e	error variance

Chapter 1

Introduction

1.1 Background

Cancer refers to abnormal and uncontrolled growth of cells in a body tissue or organ. These cancer cells then spread within the tissue/organ and to other parts of the body. Cancerous change in the breast occurs in the glandular component of the breast but what triggers the start of cancerous change is unknown. Therefore, the early detection of certain cancers can save lives, reduce extent of treatment, and improve quality of life. Moreover early detection methods improve survival rates for many patients. The American Cancer Society estimates the five year relative survival for the eight screening accessible cancer sites would increase from 82% to more than 95% if these cancers were diagnosed at a localized stage through regular cancer screenings.

[Amcs2003]

Between 1973 and 1999, breast cancer incidence rates worldwide increased by approximately 40%. Recent trends (1990s) have shown an increase in breast cancer incidence confined to early stage breast cancer, which largely reflects a rise in early detection tools used, such as mammography. [Edwa2002] An estimated 215990 new cases of invasive breast cancer are expected to occur among women in the United States during 2004. It is the most frequently diagnosed non-skin cancer in women. In addition to invasive breast cancer, 59390 new cases of in situ breast cancer are expected to occur among women during 2004. Of these, approximately 85% will be ductal carcinoma in situ (DCIS). The increase in detection of DCIS cases is a direct result of increased use of screening with mammography, which detects breast cancers before they can be felt. An estimated 40580 deaths are anticipated from breast cancer in 2004. Breast cancer ranks second among cancer deaths in women. According to most recent data, mortality rates has declined by 2.3% per year from 1990 to 2000 in all women, with larger decreases in younger (<50 years) women. These decreases are most likely the result of both earlier detection and improved treatment. In the case of Singapore, breast cancer is still the leading cause of death in Singaporean women. Singapore has one of the highest age-adjusted breast cancer incidences in Asia. [Wang2003] One in five cancers in women are due to breast cancer. Every year, more than 700 new cases of breast cancer are diagnosed. About 250 women die from the disease each year. The incidence of breast cancer is highest in the 45-49 year age group. Chinese women have a higher risk of breast cancer compared to Malay or Indian by about 10-20%. Asymptomatic women 40-49 years old are recommended to go for mammography annually while women aged 50 years and above should have it once every two years. [Heal2003] During their lifetime, 1 woman in 9 is expected to develop breast cancer, and 1 woman in 25 is expected to die from it. Early detection is a woman's hope for effective treatment and better survival rates. Unfortunately, present available adjunct detection tools are either ineffective or financially unjustifiable. Even mammography, as primary imaging modality, utilizes low energy x-rays radiated through the compressed breast to expose high resolution film, identifies only 61% to 87% of breast cancers,

and has lower sensitivity in women under 50 years of age, and false negative rates are between 5-15%. [Home1997] The specific distinguishing benign from malignant lesions on mammography is around 55%. Current limitations of mammography include the inability to evaluate radiographically dense breast, common in Asian or younger women, and postoperative breast, where scar is difficult to distinguish from recurrent tumour. [Davi1996] It is to be stressed that Biofield test is not a replacement for mammogram. Biofield is a test of the Physiology of the patient by reading the potential radiating from the surface of the body. Whereas the mammography looks into the anatomy or structure of the specimen, with tumour that has grown large enough to block X-ray beam, produces an image that is interpreted by a trained radiologist. All the tools discussed in this chapter are just detection tools and cannot diagnose breast cancer, as this can only be done by biopsies. To date, in the area of numerical simulation of a female breast, some preliminary research work has been done [Jack1998] and with the recent advancement in development of Biofield Diagnostic System, there is a very good scope for developing a pattern mathematical model in conjunction with it.

1.2 Scopes and Research Methodology

The scopes of this research and the methodology adopted will be as follows:

1.2.1 Analysis of the various bioelectric equations for their suitability to be implemented in breast cancer detection analysis.

Several investigators have presented various bioelectric analyses in human tissues and organs. However, these are not directly related to the breast. It is therefore necessary to study these equations for their suitability in the present project. The physical properties of tissues of the

breast will also be examined to develop the partial differential equation programming. The bioelectric equation will be tested in simple geometry.

1.2.2 Two dimensional analysis of the female breast model

The exact solution to the bioelectric equation can be obtained only for simple one-dimensional model and it is thus necessary to solve the bioelectric equations by numerical methods for complicated tissue geometries and change in tissue properties of various layers. The choice of parameters for the model will also be justified. A numerical model that is a close representative of the actual with varying layer-thickness needs to be developed for grid generation, grid invariant test and subsequent computation.

1.2.3 Three dimensional analysis of the female breast model

The model will be simulated for various parameters to better understand their effects on the realistic 3-D breast model. The surface potential is studied to see if the presence of a tumour can be related to underlying tumour. Analysis of difference tumour sizes at different locations will be done so to examine the feasibility of the model. The possibility of reverse engineering is discussed.

1.2.4 Parametric optimisation for tumour identification

An optimisation approach based on the Taguchi method is conducted. The focus is to capture the signal from the tumour based on its depth and size, and minimise the effect of the other major factors that can be classified as noise. The method helps to set up a protocol to assist in accurately identifying the feature of interests, the tumour.

1.3 Objectives and Present Work

In the present studies, a theoretical three-dimensional, simplified and yet realistic models of female breast is performed to investigate the feasibility and distinguishability of surface biopotential resulted from the presence of different types of breast abnormalities. An inhomogeneous female breast model, which was close enough to the actual is developed, by considering a breast as a hemisphere in supine condition the various layer were of unequal thickness. I begin with the understanding the anatomy of the breast, the various types of cancer, and tools presently available for detection and diagnosis of cancer. In order to simulate the surface potential distribution, various literatures in the relevant field of medical. bioelectric analyses were reviewed and presented. The choice of the bioelectric equation and the methodology of solving this equation using FEMLAB are discussed. FEMLAB is the latest high level PDE solver. It stands for Finite Element Modelling Laboratory. The versatility of using the software for generating two and three-dimension grids and the correctness of the results are also discussed and presented in Chapter 5 .

The bioelectric equation is solved for simple geometries in two-dimension and benchmarked with published analytical [Nune1981] or numerical result [Guha1973] to gain a basic knowledge of the software and the behaviours of the bioelectric equation and the relevance of various parameters studied and discussed.

A two-dimensional model of female breast with and without a carcinoma is considered. The breast is modelled with varying layer-thickness close to the actual shape of a female breast and numerically solved using finite element analysis. Potential profiles are obtained for a normal breast and for a cancerous one by varying the tumour size, location and different types of tumours. As a next step a two-dimension model is developed and best mesh generation achieved. This model is now studied for the same parameters. A large tumour of 3.14cm^2 (diameter of 2.0cm) was considered as this was the average size estimated in Singapore. We ensure that

biofield analysis allows promising results in the manifestation of the bulk spatial inhomogeneities in the various tissue types such as the presence of a relatively denser tumour.

Then, a three-dimensional model is developed as an extension to the previous 2-D work. Furthermore, four important parameters were identified and analysis of variance (ANOVA, Yates' Method) was performed using 2^n design (n = number of parameters 4). The effect and importance of these parameters were analysed. The Taguchi method was further used to optimise the parameters in order to ensure the signal from the tumour is maximum as compared to the noise from the other factors. Taguchi methods used proved that probes' source strength, tumour size and location of tumours have great effect on the surface potential field. For best results on the breast surface, the low amplitudes of current should be applied while having the biggest possible tumour size and nearest to the breast surface.

Chapter 2

Breast and Breast Cancer Detection

2.1 Breast Anatomy

The breast, or also known as an apocrine gland, begins developing in the embryo about 7-8 weeks of conception. From about 12-16 weeks, epithelial buds develop and branch out to lay the foundation for future ducts and milk producing glands. With the onset of puberty, the female breasts undergo dramatic changes. The most significant changes are the development of the milk ducts in response to progesterone, namely the formation of lobules. This process averages 3 to 4 years and is usually completed by 16 years of age. As a woman ages along, with the loss of estrogens at menopause, the lobules involute and are replaced by fat. This makes the reason why the breasts of younger women are primarily composed of these glandular tissues, with only a small percentage of fat, than their older counterparts. The firmness of younger breasts also makes the physical examination and mammography harder to interpret and less accurate.

The mature female breast is essentially composed of four structures namely, lobules/glands, milk ducts, adipose and connective tissues as shown in Figure 2.1. Lobules naturally group together to form lobes. On average, the parenchyma contains about 15-20 lobes, in which arranged roughly

in a wheel spoke pattern emanating from the areola area. Glands produce milk and milk is drained by lactiferous duct to the nipple. The breast lies on the pectoralis muscles, which cover the chest wall. Practically, the basic histopathological unit of the breast is the terminal duct lobular unit. This unit is composed of the smallest branches of lactiferous duct, and the extra lobular terminal duct and lobule. This is the site where half of the abnormalities, both benign and malignant occur. Although the cause of breast cancer is still unknown, but the progression of breast cancer, in the early stages, up to the point of initial invasion, is predictable. At very early stages of cancer, the probability of regional or systemic spread is also low. However, after significant mass is formed, the course becomes more randomized. This observation supports the importance of early detection and treatment. As tumour size increases, the likelihood of metastasis rises and there appears a critical volume before, in which distance metastasis does not occur. Again, screening patients for breast cancer before tumours are large enough to be palpable is the only way to decrease the risk of dying of the disease.

2.2 Breast Cancer Histopathology

Histopathology is the study of the effects of disease on tissues. Histopathology of breast cancer helps in establishing the diagnosis of the lesions and appropriate determination of patient treatment and prognosis. Tumours are usually classified histopathologically by the types and patterns of cells that compose them. A variety of masses can form within the breast, most of which are benign. Some masses are cystic or fluid filled and lined with ductal cells. Other masses are solid and can be fibroglandular tissue, fibroadenomas, hyperplasia of ductal cells, or dense stroma and breast tissue. Breast carcinomas can be invasive, extending into the surrounding stroma, through which tumours spread locally, regionally, and distantly via vascular lymphatic space; or non-invasively, in which the tumour is confined just to the ducts or lobules. Invasive carcinomas are further classified into two major types: ductal and lobular. Carcinoma refers to

any cancer that begins in the skin or other tissues that cover internal organs—such as breast tissue. [Whog1993]

Invasive carcinomas have a propensity to spread via lymphatic. Breast cancers, when they metastasize, goes to the auxiliary lymph nodes, and deposit into other metastases lodge, such as lung, bone and liver. Breast cancers compose of individual cells that have malignant changes, but confined within the ducts (forming ductal carcinoma in situ, or DCIS), or in the lobules (called lobular carcinoma in situ or LCIS). DCIS is the most common kind of non-invasive breast cancer. It is *ductal* because the cancer is confined to the milk ducts—which are the "pipes" that bring milk from the lobules to the nipple. *In situ* or "in its original place" means that the cancer has not spread to any surrounding tissues. DCIS is generally detected by a mammogram. Cancer cells inside the ducts appear on the mammogram, and may appear along with tiny specks or calcifications—the build-up of material left from dead cancer cells. LCIS is generally considered to be a pre-cancerous condition. It is *lobular* because the cancer is confined to the lobules—which are the glands that actually make milk. *Carcinoma* refers to any cancer that begins in the skin or other tissues that cover internal organs—such as breast tissue. *In situ* or "in its original place" means that the cancer has not spread to any surrounding tissues.

The stage of breast cancer is based on its size and degree of spread. Traditionally, staging of breast cancer consists of four primary stages as in Figure 2.2. At stage I, tumour is generally no longer than 2cm, and has not spread to the rest of the breast. Detection at this stage gives the highest possibility to patient survival. In stage II, 3 possibilities may exist, where tumour is no longer than 2cm, but has spread to the lymph nodes; tumour length between 2-5cm, has or has not spread to the lymph nodes; and tumour larger than 5cm and has not spread to the lymph nodes. Stage III is a stage where tumour is larger than 5cm, and has spread to the lymph nodes; or more serious, patient with tumour larger than 5cm, and has spread to lymph nodes inside chest wall. Stage IV is the last stage of cancer, where tumour has spread to other organs of the body.

The most precise and comprehensive staging system is the TNM staging system. TNM was developed by the American Joint Committee (AJC) on Cancer Classifications and is used to stage breast cancer. From Figure 2.3, one can see that the TNM system stages the tumour (T), lymph nodes involvement (N), and metastasis (M) spread separately, represents their with severity by a digit. For example, a patient with T2N1M0 is diagnosed to have tumour of 2-5cm diameter, spread to lymph nodes but not grown together or in other structures and no evidence of distant metastases.

Beside masses, calcifications are also known as a characteristic of cancer. Calcification is seen as tiny specks of calcium on mammography. Calcifications that are widely scattered, uniform size, and well defined are usually benign. Calcifications are tiny mineral deposits within the breast tissue, which look like small white spots on the films. There are two types of calcifications -- macro calcification and microcalcifications. Macrocalcification are coarse (larger) calcium deposits that are most likely changes in the breasts caused by aging of the breast arteries, old injuries, or inflammation. These deposits are related to non-cancerous conditions and do not require a biopsy. Macrocalcification is found in about half the women over 50, and in 1 of 10 women under 50. Microcalcifications are tiny specks of calcium in the breast. They may appear alone or in clusters. Microcalcifications seen on a mammogram do not always mean that cancer is present. The shape and layout of microcalcifications help the radiologist judge how likely it is that cancer is present. In most instances, the presence of microcalcifications does not mean a biopsy is needed. Instead, a doctor may advise you to have a follow-up mammogram within 3 to 6 months. In other cases, the microcalcifications look more suspicious and a biopsy is needed.

2.3 Cancer Detection Tools

The three stages model of breast disease management is shown in Figure 2.4. It is to be noted that, not all screening tools are useful for diagnostic purpose. Biofield Diagnostic System is one

of the diagnostic tools that not only can detect abnormalities in the breast; it can also localize and characterize the tumour. This can help the physician to further decide whether or not to have a biopsy for the patient. The ultimate confirmation for any diagnosis of tumour is still the biopsy and BDS, (or other tools) cannot replace biopsy as staging tool for the disease. Before any methods can be developed, a review of the characteristics is summarized. An ideal screening tool should be

- a) Have low health risk
- b) Sensitive to tumours and specific to malignancies
- c) Detect breast cancer at a curable stage
- d) Noninvasive and simple to perform
- e) Cost effective and widely available
- f) Involves minimal discomfort, so the procedure is acceptable to woman
- g) Provides easy to interpret, objective, and consistent results

Bearing that in mind, several methods discussed in this report are:

1. Self examination or palpation
2. Mammography, Ultrasound imaging and Thermography
3. Magnetic Resonance Imaging
4. Biopsy (as confirmation after identifying an abnormality in mammography and/or ultrasound. This is the only way to confirm if the abnormality is malignant)

2.3.1 Breast Self Examination (BSE) and palpation

There are two parts to BSE: Looking and feeling. Breasts are composed of fatty tissue and fibrous tissue, milk glands and milk ducts. This is why breasts feel lumpy to the touch. Actually the majority of breast self exam are not cancerous. The best time for BSE is at the end of her period, when breasts are least tender. Use a mirror wide enough to see the whole breast, with one's hand down at her sides, and with her arms over the head to spot any new changes which can be unusual, such as dimpling, denting, scaling or discoloration of the skin, which can be caused by a growing tumour. To feel, prop up with a tower while lying down, use three finger-pads; make three small circles to check the whole area. Palpation, to be more effective, has to go with a breast examination by a health care professional and mammogram. Obviously, the test is still very subjective and results can vary greatly for different people performing the test. Palpation provides rough estimation of tumour size, and often over estimate because two folds of skin and adjacent soft tissue intervene between the mass and examiner's fingers.

2.3.2 Mammography

Mammography utilizes low energy x-rays radiated through the compressed breast, produces a black and white image of the breast tissue on a large sheet of film, which is "read" or interpreted by a radiologist. The sensitivity of mammogram is dependent on the density of the breast tissues. Therefore, for denser breast, a diagnostic mammogram may show that what appeared to be an abnormality actually was quite normal on closer examination. It also could show that an area of abnormal tissue has a high likelihood of not being cancer (being benign). For these, it is common to ask the woman to return to be rechecked, usually in 4-6 months. On the other hand, a diagnostic mammogram may show that the abnormal area is not worrisome at all and the woman can then return to routine yearly screening. Finally, the diagnostic work-up may suggest that a biopsy is needed to tell whether or not the abnormal area is cancer. If your doctor recommends

that you have a biopsy, it does not mean that cancer is present. About 80% of all breast changes that are biopsied are found to be benign when looked at under the microscope. If a biopsy is needed, the woman should discuss the different types of biopsy with her doctor to decide which method of biopsy is best for her.

2.3.3 Ultrasound

Ultrasound, also known as sonography, utilizes high frequency sound waves transmitted through the breast, which echo off structures and interfaces in breast. The sound wave echoes are picked up and translated by a computer into an image that is displayed on a computer screen. Ultrasound is primary used in assessing solid calcified tumour with fluid cysts, visualizing suspected carcinomas, and guidance for biopsy. Ultrasound has become a valuable tool to use with mammograms because it is widely available and less expensive than other options. However, the effectiveness of an ultrasound test depends on the operator's level of skill and experience. Larger calcified carcinomas, irregular or stellate tumours may be more difficult for sound waves to penetrate and thus, difficult to measure. Statistics shows that a large percentage (approximately 30%) of small non-palpable invasive and the majority of pre-invasive carcinomas are not detectable with ultrasound. [Sudh1999] Ultrasound is useful for evaluating some breast masses and is the only way to tell if a suspicious area is a cyst without placing a needle into it to aspirate fluid. Cysts cannot be accurately diagnosed by physical exam alone. Breast ultrasound may also be used to help doctors guide a biopsy needle into some breast lesions.

2.3.4 Thermography

Thermography is used to record the skin temperature of the subject. Any abnormality in the thermal profile could be used as a method of identifying presence of tumour. [Sudh1999]

There are three methods of obtaining the thermal pattern [Milb1987]. These are:

- (a) Tele-thermography;
- (b) Contact Thermography; and
- (c) Computerized Thermography.

In Tele-thermography, an electric infrared detector measures infrared radiation emitted by the body. A more common method is that an infrared radiation is focused by an optical mirror on a thermistor. Infrared energy is converted to electrical signal and displayed on a cathode ray tube. The image may then be photographed for record. The images are usually analyzed by comparing corresponding areas of each breast and judgment is based on symmetry. If the image is very asymmetric, the thermogram may be classified as abnormal and if there is lesser degree of asymmetry, it may be considered as normal.

In contact thermography a sheet of thin plastic containing highly sensitive liquid cholesterol esters is placed on the breast. Infrared radiation causes the esters to change colour and the plate is photographed.

In computerized thermography, multiple thermistors are used to detect infrared radiation. The signal obtained is fed into a computer, which runs several algorithms to calculate whether the measurements obtained are normal or abnormal (i.e. virtual reality approach).

The main draw back of thermographs is that the sensitivity in detecting a cancer is less than 50%. The sensitivity increases directly with the size of the tumour, therefore poorer results are obtained for those patients with very minimal cancer. However, recent advances in digital infrared thermography promise better results (APS Equipment).

2.3.5 Magnetic Resonance Imaging (MRI)

Another common detection tools are MRI and ultrasound. MRI is superior to mammography in assessing small lesions (approximately 1cm) [Sudh1999], and much more capable in distinguishing post chemotherapy fibrosis than palpation. MRI uses magnetization and radio waves, instead of x-rays, to produce very detailed, cross-sectional images. The most useful MRI examinations for breast imaging use a contrast material (Gadolinium DTPA) that is injected into a small vein in the arm before or during the examination. This contrast material improves the ability of MRI to clearly show details of breast tissue. MRI is found to be able to image the denser breast. However, MRI is known to have its low diagnostic specificity, lack of standardized techniques, complexity of interpretation, and expense. Therefore, MRI is unlikely to be used for very high risk and urgent cases. A summary of the current research done on use of breast MRI shows an overall sensitivity to breast cancer of 96%. However, MRI is more costly, lacks standard exam techniques and interpretation norms, cannot detect microcalcifications and perhaps has a higher false-positive rate.

2.3.6 Biopsy

A biopsy is the removal of a sample of tissue from the body for examination. The tissue will be examined under a microscope to assist in diagnosis. Therefore, only very small samples are needed. One method called fine-needle aspiration (FNA) uses a hypodermic needle to pierce the skin and suck out the sample. This may sometimes be done under ultrasound or X-ray guidance. Another option is a surgical biopsy, where the whole lump is removed.

2.3.7 Conclusions and Remarks

The above short review indicates that each one of the detection and diagnostic measures have their own weaknesses and disabilities. This motivates us that new techniques are needed to decrease false positive results while maintaining high sensitivity. The Biofield Breast Cancer Diagnostic System (BDS) is a novel approach based on measurement of alterations in electrical biopotential differences, which are known to occur concurrently with abnormal epithelial proliferation. The basis for these alterations is changes in the distribution of various ionic species across the cell membrane. Thus, normal resting epithelial cells are electrically polarized by an ionic gradient. An electrochemical gradient is maintained in part by the Na^+/K^+ ATPase pump by pumping Na^+ out of the cell and K^+ into the cell, against their respective gradients. During mitosis the cell membrane becomes permeable to these and other ions, and the gradient dissipates, resulting in electrical depolarization of the cell membrane. The unrestricted reproduction of cells in a developing breast cancer results in a "pocket" of relative depolarization, which can produce a localized differential in electrical potential measurable even at the skin surface. In addition, larger lesions have a positive charge in relation to surrounding breast tissue, which may also be detected at the skin surface. [Dixo1996]

Women undergoing assessment for breast cancer are examined by a physician and/or have imaging diagnostics (x-ray, mammogram or ultrasound). Both of these methods have limitations that are well described in the literature. Numerous recent articles demonstrate that the upper limit for the detection of breast cancer by physical examination or mammography does not typically exceed 90% sensitivity. [Fent1990] Moreover, sensitivity for both physical examination and mammography is considerably less in the under 50-age group and in cases where lesion size is less than 2 cm. The sensitivity of mammography is limited in the under 50-age group due to the density of the breast tissue in this population. Diagnostic criteria for mammography and the

interpretation of mammograms are not uniform and this has resulted in wide variations of reported specificities, ranging from about 9% to 47%. The specificity of distinguishing benign from malignant lesions on mammography is around 55% [McKe1993]. This considerable degree of diagnostic uncertainty that remains after physical examination and Mammographic evaluation and as a result only about 20% of the open biopsy procedures performed in the United States yield a tissue diagnosis of malignancy. Therefore, the author believes that although mammography can identify the presence of a mass, does not accurately characterize the size and extent of disease, especially if extensive intraductal cancer is present. [Esse1999]

Because of the diagnostic uncertainty that results from screening, physicians must use a number of diagnostic tests such as supplemental mammography, physical examination, fine needle aspiration cytology, ultrasound, gadolinium-enhanced magnetic resonance imaging (MRI) and/or positron emission tomography (PET). These tests are time consuming, expensive, sometimes invasive, and require subjective interpretation. In population based screening programs like those that exist in Sweden and the Florence District in Italy, 2-4% of women who participate require additional diagnostic evaluation (i.e., post-screening call back population). A large number of these women (30-50%) return to routine screening after supplemental diagnostic mammography, and the rest will go on to have additional diagnostic tests, which may include, but is not limited to, physical exam of the breast, fine needle aspiration cytology, ultrasound, stereo tactic biopsy, or open surgical biopsy. Of the total number of women participating in a screening program 0.5% will undergo excision biopsy, with a cancer yield of the total screening population of 0.4%. This represents about 20% of the call back population. In the U.S. study referred to above, Harvard Medical School of Public Affair once published, it was estimated that for every \$100 spent for screening, an additional \$33 was spent to evaluate false-positive results [Harv1998].

Figure 2.1: Anatomy of a Normal Pre-menopausal Breast with associated mammogram. Note that the radiograph shows no dominant or irregular mass and no evidence of any microcalcifications[Yale2000].

Stage		Descriptions
I		1. Tumour of 2cm in diameter or less 2. No sign of spread
II		1. Tumour of 2cm in diameter, has spread to the lymph nodes 2. Tumour of 2-5cm, has or has not spread to lymph nodes 3. Tumour is larger than 5cm, has not spread to lymph nodes
III	IIIA	1. Tumour is larger than 5cm and has spread to the lymph nodes
	IIIB	1. As IIIA, has spread to lymph nodes in chest wall.
IV		1. Tumour has spread to other organs

Figure 2.2: The Conventional Staging of Breast Cancer.

Figure 2.3: The TNM (Tumour Nodes Metastases) Breast Cancer Staging System.

Figure 2.4: The three-stage model of breast disease management [Mers1996]

Chapter 3

Literature Review

3.1 Applications of Biofield in Medicines

The author will not attempt to give all details discussion of any of the specific applications, but instead, point out several applications of Biofield in each field. It is noted that the numerical techniques discussed henceforth are pertinent to all the applications below but none of them deals with breast in particular except Electrical Impedance Tomography (EIT).

3.1.1 Electrocardiology

There is rich history of numerical techniques in Biofield application for solving forward and inverse problems in Electrocardiology. An example of large-scale computer modelling and simulation to a specific class of bioelectric field problems was described by Christopher Johnson [John1993]. Besides solving the problems that arise in electrocardiography, they estimate the electrical activity inside a bounded volume conductor, either from potential measurements on an outer surface or directly from interior bioelectric sources. Johnson developed two visualization systems for bioelectric field problems. One system is an interactive program, written with the aim

of viewing large amounts of data as rapidly, and with as much flexibility, as possible. The second system represents a batch mode approach, where the goal was to produce high quality images of selected data sets for use in presentation and publication of his results. The model geometry was derived from a set of nuclear magnetic resonance images (MRI), digitized into a set of discrete contours. After some smoothing, additional points were added between the contours, and the complete set was then tessellated into tetrahedral volume elements using a Delaunay tetrahedralization algorithm.

3.1.2 Cardiac Defibrillation

The use of external and implantable cardioverter defibrillator has proven to be effective in reducing the mortality rate of patient with heart diseases. Many studies have been preformed demonstrating the power and sophistication of computer simulations for defibrillation studies using biopotential field modelling. Jorgenson et al constructed and solved detailed patient specific 3D finite element model of the human thorax use in defibrillation studies. The method utilizes the patient's own CT scan and simplified meshing scheme to quickly and efficiently generate a model typically composed of approximately 400000 elements. [Jorg1995] Laplace's equation with boundary conditions is to be solved in order to determine the voltage distribution that results from the application of stimulating electrodes held at fixed input voltages. She was able to efficiently construct detailed three dimensional finite element models of up to approximately 500000 unknowns. These models can then be used to investigate various electrode configurations for use in transthoracic and transvenous defibrillation with the aim of optimizing the current delivered to the heart and voltage gradient distribution in the myocardium.

3.1.3 Electromyography

Electromyography was defined by [Buch1998] as the registration of muscle action potentials. These potential gives information as to the state of the muscle and indicate the activity of the motor neurons in reflex and voluntary contraction. Of diagnostic importance are the spontaneous electrical activities in an apparently relaxed muscle as well as the electrical activity that accompanies voluntary or reflex contraction and the action potentials evoked by electrical stimulation of muscle and nerve. Deviation from the normal electromyogram can contribute to the differential diagnosis of disorders of the motor system. Until recently, EMG was recorded primarily for diagnostic purposes. In advancement of biotechnology, electromyogram has also become a tool in monitoring and controlling movement in artificial limbs and is used in conjunction with functional electrical stimulation. Modelling of EMG electrodes can be found in [Henn1994]. He used computer simulation to study the propagating action potential in skeletal muscle. His model considered the influence of the transverse tubular system and the electrical interaction between an active fiber and a single layer of surrounding passive fibers in a fiber bundle. It was found that passive fibers adjacent to the active fibers undergo a small hyperpolarization resulting inter-fiber coupling current of about 1% of that of the sarcolemma current.

3.1.4 Electroencephalography

One of the fundamental problems in computational electroencephalography is the inverse EEG problem. If accurate solutions to the inverse EEG problem could be obtained, neurologists would be able to non-invasively view and interpret patient specific cortical activity, gaining data important to surgeons and researchers. Buchner et al [Buch1997] presented finite element procedures for inverse localization of multiple sources in realistically shaped head models. Dipole sources are modelled by placing monopole sources on neighbouring nodes. Two different

strategies for the solution of inverse problems were presented and compared. Fletcher et al [Flet1995], [Flec1995] presented new computational technique for the calculation of potentials on the surface of a realistic head shaped volume conductor model based on Boundary Element Method and the reciprocity theorem. The method offers improved computational efficiency and lower storage requirement. Daniel successfully yielded more accurate surface potential results in the face of varying dipole source locations for a head shape BEM with a given number of nodes. An accurate inverse EEG solution would allow surgeons to dramatically reduce the amount of brain tissue removed during neurosurgery, as the anomalous regions responsible for the electric discharges triggering the seizures could be pin pointed rather than merely estimated.

3.1.5 Electric Impedance Tomography (EIT)

In EIT, an approximation for the internal resistivity distribution is computed based on the knowledge of the injected currents and measured voltages on the surface of the body. Vauhkonen et al [Vauh1997] presented finite element method for the reconstruction of three dimensional resistivity distributions. Both the forward and the inverse problems were discussed and the results were based on the knowledge of the injected currents and measured voltages on the surface of the body. Model presented was based on a complete electrode model. A simple cylindrical object was used. [Muzw1994] et al constructed electric impedance computed tomography technique, which reconstructs the image within a body based on the variation of electric conductivity and permittivity by using electrical measurements on its boundary. Mu et al solved the Laplace's equation to describe the potential distributions with the finite element method. He also studies the excitation and measurement pattern effects on image quality, and presents the simulation results. [Muzw1994] For breast cancer detection in particular, Radai et al used the EIT technique on the extracted tissue types, such as the lung, blood, ribs breast fat, skin, skeletal muscle and heart muscle with assigned isotropic homogeneous impedivity to determine the potential distribution developed due to the dipole source. Cases with and without artificial cancer were solved

numerically. [Rada1999] Although the science of impedance imaging looks promising but it remains unproven. Currently EIT is not recommended as detection tool for breast cancer by physicians. [Moor2001]

3.2 Underlying Mechanisms of the Techniques

3.2.1 Background

Cell membranes are semi-permeable lipid-protein bilayer that behaves as leaky electrical capacitors. Cells have ions pumps asymmetrically distributed across it called the ATPase. These pumps maintain this ionic gradient across the membrane results in an electrical potential, which is about 70mV. Any changes in ionic transport and permeability characteristics of the cell membrane can alter the electrical field. Permeability here means cell membranes are permeable to some ions but not to others. K^+ is the predominant intracellular cation. If the cell membrane is semi-permeable to K^+ but not to Cl^- , then K^+ will diffuse across the cell membrane down its concentration gradient, resulting in a positive electrical potential on the outside of the cell and a negative charge on the inside of the cell membrane. This will continue until the equilibrium potential about 61mV is reached (the Nernst potential) at which the further outflow of K^+ is opposed by the inner negative potential. In contrast, the Na^+ , which is the predominant extracellular cation, will tend to flow down its electrical and chemical gradient and enter the cells. ATPase pump acts as a regulator, as it pumps sodium out and potassium in against their respective gradients to maintain membrane potential.

In 1971 Hulser and Frank observed that the addition of serum to quiescent fibroblasts resulted in rapid cell membrane depolarization. [Huls1971] The addition of serum to cultured cells is required to stimulate cell division and growth. This observation therefore led to the notion that cell membrane depolarization was an early event associated with cell division. Later, a number of studies have also confirmed that proliferating cells are relatively depolarized when compared to

their non-dividing or resting counterparts. [Chap1984] However, from another angle, there is the potential for interaction between other intracellular messengers and cell membrane potential; but nonetheless, it doesn't appear that cell membrane depolarization is a prerequisite for cell division even though it is a frequently associated event in cultured cells. One problem with many studies is that the majority of them have used cultured tumour cells and therefore it may be misleading to extrapolate from these cells to non-transformed cells undergoing proliferation.

After the development of the patch clamp studies in mammary epithelial cells, the electrical properties of a cell or individual ionic channel can be examined. It is ionic channels, which have the greatest influence on cell membrane electrical potential [Dix1996]. Therefore, it does appear that sustained electrical changes occur in breast epithelial cells as a consequence of altered proliferation, and further postulated that malignant transformation resulted from sustained depolarization and a failure of the cell to repolarize after cell division. [Cone1974]

3.2.2 Transepithelial Electrical Potential

Breast is one of the sites of common malignancy. It absorbs and secretes various ions and water. Physiologically, the cell membrane is negative inside in relation to the outside of the cell. The reason for this is that, the permeability properties are quite different for the apical compared with the basolateral cell membrane. Taking sodium permeability as example, the Na/K ATPase pump then extrudes sodium into the abluminal space across the basolateral membrane and water either follows through the cell or through tight junctions between cells.

Normal epithelial cells, including those that line breast ducts, are electrically polarized by an ionic gradient across the cell membrane. The charge gradient is asymmetric between the apical and basolateral cell membranes and is known as the transepithelial electrical potential. This concept is illustrated in Figure 3.1, which shows the electrical gradients across the normal epithelium that lines the terminal ductal lobular units of the breast. The electrical gradient across the membrane is maintained by the different permeabilities to ions (predominantly K^+ and Na^+)

and water at the luminal aspect of the duct as compared to the abluminal side and results in a transepithelial potential difference of about 30 mV. The vectoral transport of ions that maintain the transepithelial potential difference is facilitated by the tight junctions, which divide the cell membrane into distinct apical and basolateral domains. As epithelial cells divide, the charge gradient across the epithelial layer is dissipated, resulting in electrical depolarization.

When epithelial cells in certain areas of the breast divide more rapidly than those in other areas of the breast, as when a cancer develops, a pocket of relative depolarization results, which can produce a differential in electrical potential at the skin surface. These differentials have been measured using a specially designed sensor array and measurement device.

In cancers proliferation becomes uncontrolled, and genetically altered cells accumulate in the lumen of the duct, as in Ductal Carcinoma In situ (DCIS). The normal luminal structure of the duct is obliterated by this process. As the malignant process progresses to invasive carcinoma, the basement membrane is invaded by the malignant cells and the ductal structure is destroyed. The permeability of the malignantly altered cells to Na^+ is increased, and Na^+ enters the cell increasing the intracellular Na^+ concentration while the extracellular K^+ increases. The transmembrane potential then becomes more positive electrically with a decrease in the transmembrane electrical potential. Movement of ions is equivalent to an electric current. The differential between the malignant cell mass and the normal cells is transmitted to the breast surface by means of volume conduction, referred to as the three dimensional Ohm's Law.

3.3 The Biofield Diagnosis System (BDS)

The Biofield Breast Cancer Diagnostic System is manufactured by Biofield Corporation U.S.A. [Biof2003] The BDS is designed to detect cellular changes associated with breast cancer, using proprietary, single-use sensors. During analysis, the electrical signal is measured on the surface of the breast using the same principle of electrical volume conduction used with the

electrocardiogram (ECG). The picture and schematic diagram of the Biofield Diagnostic System are shown in Figure 3.2 and Figure 3.3.

Like an ECG the non-invasive BDS measures the net electrical activity in the breast based on the ion motion principle. This principle shows that membrane depolarization, essential for cell division and proliferation results in movement of potassium (K^+) out of the cell and sodium (Na^+) in to the cell. The net electrical activity is proportional to the rate of membrane depolarization. According to the Goldman principle ion motion equals electric current. This electric current can be measured with a sensitive voltmeter such as that of the Biofield device. This precise measurement provides an indication of the proliferate status of the lesion. A differential in biopotential measurement results when there is an increase in electropositive at one breast site compared to another site. These differentials are an indication of the proliferation rate of the underlying mammary tissue. Highly proliferating areas are more electropositive. Clinical data provide support for the electrochemical basis for biopotential measurement of cancer.

Biofield is a subtle material structure that corresponds closely with the molecular structure of living organisms. It is quite different from the world of atoms and molecules. However, it is a part of the same material world and can be explained in physical terms. There are many arguments [Andr1998] that Biofield is based upon electromagnetic phenomena, or at least, is closely tied with them.

One of the very early applications of Biofield was done by Carlo Matteucci (Italian, 1811-1865) when he first measured muscle impulse in frog muscle by using the astatic galvanometer. Later Augustus Waller (British, 1856-1922) extended the application of Biofield to electrocardiogram (ECG). His recording was made using a capillary electrometer [Wall1887]. The research on ECG has extended even until today. Following the invention of high-performance computer and diagnostic facilities, sophisticated modelling has been made possible.

3.4 Literature Review on Dielectric Properties of Breast Tissues

3.4.1 Theoretical Background

Electrical properties of biological tissues differ, depending on their structures. The histology of a cell is in such a way, that its membrane constituted by a thin lipid bilayer with leaky ion-channels is both capacitive and resistive. These membrane-enveloped cells are surrounded by fluids, which contain water, electrolytes etc. and basically resistive. The conductivity of cells is basically complex and can be described by

$$Z = R + jX \quad (3.1)$$

where $Z = \frac{1}{\sigma}$ is the impedance, σ the conductivity, R the resistance and X the reactance;

$$Y = G + j\omega C \quad (3.2)$$

where $Y = \frac{1}{Z}$ is the admittance; G the conductance, C is the capacitance and ω is the angular frequency. Alternatively, the admittance can be represented by the admittivity, expressed as:

$$\sigma^* = \sigma + j\omega \epsilon_0 \epsilon' \quad (3.3)$$

where, σ^* is tissue admittivity, σ the tissue conductivity; ϵ' is tissue permittivity and ϵ_0 the dielectric constant of free space.

It is also widely known that the conductivity of tissue varies with the frequency of the applied electric field, temperature and time. Therefore, it is highly anisotropic. In this study, we ignore first the effect of temperature towards conductivity. For frequency, the α - (10 Hz to 10 kHz) and β - (10 kHz to 10 MHz) dispersion regions are more interested since most changes between pathological and normal tissues occur in this range. [Blad1996]

Any electromagnetic based measurement tool (e.g. BDS) will only be effective if there exists sufficient variation of electrical properties among domains (e.g. breast tissues and malignancy) we target at. Far before the discovery of any screening tool, Fricke and Morse [Fric1925] has

found that, certain types of malignant tumours have a rather high capacity and significantly higher permittivity of breast tumour tissues in vitro at 20 kHz, in comparison with benign tumours or with inactive tissues of the same or similar characters. They also find in their study, those most important types of tumours, malignant tumour has a high capacity as compared with benign tumours of a similar character and also with the normal tissue in which it lies. The characterization of the biophysical features of cancerous breast tissue has captured great interest of researchers, both from a screening or therapeutic point of view. Many analytical and critical reviews of the literatures on dielectric properties of breast tissues at radiowave and microwave frequencies are presented. The frequencies of measurements are reviewed objectively, and the frequency employed the current proposed study is justified.

Jossinet and Schmitt [Joss1999] studied the definition and evaluation of dielectric properties at the characterization and differentiation of freshly excised breast tissues. Their work mainly was between the frequency ranges of 0.488 kHz to 1MHz. They showed significant differences between most of the tissue groups, especially between cancerous tissue and all the other groups. This further confirmed that tissues electrical properties can be considered as potentially suitable for the distinguishability of the presence of malignancy in breast tissues.

Another reliable finding is from Surowiec *et al* [Suro1988]. Surowiec *et al* worked on the relative permittivity of infiltrating centre part of breast carcinoma, tumour surrounding tissue and the peripheral tissue. Their experiments were performed at frequencies from 20 kHz to 100MHz at 37°C using an automatic network analyzer and an end of the line capacitive sensor. The results also seem to indicate modality for the detection of human breast carcinoma.

The same results were achieved by Chaudhary *et al* [Chau1984]. Chaudhary measured the dielectric constant of malignant tissues at frequencies below 100MHz and threw some light on the future electromagnetically-based techniques for cancer treatment and detection tools. They observed that the relative dielectric constant of malignant tissue is strikingly higher than that of

the normal tissue, particularly at frequencies below 100MHz. The relative permittivities of normal and malignant tissues at frequencies below a few MHz would be wider. This encourages researchers in EM radiation scanning technique to develop or refine their equipments for detection of an early stage of breast cancer.

Joines et al [Join1994] measured the electrical conductivity and relative permittivity of malignant and normal tissues from various tissue origins including mammary gland. Joines concluded that at all frequencies tested, both parameters show greater in magnitude in malignant tissue than in normal tissue of the same type, especially in tissues from the mammary gland.

Among the studies, the work of Surowiec *et al* [Suro 1988] and Jossinet *et al* [Joss1999] appear to be most reliable and relevant to our analysis. Studies by both Surowiec and Jossinet were done on the centre and surrounding breast tissues of tumour at normal body temperature. This reflects the general knowledge and understanding of the natural proliferating tumour. The measurement frequencies of both literatures are from 20 kHz to 100MHz. However, Morimoto *et al* [Mori1993] argued that this does not say that at lower frequency, biopotential analysis cannot provide adequate variation in dielectric parameters for potential diagnostic purpose. In fact, based on In vivo measurement of electrical properties up to 200 kHz, elements of the Fricke [Fric1926] equivalent circuit model for breast tumours differed significantly from those for benign tumours. Further justification on the choice of frequency zone is given in Chapter 4 (Formulation of Biopotential Equation) of this report. But one common conclusion can be drawn from all the studies above, that there are significant differences in electrical properties between normal and malignant human breast tissues. Compared with surrounding normal tissues, malignant tumours showed typically higher conductivity [Suro 1988] [Chau1984], and/or permittivity [Fric1926] [Suro1988] [Chau1984] [Joss 1999].

3.5 Review on Solution methods

For simple cases, such as in a circular geometry with homogeneous conductivity distribution, an analytical solution for the forward continuum model can be obtained [Fuks 1991] [Pidc 1995]. However, in most physiological models, solutions of bioelectric field problems are usually tractable (except in the most simplified of models) only when one employs a numerical approximation method such as the Finite Difference (FD), the Finite Element (FE), or the Boundary Element (BE) to solve the governing field equation(s). This is due to the geometrical complexity of and numerous inhomogeneities inherent in, anatomical structure in physiological models.

3.5.1 The Galerkin Method

The Galerkin method is one of the most widely used methods for discretizing elliptic boundary value problems such as the Poisson equation, and for treating the spatial portion of time-dependent parabolic problems, which are common in models of cardiac wave propagation. [John1997] Galerkin method is not essential to the application of any techniques, it provides for a unifying bridge between the various numerical methods.

3.5.2 The Finite Difference Method (FDM)

The finite difference method is one of the oldest traditional techniques in computation of electromagnetic for solving the Maxwell Equations. Yee developed a basic approach in solving the initial boundary value problems involving Maxwell's equations in isotropic media [Yee1966]. In the Finite Difference (FD) method, the solution domain is approximated by a grid of uniformly spaced nodes, so called the staggered grid. At each node, the governing differential equation is approximated by an algebraic expression, which references adjacent grid points. Originally, the staggered method was formulated by Yee for Cartesian coordinates and, later,

further expanded by Holland to structured boundary fitted grids. [Holl1983]. In 1992, Taflove published a review of finite difference time-domain schemes for the Maxwell Equations and their applications [Taf1994]. Lai [Lai2000] published a note on finite difference discretization for Poisson Equation on a disk with second order convergent finite difference treatment of polar coordinate singularity. Lai further extended his work to a 2D elliptical domain, in which he developed a direct solver for the Poisson equation with truncated Fourier model equations. These Fourier equations were then solved using finite difference method [Laim2004]. In particular to bioelectric problem, Saleheen *et al* 1997 model the anisotropic, inhomogeneous and non-diagonal fiber structures of muscles, where the fiber can lie in any arbitrary direction, with two and three dimensional finite difference formulation. Large problems were solved using parallel computing [Sale1997].

One of the most recent works on finite difference method in computation of bioelectric problem is done by Nixon et al. [Nixo2003] Nixon constructed a realistic human head model based on magnetic resonance imaging data with three-dimensional finite difference method. In the paper, Nixon assigned electrical conductivities inhomogeneously to tissue types within each head segments. Electrical potential was reconstructed non-invasively on the head surface. Nixon et al also showed that the successive over-relaxation (SOR) iterative method gave the best convergence properties.

3.5.3 The Finite Element Method (FEM)

A large amount of literature on the solution of Maxwell's Equations using finite element method has been published since the invention of high speed computational solvers. Analytically, Maxwell's equations can only be solved within a simple geometry, of relatively simple conditions that, even considered unrealistic to represent the real phenomenon. Researchers switched over to numerical analysis together with the help of modern computer. Generally, far back in the year of

1971, Wexler *et al* described the solution for Poisson's equation over the union of a number of piecewise homogeneous regions using the finite element method. He formulated the Dirichlet Boundary Condition, as a natural one, and Cauchy boundary condition to solve his problem [Wexl1971]. The method keeps on revolutionizing and widely used in the world of biomedicine even until today. In the year of 1990, Lynch and Paulsen developed an explicit time domain integration scheme for finite element spatial discretization of the Maxwell's equations [Lync1990]. This time domain integration combines the advantage of the economy of the finite difference method, with the geometry flexibility of finite element method, without compromising the accuracy. He tested his formulation in a practical hyperthermia application. Sahalos *et al* 1994 further developed an efficient finite element method algorithm for complicated three dimensional layered type models [Saha1994]. Recently, the effect of skin, muscle, fat and bone tissue on simulated surface electromyographic signals was also examined by finite element model. [Lowe2002]

In particular to Biopotential problems, Miller and Henriquez [Mill1988] demonstrated the use of three-dimensional solution in bioelectric phenomena analysis. She studied a three-dimensional current flow around an erythrocyte in an extracellular medium. In the area of electrocardiography, Yamashita and Takahashi 1984 used the finite element to determine epicardial from body surface potentials under a realistic torso model [Yama1984]. Pilkington *et al*, in their paper [Pilk1985] made a comparison of the finite element and integral equation formulations for the calculation of electrocardiographic potentials. Klepfer *et al* 1997 studied the effects of inhomogeneities and anisotropies on electrocardiographic fields with a three-dimensional finite element study [Klep1997]. Their model was based on the Utah torso model [John1992], in which major anatomical structures were included such as subcutaneous fat, skeletal muscle, and lungs as well as veins, arteries and so on. Their formulation is referred and extended to the breast specifically in this proposed study. Johnson and MacLeod, 1993 worked on the transthoracic current flow within the human thorax, and represent them with simpler geometry, isotropic and homogeneous and

conductivity tensor. Johnson [John1993] in his review paper, studied the bioelectric fields from the heart, and designed and optimized the implantable defibrillators. [John1995]

Figure 3.1: Breast Epithelial Electrical Gradients [Davi1995]

Figure 3.2: Diagram of a Biofield Diagnostic System (BDS) M4 Device. [Biof2003]

Figure 3.3: Biofield Diagnosis System in Block Diagram

Specification of the Biofield Diagnostic System (BDS)

The Biofield Breast Cancer Diagnostic System is manufactured by:
Biofield Corp.
1025 Nine North Drive, Suite M
Alpharetta, GA 30004
U.S.A.

The Biofield Diagnostic Device, method and technology, and Biofield Sensors are protected under one or more of the issued U.S. Patents and international patent applications as listed below:

4,328,809	4,955,383
5,099,844	5,415,164
5,678,547	5,427,098
5,660,177	6,351,666
U.S. Design Patent No. 374,184	
European Patent No. 0377887	
German Patent No. 68924058.9-08	
Other U.S. and International Patents Pending	

Biofield® is a U.S. registered trademark of Biofield Corp.

Chapter 4

Formulation of the Bioelectric Equation

4.1 Poisson Equation

Most bioelectric applications involve signals of sufficiently low frequency that the displacement current, which is governed by the permittivity of tissue, is much smaller than the conduction current. The distribution of electrical potential ϕ within an inhomogeneous anisotropic conducting medium is given by the quasi-static *Poisson Equation*.

$$\nabla \cdot (\sigma \nabla \phi) = I_v, \quad (4.1)$$

where ϕ is the electric potential, σ is the tissue space variant conductivity tensor and I_v is the any source term exists in the solution domain. Therefore, it is proposed to use Poisson Equation for further two-dimensional and later, three-dimensional breast model analysis in the following chapters.

In biopotential reconstruction, as in other bioelectric phenomena, we make the following two assumptions:

4.2.1 Potential distribution is mapped in static conditions.

The electric field is composed of gradient of potential (ϕ) and time varying magnetic vector potential (A):

$$E = -\nabla\phi - \frac{\partial A}{\partial t} \quad (4.2)$$

The latter is neglected due to static condition. In other words, the effect of magnetic induction that causes the induced electric field is neglected. In [Nune1981] it has been shown that if

$$\omega\mu\sigma L_c \left(1 + \frac{\omega\epsilon}{\sigma}\right) \ll 1 \quad (4.3)$$

where L_c is the distance over E varies significantly, then the effect of magnetic induction can be neglected. In particular, for the case of breast biopotential analysis,

The magnetic permeability (μ) $\approx \mu_0 = 1.2566 \times 10^{-6} \frac{Vs}{Am}$

$L_c = 0.144m$ (Diameter of one side of breast)

$\sigma = 0.50 (\Omega m)^{-1}$ (As breast mammary gland conductivity, since the breasts of younger women are primarily composed of glandular tissue)

$$\epsilon = 8.85 \times 10^{-12} \frac{C^2}{Nm^2}$$

$\omega = 10 \text{ kHz}$ (frequency used throughout the whole numerical analysis)

With all the parameter above, Equation (4.3) gives $4.684 \times 10^{-4} (\ll 1)$

Hence, we have a strong approximation that the magnetic induction effect can be neglected.

4.2.2 The capacitive effects of Biopotential reconstruction can be neglected.

This approximation is often made in bioelectric analysis. From [Nune1981], this approximation is valid if

$$\frac{\omega\epsilon}{\sigma} \ll 1 \quad (4.4)$$

With the values utilized in the above approximation, equation (4.4) gives 0.0354 ($\ll 1$)

Hence, we have a strong approximation that the biopotential reconstruction effect can be neglected.

One can be questionable why the capacitive effect of potential induction analysis can be neglected but this approximation will still be used. Nonetheless, the results are verified in pure conductive medium, the capacitive effect still can be incorporated to more complex formulation of the same analysis.

From the above justifications of the two assumptions, one can write (4.6) and (4.7) as

$$E = -\nabla\phi \quad (4.5)$$

$$\nabla \wedge H = \sigma E + J_s \quad (4.6)$$

The modified Maxwell Equations are linear, isotropic medium, quasistatic conditions and inhomogeneous. Substituting (4.5) into (4.6), taking the divergence of (4.6) on both sides, one obtains the classical *Poisson Equation*.

$$\nabla \cdot (\sigma \nabla \phi) = I_v \quad (4.1)$$

I_v , has been defined earlier as any source term present in the solution domain. The choice of I_v is further discussed in Chapter 5.

4.3 Current Female Breast Modelling

As first step, we develop a female breast model, which is close enough to the actual. Sudharsan *et al*[Sudh1999] considered a breast as a hemisphere in supine condition the various layer are of unequal thickness, based on cross sectional view of the anatomy of female breast as presented in Romrell *et al* [Romr1991]. We assumed the breast to be of hemispherical shape with a 5mm of subcutaneous layer, followed by a gland and muscle layer of varying thickness. The model is presented as in Figure 4.1, based on the breast mammogram from Yale Medical School in Figure 2.1. Do note that the nipple is not modelled at this stage for numerical simulation due to its complexity in surface potential. For the dimension of the breast, we considered a diameter of 144mm in diameter and 70mm in height, where these parameters are more closely mimic the average size of an Asian woman's breast in supine condition.

This geometrical model is assumed to be more accurate for the following assumptions and parameters:

- The actually varying thicknesses of the breast layers were also taken into consideration.
- The curves representing each layers and boundaries were drawn using a polynomial equation of 2nd order.
- Specimen was assumed to be in supine position (laying down flat). Therefore, it is acceptable to assume the model to be near hemispherical. Further complexities in geometry will be considered as part of future works.
- Room temperature is assumed to be the same as the temperature of the skin surface. Studies of the treatment of the room temperature effect in the overall of bioelectric field in the solution domain are beyond the scope the present analysis.
- The surface of the breast is assumed to have no electrical conduction with the ambient. Hence, the Neumann condition applies.

4.3.1 The boundary conditions

In order to obtain a sensible physical model of biopotential field, the following boundary conditions were derived briefly. Further detail on the mathematical aspects can be obtained from [Some 1992].

4.3.1.1 Calculation of conductivity (σ) and current flux distribution (J) with Neumann Boundary Conditions.

Assuming an inhomogeneous domain with constant homogeneous conductivity (σ) for each layer, the potential distribution is computed by solving Poisson Equation with known imposed currents applied at appropriate surface node locations. The air in contact with the body has negligible conductivity, and the ratio of body conductivity to air conductivity is infinite. The electrical conduction system of the breast is taken to be isotropic. Although in reality, there exists different conductivities differ depend on the direction, due to the muscle fibers and subunits are not aligned in parallel. Additional complexities arise because the breast wall is not just muscle but contains bone, adipose tissue and skin. Hence, at the surface of breast that is in contact with the ambient, the surface inhomogeneous Neumann current boundary condition:

$$(\sigma \nabla \phi) \cdot n = h \quad (4.7)$$

is specified. h describes the electrical current flux density (mA/m^2) entering and leaving the breast over the dipoles, as excitation current. With this boundary conditions, and a homogeneous conductivity distribution estimated throughout all layers of tissues at the interior of the breast, the potential distribution can be solved using numerical method, in particular the Finite Element Method (FEM) in this study. Once ϕ is known at each node points, electrical intensity E can be computed using negative gradient of potential,

$$E = -\nabla \phi \quad (4.8)$$

4.3.1.2 Calculation of ϕ from Dirichlet Boundary Conditions.

The measured voltages will cause a change in the conductivity distribution, and thus cause a change in the surface voltages. To tend toward minimization of the surface voltages and the calculated voltages, the Dirichlet boundary conditions were applied. Dirichlet boundary condition gives:

$$\phi(s) = g(s) \quad (4.9)$$

$g(s)$ is the boundary potential distribution and often set to zero for simplicity. Simulation results showed that reasonable isopotential patterns were constructed on the breast model from the above formulation. In this model, the boundary in contact with the torso is tagged to zero. The reason is to prevent any potential field (noises) from interfering with the potential distribution of breast by the dipole and to confine all the excitation force in the breast without passing to the torso.

Solution to Eq. (4.1) is defined in terms of a given potential on the boundary of the problem domains. We neither have the value $\phi(x, y)$, nor any knowledge of its value at specific points except for the predetermined boundary of the domain. We approximate ϕ by $\bar{\phi}$ to have the residual, R of an approximation.

$$R(J) = \phi(\bar{x}) - \bar{\phi}(\bar{x}) \quad (4.10)$$

Overbar in Eq. (4.10) indicates multidimensional variables. For well-posed problems having a single solution, an approximation that nearly satisfies the governing equation, resulting R near zero is desired. We select a set of polynomial coefficients that minimizes a set of weighted averages of this residual over the domain of interest such as

$$\int_{\Omega} R(J) w_j(\bar{x}) d\Omega = 0 \quad j = 1, 2, \dots, n \quad (4.11)$$

where w_j is the weighting functions, for $\bar{\phi}$, we write it in a general form

Formulation of the Bioelectric Equation

$$\bar{\phi}(\bar{x}) = \sum_{i=1}^n \phi_i N_i \quad \text{and} \quad w = \sum_{i=1}^n w_i N_i \quad (4.12)$$

N_i is the typically a polynomials of some specified order p , and they are called shape functions.

Substituting Eq. (4.10) and Eq. (4.11) into Eq. (4.12) results in n equations of the form:

$$\sum_{i=1}^n \left[\int_{\Omega} (\nabla \cdot \sigma \nabla N_i) N_j d\Omega \right] \phi_i = 0 \quad j = 1, 2, 3, \dots, n \quad (4.13)$$

Integrating by parts and applying the divergence theorem results in the weak formulation

$$S(\bar{\sigma}) \bar{\phi} = b(\bar{\sigma}) \quad (4.14)$$

$$S_{ij}(\bar{\sigma}) = \int_{\Omega} \{\nabla N_i\}^T \sigma \{\nabla N_j\} d\Omega \quad i, j = 1, 2, 3, \dots, n \quad (4.15)$$

where

$$b = \int_{\Gamma} (\sigma \nabla \phi \cdot \bar{n}) N_j d\Gamma \quad i, j = 1, 2, 3, \dots, n \quad (4.16)$$

Γ represents the boundary of the domain Ω , $\bar{n}$ is a unit vector in the direction of the outward normal to Γ , and n the number of degree of freedoms, DOF. σ is a tensor in anisotropic problems.

$S(\bar{\sigma})$ is referred to as the stiffness matrix, and b as the force vector. b can be solved by using appropriate Neumann boundary conditions. Applying integration by parts lower the highest derivative in the residual equation to first order, allowing the use of piecewise linear basis functions.

4.4 The Biopotential Equation in Simple Geometry

In order to gain confidence in the usage of a PDE calculator, FEMLAB [Feml2004] and the governing equation, the Biopotential equation is applied to two simple geometries and the results are benchmarked. Both models being considered were having the similar governing equation with slight differences. In order to solve these two models, it was decided to use the commercial PDE calculator; called FEMLAB. FEMLAB is a high level state-of-the-art PDE stands for Finite Element Modelling Laboratory. It is an advanced software package for modelling and simulation of any physical process governed by partial differential equations one can describe for the law of science. FEMLAB has built-in high-performance state-of-the-art solvers that address extremely large problems yet quickly yield accurate results. FEMLAB allows user to work in a built-in easy-to-use graphical interface, as well as full controlled equation-based modelling to have a full access of creating custom equations. A particular strength of the package is its PDE modelling capability, whereby it can link and solve coupled equations from arbitrary fields. FEMLAB is also closely incorporated with MATLAB, whereby results from FEMLAB can be exported out easily into MATLAB language and further simulated in MATLAB environment. Other strengths of FEMLAB include:

- Powerful direct and iterative solvers based on C++. Java-based graphical user interface makes the modelling process interactive and user friendly.
- Built in CAD tools for solid modelling in 1D, 2D and 3D. CAD generated files such as DXF or IGES can easily imported and exported for pre- and post-processing.
- Fully or partially automated and adaptive mesh generation with explicit and interactive control of mesh size. The importance of this feature is discussed further in later sessions.
- Total freedom in the specification of physical properties, analytical expressions and functions.

4.4.1 The Three-sphere Model

The *Three-sphere Model* is constructed and numerical results obtained using in-house developed code based on FEMLAB is compared with the analytical result of the model obtained from [Rush1969]. The objective of this verification process is to access the model's ability to handle significantly differing conductivities across zones and to compare the numerical method accuracy to the analytical method. The governing equation determining the electrical potential in an inhomogeneous medium was given by [Nune 1981] :

$$\frac{\partial}{\partial x} \left(K_x \frac{\partial \phi}{\partial x} \right) + \frac{\partial}{\partial y} \left(K_y \frac{\partial \phi}{\partial y} \right) + \frac{\partial}{\partial z} \left(K_z \frac{\partial \phi}{\partial z} \right) = \alpha \frac{\partial \phi}{\partial t} + Q \quad (4.17)$$

x , y and z are the Cartesian coordinates (m); t is the time (s); α is the accelerator ($\Omega \text{m}^3 \text{s}^{-1}$) determining the electrical potential activity response time; ϕ is the electrical potential (V); K_x , K_y , K_z are the electrical conductivities in the x , y , z directions, respectively (Ωm)⁻¹ and Q is the net source/sink of potential (Am^{-3}). In the current case, after the steady state of the simulation is achieved, we take the cross section over the centre of the sphere, and results are shown in Figure 4.4.

Electrical conductivity is considered as a vector quantity in the three Cartesian directions (3D model). α is considered as zero for non-transient problem, and the boundary condition across the outer surface is implemented as zero.

$$K_n \frac{\partial \phi}{\partial n} = 0 \quad (4.25)$$

n is the direction normal outwards from the surface. K_n is the conductivity in that direction.

The analytical solution for this three concentric spheres model is given by [Rush1969] as

$$\phi(r, \theta) = \frac{A}{6\pi\sigma_c c^2} \left[2\frac{r}{c} + \left(\frac{c}{r} \right)^2 \right] ID \cos \theta \quad (4.18)$$

Formulation of the Bioelectric Equation

where r is the radial distance from the centre of the dipole to the measurement of potential (m); θ is the angle between the line joining the dipole centre to the measurement location (radians); I is the strength of the dipole source (A); D is the distance between the source and sink (m);

$$A = \left(\frac{27}{2} \right) \left\{ \left(\frac{\sigma_a}{\sigma_b} - 1 \right) \left(\frac{\sigma_b}{\sigma_c} - 1 \right) \left(\frac{a}{b} \right)^3 + 2 \left(\frac{\sigma_b}{\sigma_c} - 1 \right) \left(\frac{\sigma_a}{\sigma_b} + 2 \right) \left(\frac{b}{c} \right)^3 \right. \\ \left. + 2 \left(\frac{\sigma_a}{\sigma_b} - 1 \right) \left[2 \left(\frac{\sigma_b}{\sigma_c} + 1 \right) - 1 \right] \left(\frac{a}{c} \right)^3 + \left(\frac{\sigma_a}{\sigma_b} + 2 \right) \left(\frac{\sigma_b}{\sigma_c} + 2 \right) \right\}^{-1} \quad (4.19)$$

σ_a , σ_b , σ_c are the conductivities of the inner, middle, and outer spheres A, B and C (Ωm)⁻¹ with radii a , b , and c (m), respectively. The diagrammatic illustration of this model is shown in Figure 4.2.

4.4.1.1 Verification of the numerical model using coarse and fine grids

A grid of 1192 elements was used to solve the numerical model generated using FEMLAB. This coarse grid was used to minimize the computation time requirement of the convergence by compensating the result accuracy. The model was built with inner, middle, and outer spheres, radii (a , b , c) of (0.04, 0.07, 0.1) m respectively and corresponding tissue conductivities (σ_a , σ_b , σ_c) of (0.148, 0.5, 0.09) (Ωm)⁻¹. These conductivities were used as mimic to the real condition of current 2D breast biopotential modelling. A source and sink of current +1 and -1 Am⁻³ oriented parallel to the y-axis, were placed 0.01m apart at the origin respectively in Figure 4.2.

For the second verification using fine grid a finer grid 4 times of 4768 elements was used. It is expected that this finer dimension of mesh will give more accurate results. The dimension of the 3 spheres was fixed the same as the coarse grid case, with same conductivities and same source and sinks potential of +1 and -1 Am⁻³. After steady state solution was achieved, potentials at the outer sphere were taken and plotted in Figure 4.3.

A comparison study was done among the analytical solution, the coarse grid numerical method and the fine grid one. As one can see, inaccuracies were generated using the coarse grid as opposed to the fine grid. This may due to poor approximation of the potential near the edge of the sphere. This observation also suggested the need of a mesh independency test for the biopotential breast model generated. Further discussion on this matter is presented in Chapter 5. Although the numerical results are not exact, nevertheless, they still achieve satisfactory agreement. The isopotential plot for the case of fine coarse case simulation is attached at Figure 4.4.

4.4.2 Laplace's Equation in Thoracic Cross Section.

The *Thoracic Cross Section Model* is also studied and compared with [Guha1973]. The objective of this study is to identify the model ability to handle complicated geometry, isotropic and irregular shaped subdomains. Thoracic domain is taken as illustrated in Figure 4.5. This test case gives the basis for applying electromagnetic field equations to the determination of surface potential patterns non-invasively. Some simple analysis were done based on the numerical model, and results showed that the current densities vary over the thoracic cross section and the size of the excitation electrodes affects the field patterns and intensities. Although these observations may not be useful as for the 2D analysis of biopotential model presented in Chapter 5 because a point source is used instead of an electrode with surface area. Nonetheless, for future 3D analysis, and mimic of the realistic Biofield Diagnostic System hardware settings, the configuration of electrode and sensors will definitely needed to be taken into account.

For steady state condition, the total current flowing into a closed region must be equal to the current flowing out. Therefore, by divergence theorem:

$$\frac{\partial}{\partial x} \left(\frac{1}{\rho_x} \frac{\partial V}{\partial x} \right) + \frac{\partial}{\partial y} \left(\frac{1}{\rho_y} \frac{\partial V}{\partial y} \right) + \frac{\partial}{\partial z} \left(\frac{1}{\rho_z} \frac{\partial V}{\partial z} \right) = 0 \quad (4.20)$$

In an isotropic region,

$$\nabla^2 \phi = 0 \quad (4.21)$$

Although it is not realistic to consider the domain as isotropic but for the current study purpose, generation of a detailed thoracic model is far too complicated and will go beyond the scope of this report. The air in contact to the surface of the body is taken to have negligible conductivity, or in other words, the ratio of body conductivity to air conductivity is infinite. Again, the Neumann boundary conditions applied. For the conductivities, the lungs, are assigned with a median conductivity of $0.0833 (\Omega\text{m})^{-1}$; the heart, $0.8 (\Omega\text{m})^{-1}$; and the thoracic wall with muscles and blood, $0.1666(\Omega\text{m})^{-1}$. The outer boundary of the body and the interface between internal organs are curved and irregular in shape as shown in Figure 4.5. Lines in the solution domain (Figure 4.6) are the equipotential lines. It can be compared that the numerical results are very agreeable with the results published.

Figure 4.1: Two Dimensional Breast Model of a Female Breast. (Dimensions are in mm)

Figure 4.2: Three concentric spheres model

Figure 4.3: Comparison of the numerical results of fine grid with total of 4768 elements (dash line) and coarse grid of 1192 elements (dotted jagged line) with the analytical method (solid line) of the *Three Sphere Model*.

Figure 4.4: Isopotential distribution *Three Sphere Model* (fine grid case). One can see that a dipole source is inserted in the centre of the model. It is also well known that better numerical solution can be obtained when the dipole are closer to each other.

Figure 4.5: *Thoracic cross section model for analysis.*

Figure 4.6: Isopotential distribution of the *Thoracic cross section* model

Figure 4.7: Numerical solutions of the *Thoracic Cross Section Model* [Guha1973]

Chapter 5

Two-dimensional Analysis

5.1 Mesh Generation and Solution

The two-dimensional model of a female breast presented in Figure 4.1 is to be meshed for further analysis. The mesh was generated using the built-in FEMLAB mesh generator, with refined mesh near the probe (point source, where the steepest potential gradient is observed) and the sensor (location at which potential is mapped). The governing equation and boundary conditions were programmed using FEMLAB user integrated GUI. Results were visualized using FEMLAB built-in post processing software. Experiment was started with a homogeneous grid first, but one can vary the parameters like the element type and density of each individual layer separately to achieve good mesh invariant approximation. Different mesh density is needed when special effect of certain parameters or certain area of special interest was to be mapped precisely. The model uses six-node triangular element with quadratic interpolation. A 2D meshed model was presented in Figure 5.1

5.1.1 Mesh Independent Prediction of Biopotential Breast Model.

Finite element model is obtained by solving Equation 4.1. In order to gain a good mesh invariant approximation, the programme was executed with several element numbers until a mesh independent solution was achieved. Element numbers of 758, 852, 973, 1104, 1919, 2467, 3199 and 4107 were used. The potential at a specific location was observed as a test for convergence. For a model presented in Figure 5.1, the maximum reduction of potential will happen at a point closed to the tumour, and therefore, location (x, y) of (-1.0, 0.2) was taken as our test point. Another reason for the selection of the point is that, the parameters of interest ultimately are the size and location of tumour. Therefore, a point, which can represent the disruption of potential distribution with the presence of tumour, was selected to minimize the effect of noise. A new parameter, the *confidence level* is defined as the percentage ratio of the absolute potential value taken at respective element number to the one from the finest grid (in which convergence has been achieved). Or in other words, a confidence level of 100% implies a saturation point where no change can be observed on increasing element number (mesh number 2467 in this case). Result is shown in Figure 5.2. Validation of the model is shown in later sessions.

5.2 Justification on Selection of Physical Properties

5.2.1 Measurement Frequency Range and Tissue Conductivities

One can easily see that, of all the physical properties involved, the dielectric constants are of the greatest interest in distinguishing normal breast tissues from any malignancy. From Equation (4.1) and Equation (4.2) a prerequisite is needed to solve these equations, and that is the knowledge of conductivity of the volume being modelled. These are heterogeneous problems, and depend among the tissue composition, structure, fat and water contents and vary with the pathological state of the tissue. Therefore, alterations caused in a tissue by a tumour would result in observable conductivity changes. The purpose of this work is not to determine the

conductivities of breast tissues, despite the importance of them in this analysis. Nonetheless, a comparison of the values of conductivity at a frequency spectrum was performed, to obtain the optimum conductivity for the upcoming analysis. A new contrast of conductivity (C) was defined as the absolute value of the quotient of the conductivity of the diseased breast tissue (σ_d) to that of the normal tissue (σ_n) as a function of frequency.

$$C = \left| \frac{\sigma_d}{\sigma_n} \right| \quad (5.1)$$

The plot is shown in Figure 5.3

Although at higher frequency, corresponding conductivities of tissues will give a clearer surface potential tomography, but in this study, frequency domain of β -relaxation ($1 \text{ kHz} < f < 100 \text{ MHz}$) is still preferred. The reason for that is, at low frequencies, the conductivities of the tissue is constant, and the quasistatic condition holds, as for practice alternating currents are used rather than steady currents. Moreover, the significance of electrode contact impedance can be reduced by making the measurements at highest possible low frequency. From dielectric measurement of 3.2 GHz, Campbell [Camp1992] commented on the "similarity of the dielectric properties of benign and malignant breast tumours", which confirmed the lack of specificity of the dielectric mechanisms occurring at such frequencies. This observation seems to consent with Heinitz [Hein1995]. Heinitz found "highly significant differences between carcinoma and mastopathy forms" in the values in the resistances of the Fricke equivalent circuit model. From literatures, it is decided to use the frequency region at which the studies of Morimoto *et al* [Mori1990], Joines *et al* [Join1994], Jossinet *et al* [Joss1998], and Surowiec *et al* [Suro1988] overlap. A summary of the conductivity with respect to the frequency region studied by several researchers was given in Figure 5.4. At the chosen frequency range, tissue properties are taken from various literatures listed above. The summary of the tissue conductivities is given in Table 5.1. Although only

adipose (fat), mammary gland, skeleton muscle and malignant tumour regions are modelled, it can be easily extended into more complicated model with more layers.

5.2.2 Current Density

Another important parameter is the current density of the source term. One reason for using a dipole source in this study at the beginning stage is for its simplicity. In fact, in bioelectricity, one can never have a single isolated monopole current source because of the need to conserve charge. But collections of positive and negative monopole sources are physically realizable if the total sum is zero. The simplest collection, and one that reflects a fundamental bioelectric source, is the dipole. The dipole consists of two monopoles of opposite sign but equal strength I_s (often termed source and sink) separated by a very small distance, d . In fact, the strict definition requires $d \rightarrow 0$, $I_s \rightarrow \infty$ with $\mathbf{p} = I_s d$ remaining finite in the limit. The quantity $\mathbf{p}$ is the dipole moment or dipole magnitude. The dipole is a vector whose direction is defined from the negative point source to the positive. Again, for simplicity purpose, the detail modelling of the dipole source is left as future work at this stage, and an equivalent series R-L-C circuit is considered when it comes to determination of source strength. In this model, a small magnitude of $\pm 1\text{mA}$ at the two poles, and 0 at elsewhere were applied. This value is acceptable by conventional bioelectric analysis (-5 to +5mA) to the patient's breast.

$$I_v = \begin{cases} +1\text{mA}, & (r, \theta) = (0.7, 90^\circ) \\ -1\text{mA}, & (r, \theta) = (1.4, 179^\circ) \\ 0, & \text{elsewhere} \end{cases} \quad (5.2)$$

5.3 Numerical Results of 2D Biopotential Breast Model

A polar coordinate system (r, θ) is employed on the breast model with 1126 mesh points, giving a total of 2467 elements. A bipolar current source of 1mA, simulating the external current source, is

located on the surface of the torso, at both sides of the right breast (the negative pole at $\theta = 90^\circ$ under the nipple, and the positive at $\theta = 179^\circ$). Again, the nipple is not modelled at this stage due to its complexity. The discrete equations resulting from the finite element method were solved using MATLAB, by elimination method and fixed-point iteration for the Jacobian matrix. The simulation is carried out in a Pentium IV PC, consuming about 1 to several minutes per run. The largest tumour was artificially inserted at the circumferential angle of $145^\circ \leq \theta \leq 160^\circ$ with an area of 6.28cm^2 (diameter of 2.83cm). This size of tumour is used because it is the commonest size that can be first detected in clinic. The present theoretical study is an additional verification step for the feasibility study of Biopotential in detection of breast cancer. Although it has been found that significant changes occur in the surface potential due to a current source when a malignant tissue is present, the model should be further benchmarked to obtain conclusive results. Also, the sensitivity of the model to the tumour location and size has to be tested.

Figures 5.5 and 5.6 show the predicted equipotential lines in cases without and with artificial tumour respectively. One can see a noticeable change in the drop of equipotential lines in the vicinity of the tumour area. Equipotential lines are distorted and their density is lower in the case of inserted tumour. Surface potential is mapped for the entire breast domain, not just the area near to tumour or the boundary lines. This is crucial for the interpretation of the complete surface tomography.

Figure 5.7 presents the surface potential mapped over the breast for different tumour sizes. It can be seen that the larger the tumour, the more prominent the reduction of potential. This plot indicates the ability of the model to identify the size of the tumour. Shaded area is the region where tumour is inserted.

Figure 5.8 shows the percentage of difference of surface potential over a single location with varying realistic tumour sizes at $\theta = 165^\circ$. A reduction of about 16.4% is observed with the largest tumour size of 6.28cm^2 (diameter of 2.83cm). This finding is in slight disagreement with

[Rada1999] that shows about 18% reduction between the malignant and the normal breast. However, in their study, they were working with a whole torso cross section as 8 different compartments. The extracted tissue types were lungs, blood, ribs, bone marrow of the cord, breast fat, skin, skeletal muscle, and heart muscle. As one can see, Radai et al assumed the breast as a whole compartment with only properties of breast fat alone, whereas this research focus specifically on breast with different layers. Torso model is highly anisotropic relatively because compartment like rib muscle alone not only contains muscle only but also bone, blood and so on. Moreover, we only use 3 compartments to continue mapping with us. The reduction of surface potential follows a strong R^2 value ($R=0.996$) for tumour ranging from 0.40 to 6.28 cm² in area. This trend is of good agreement with the Radai's torso model. Percentage of different in surface potential is calculated from

$$\frac{\phi_{normal} - \phi_{tumor}}{\phi_{normal}} \times 100\% \quad (5.3)$$

R is defined as an indicator from 0-1 that reveals how closely the estimated values for the trendline correspond to the actual data. A trendline is most reliable when its R^2 value is at or near 1.

$$R^2 = 1 - \frac{SSE}{SST} \quad (5.4)$$

$$SSE = \sum (y_j - \hat{y})^2 \quad (5.5)$$

$$SST = \left(\sum y_j^2 \right) - \frac{\left(\sum y_j \right)^2}{n} \quad (5.6)$$

where $\hat{y}$ is the mean value of y , n is the total number of data points.

Figure 5.9 presents the absolute potential difference in the circumferential surface potential distribution between the normal and the case of largest tumour. The largest difference of about

1.5mV is observed in the region of the tumour. This gives a reduction of about 16.4% as compared to the normal case (without tumour).

Figure 5.10 shows the difference in surface potential versus the depth of tumour. One can see that at circumferential angle of 90° (centre line of the model), the nearer the tumour location to the dipole source, the more profound the difference in surface potential. At tumour location of 0.1 cm from the source, the change of surface potential is of 4th order. Figure 5.11 shows the difference in surface potential versus location of tumour circumferentially. The depths of tumour were fixed at 0.50cm, 0.70cm, 0.90cm, 1.10cm and 1.25cm. One can see, at depth of 1.25cm, which is closest to the breast surface, there is a sharp increase in the difference of surface potential when tumour gets closer to the source. Both Figure 5.10 and 5.11 suggest that, tumour is easier to be detected if it lies closer to the surface, and the placement of source probes, should be as close to the predicted location of tumour as possible, in order to get a more profound surface potential distribution.

Figure 5.1: Computational grid for two-dimensional model of breast. A tumour is artificially inserted at (r, θ) of $(0.95, 160^\circ)$, and a dipole of +1 and -1mA at 90° and 179° respectively.

Figure 5.2: Convergence of surface potential in terms of confidence level vs. element number.

Figure 5.3: Contrast of Conductivity ratio versus Frequency

Figure 5.4: Published Conductivity verses respective frequency regions

Tissue Regime	Mean and Standard Deviation Values of Tissues Conductivities
Skin	0.10 ± 0.05
Adipose (fat)	0.04 ± 0.01
Connective tissues	0.09 ± 0.04
Mammary gland	0.50 ± 0.22
Mastopathy	0.39 ± 0.16
Fibroadenoma	0.44 ± 0.13
Cancerous	0.71 ± 0.11
Muscle	0.148 ± 0.065

Table 5.1: Values of mean and standard deviation of tissues conductivities at frequency range of ~10-100 kHz used in this research.

Two Dimensional Analysis

Figure 5.5: Equipotential distribution (mV) inside a normal breast

Figure 5.6: The potential distribution (mV) inside the breast model with artificially inserted malignant tumour ($\sigma = 0.71$).

Surface Potential vs Circumferential Angle

Figure 5.7: Surface potential distribution (mV) over the breast in several inserted tumour sizes.

Figure 5.8: Percentage difference (%) in surface potential (mV) between tumours of various sizes with the normal zero tumour case.

Figure 5.9: Potential difference (mV) in terms of circumferential angle between the largest simulated tumour size of 6.28cm² (diameter of 2.83cm) and the normal case.

Figure 5.10: Difference in surface potential (mV) vs. depth of tumour (cm)

Figure 5.11: Difference in surface potential (mV) vs. location of tumour in circumferential angle (degree)

Chapter 6

Three-dimensional Analysis

6.1 Introduction

Previous chapter has conducted preliminary analysis of the effects the efficacy of skin surface electrical potentials due to the underlying lesions. In the present studies, we performed a theoretical three-dimensional, simplified and yet realistic models of female breast to investigate the feasibility and distinguishability of surface biopotential resulted from the presence of different types of breast abnormalities. We developed an inhomogeneous female breast model, which was close enough to the actual, by considering a breast as a hemisphere in supine condition the various layer were of unequal thickness. Isotropic homogeneous conductivity was assigned to each of these compartments and the volume conductor problem was solved using finite element method to determine the potential distribution developed. From simulation results, tumour location influences the surface potential profoundly and is easier to be detected if it lies closer to the surface. It is suggested that detection probes to be placed as close to the predicted location of tumour as possible.

6.2 The Three-dimensional Realistic Model

As first step, we extended our finite element female breast model, which was close enough to the actual, from our previous two dimensional works [Ngyk2005]. A general solution of the equation was not possible since the anatomy of breast was rather too complex for mathematical description in this entirety. We modelled a breast with size of a 34 cup 'C' brassiere, as a hemisphere in supine condition with various layers of unequal thicknesses, based on cross sectional view of female breast as presented in [Ngyk2005] [Ngds2001] [Harv1998]. The 3-D model with the three layers of varying thickness is presented in Figure 6.1. Breast was assumed to be of hemispherical shape, with a 5mm of subcutaneous layer, followed by a gland and muscle layer of varying thickness. We also modelled the areola by assuming it as a separate homogeneous entity of milk duct properties [Moor2001]. Figure 6.2 shows the cross sectional cut away view of the breast model with the probes excluded. This size of tumour was used because based on free mammography conducted for 1000 Singapore women on the eve of the breast cancer awareness month (October 1998), this size was even smaller than the average cancerous lump size (20mm) first detected in clinic [Wang2003]. The property of this tumour volume is switched to glandular property while simulating a normal breast. Isotropic homogeneous conductivity was assigned to each compartment. The conductivity (in Sm^{-1}) of different tissue regimes were for adipose layer (0.04 ± 0.01), glandular layer (0.50 ± 0.22), muscle layer (0.148 ± 0.065), mastopathy (0.39 ± 0.16), fibroadenoma (0.44 ± 0.13) and malignant tumour (0.71 ± 0.14). Noted that only malignant tumour was used in the simulation because the contrast of the conductivity was the biggest and easier for the reader to analyse. The conductivity values used are similar to the one with our previous 2D work [Ngyk2005] for easier comparison later. Five probes model was simulated, by placing 4 equal size probes as closed as possible on top of the tumour and one bottom at the breast-torso boundary of the model. Since there is no electric passing through the breast-torso boundary, we can fairly mimic this with the control probe we placed on the palm of patients [Davi1995].

6.3 Results and Discussion

A Cartesian coordinate system was used on the segmented breast model. Solution domain was discretized using quadratic Lagrange elements. The number of elements in this model is close to 36000 and satisfies the mesh invariant solution. Four independent probes were located at $(-0.237, 0, 0.66)$, $(0.237, 0, 0.66)$, $(0, 0.237, 0.66)$ and $(0, -0.237, 0.66)$, and one ground electrode at $(0, 0, 0)$. Equation 1 was solved using the classical Finite Element Method (FEM). The in-house highly efficient GMRES solver was used to solve the domain. For this linear solver we provided a relative tolerance of $1.0\text{E-}3$ for the linear iterations and unlimited number of iterations for the solver to achieve convergence. We also set a factor of 40 in the error estimate, which acts as a safety factor. Finally, set the restart value of 50 to specify the number of iterations the solver performs until it restarts. This larger value we select can lead to high accuracy in the iterative process but at an increase in memory use.

For the convergence criterion of the total residual that we initially set to $1.0\text{E-}3$, the iterative algorithm, the sensitivity matrix calculated may contain large errors at area of interest. We designed the meshing of the domain such that, area at which we predict a steep electric potential gradient, denser mesh was applied. The simulation was done on a Pentium IV PC with 6-7 minutes of CPU time per run.

Figure 6.3 shows the predicted 3D biopotential contour plots in cases of with artificially inserted tumour. One can see a noticeable drop of surface potential in the vicinity of the tumour area. To compare qualitatively, Figure 6.4 shows an abnormal thermogram taken from a volunteer aged 47 years, who had a lump in the abnormal left breast that was diagnosed as benign in 1994 and recently has pain in her right breast. Arrow A in Figures 6.3 and 6.4 indicates abnormally increased underlying activities with extensive density that corresponds to presence of tumour. Equipotential lines are induced to the area of the tumour and their density is lower in the case of inserted tumour. As for other surface area, the changes in surface potential and electrical density

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give only slight alteration due to inadequacy of small magnitude excitation current to induce the whole domain. Surface potential is mapped for the entire breast domain for the interpretation of the complete surface tomography.

Figures 6.5a to 6.5f present the surface potential mapped over the breast for location of tumour. Tumour is artificially shifted circumferentially to study the surface potential patterns. As the total height of areola region is 72mm from the base, the 9.2mm diameter tumour is positioned at $R = 60\text{mm}$, to the centre of the breast, for more significant surface changes. Figure 6.5a represents the normal breast without inserted tumour, 6.5b represents breast with tumour in the middle, 6.5c and 6.5d with the tumour at the centre shifted 5 degree circumferentially to the left and right respectively, and lastly, 6.5e and 6.5f, with tumour shifted 10 degree circumferentially to the left and right respectively. One can see a noticeable increased in surface potential as the tumour moved. This is due to the induction effect of tumour, with a higher conductivity with respect to the surrounding tissues; the area close to the tumour will give lower potential. As for the sensitivity of the device, we captured the surface potential with respect to gradually reduced tumour size. Figure 6.6 presents an almost negative linear relationship between the difference in surface potential of breasts with artificially inserted tumour of different sizes, with respect to normal breast. Quantitatively, we also studied the effect of probes towards the detectability of tumour. Figure 6.7 captures the surface potential at the area under the areola as the tumour shifted circumferentially as above. Nomenclature left and right in the figure mean tumour shifted 5 to the left and right respectively; whereas; far left and far right indicate 10 degree movement. One can see clear discrepancies when tumour moved between the two probes. For area outside the two probes, the potential changes are relatively negligible as expected. Together with Figure 6.8, we can deduce that as the tumour is moved closer to the probes, we can capture more significant changes in surface potential as compared to other area of the breast. The basic reason for the weakening of the surface biopotential signature when probes are further away from the tumour arises from the fact that the conductivity of tumour has a magnitude of the order of 10^{-1} and 10^{-2}

for normal tissues. These high values of the conductivity (analog to low resistance in electricity) cause small changes in surface tissue potential to amplify the current flow between the 'deeper' tumour and nearby tissue significantly. Hence, the same current released from the probes 'advects' quickly by the tumour to the surrounding tissue. This reduces the signatures of the 'deeper' (further away) tumours on the breast surface.

For the effect of the four adjacent probes, we studied their effect by suppressing two opposite probes while keeping the other two active. Figure 6.9 shows the surface potential plotted circumferentially along the suppressed probes direction. We found the changes in surface potential became very insignificant, except for the central area. We deduce that, the adjacent probes indeed have effect detecting the tumour, but nevertheless, their effects are relatively small with respect to the probe directly on top. Simulation also suggests that, the percentage different in surface potential for the tumour of the same size as in our earlier 2-D paper [13], at the same location and physical properties, we obtained a reduction about 20%, as compared to 2-D of about 16%. The discrepancy is easily justifiable because in our 3-D analysis, 4 excitation probes were used instead of just 1 probe in 2-D simulation. With greater current passing through the computation domain, we thus expect to get a higher difference in surface potential.

6.4 Conclusion remarks

We can draw a conclusion that, tumour is easier to be detected if it lies closer to the surface, and the placement of source probes, should be as close to the predicted location of tumour as possible, in order to get a more profound surface potential distribution as well as other functional image information related with tumour. Therefore, in reality, a probe is placed directly on top of the tumour during measurement is a wise strategy. As for the tumour size, theoretically observation from simulation holds true but the detectability of tumour varies depends on the sensitivity and

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limitation of the measuring devices. It has been documented that BDS is unable to detect tumour size less than 1 cm [Davi 1995].

Figure 6.1: Three-dimensional Model of Breast Comprising Various Layers [Ngsd2001].

Figure 6.2: Cross-sectional Cut Away View of the Breast Model [Ngsd2001].

Figure 6.3: Numerical Simulation of the Right Breast with a Tumour inserted in the Centre.

Figure 6.4: Abnormal Thermogram of a Right Breast with Numerical Simulation (Volunteer age 47. Arrow A indicates abnormally increased underlying activities with extensive density that correspond to tumour existence)

Figure 6.5a: Distribution of Surface Potential for a Normal Breast

Figure 6.5b: Breast with Tumour in the Middle

Figure 6.5c: Breast with Tumour Located 5° Circumferentially Offset to the Left

Figure 6.5d: Breast with Tumour Located 5° Circumferentially Offset to the Right

Figure 6.5e: Breast with Tumour Located 10° Circumferentially Offset to the Left

Figure 6.5f: Breast with Tumour Located 10° Circumferentially Offset to the Right

Figure 6.6: Difference in Surface Potential vs. Size of Tumour (cm).

Figure 6.7: Surface Potential at the Area under the Areola as the Tumour Shifted Circumferentially

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Figure 6.8: Surface Potential at the Area under the Areola as the Tumour Shifted 5° and 10° left and right respectively

Figure 6.9: Surface Potential Plotted Circumferentially Along the Suppressed Probes Direction.

Chapter 7

Parametric Optimisation for Tumour Identification

7.1 Introduction

A female breast model, which was close enough to the actual, by considering a breast as a hemisphere in supine condition the various layers were of unequal thickness was developed. Isotropic homogeneous conductivity was assigned to each of these compartments and the volume conductor problem was solved using finite element method to determine the potential distribution developed due to a dipole source. First of all, for 3-D, proper choice of element size and refinement method needs to be taken care of. The grid generation in the three-dimensional model is very critical. It is possible to obtain only a mesh less-sensitive solution as compared to mesh insensitive design obtained in 2-D, as the grid generation is by trial and error in order to ensure nodal connectivity across layers with varying thickness. We perform the classic h_2 Richardson Extrapolation for grid invariance test to ensure the result is of reliable accuracy. Furthermore, four important parameters were identified and analysis of variance (ANOVA, Yates' Method) was performed using 2^n design (n = number of parameters 4). The effect and importance of these

parameters were analysed. The Taguchi method was further used to optimise the parameters in order to ensure the signal from the tumour is maximised as compared to the noise from the other factors. However, it is also to be noted that each and other parameters such as probe source strength and tumour conductivity have different degree of influence towards the end results. In this paper we conduct an Analysis of Variance (ANOVA) to better explain the precedence and the importance of the various factors. Once this is identified it would help in classifying the factors as noise or nuisance factors. If these factors can be controlled then it would help in setting up a protocol and help in identifying the factor of interest that is the existing of tumour.

7.2 Grid Generation and Refinement Studies

The grid generation in the three-dimensional model is very critical. It is possible to obtain only a mesh less-sensitive solution as compared to mesh insensitive design obtained in 2-D, as the grid generation is by trial and error in order to ensure nodal connectivity across layers with varying thickness. For 3-D, proper choice of element size and refinement method needs to be taken care of. They are the subcutaneous region, the gland region and the rib muscle region.

7.2.1 Uniform Reporting of Grid Refinement Studies based on h^2 Richardson Extrapolation

We are concerned here to verify our calculation by analyzing grid convergence accuracy of the discretized domain. Roache [Roac1994] believed that a code and a particular calculation can be verified, and not with excessive difficulty. However, a code cannot be validated in any general sense, i.e., by comparison with experimental values [Davi1995]. The modest purpose herein is to get minimal two calculation grid refinement exercises onto a uniform reporting basis. Ostensibly, we would prefer to use the finer grid solution so as to obtain a more accurate result. However, a practical scenario occurs for which the contrary situation applies; we use the coarser grid possible solution for optimization between accuracy and cost. Mesh refinement studies are then necessary, not as a correction to the fine grid, but the coarse grid solution, and to ensure that the calculations

are within the asymptotic range of convergence, and reasonable error band, in the flavour of a statistician's 2- σ range or an experimentalist's 20:1 odds. We focus on posteriori error estimation, being of the opinion that useful priori estimation is not possible in the physiological measurement problems.

7.2.2 Grid Convergence Index

The ideal behind the proposed Grid Convergence Index (GCI) is to approximately relate the ϵ with the fractional error E_1 for the fine grid solution f_1 by

$$\epsilon = \frac{f_2 - f_1}{f_1} \quad (7.1)$$

obtained by whatever grid refinement study is performed to the ϵ , the error band, that would be expected from a grid refinement study of the same problem with the same fine grid using $p=2$ and $r=2$, i.e., a grid doubling with a second-order method. f_1 and f_2 are the separate discrete solutions on the fine grid and coarse grid respectively with discrete spacing. We can generalize Richardson extrapolation, eliminating the leading term in the error expansion as follows;

$$f[exact] \approx f_1 + (f_1 - f_2)/(r^p - 1) \quad (7.2)$$

The relation is based on equality of the error estimates. r is the refinement ratio and p is order of the basic numerical method. Given ϵ from an actual grid convergence test, the GCI is derived by calculating the error estimate of fine grid, E_1 [fine grid] from

$$E_1 [fine grid] = \epsilon / (r^p - 1) \quad (7.3)$$

Defining the Actual fractional error, A_1 of the fine-grid

$$A_1 = (f_1 - f[exact]) / f[exact] \quad (7.4)$$

and using Eq. (7.3)- (7.4) and the binomial expansion gives

$$A_1 = E_1 + O(h^{p+l}, E_1^2) \quad (7.5)$$

where $l=1$ generally or $l=2$ if centred differences have been used.

The absolute value of that equivalent ϵ is the proposed GCI for the fine grid solution, which is conveniently expressed as

$$GCI [fine\ grid] = 3 |\epsilon| / (r^p - 1) \quad (7.6)$$

For the bulk of the stack of calculations, we would be using the coarse grid solution;

$$GCI [coarse\ grid] = GCI [fine\ grid] + 3 |\epsilon| \quad (7.7)$$

The coefficient "3" is just a judgment call. It can lie between 1 and 3. Using the value '3' for our breast modelling makes grid doubling with second-order methods into the standard of comparison. It means that for $p=2$ and $r=2$, we obtain $GCI [fine\ grid] = \epsilon$.

Using the value '1' would make the GCI equal to the error estimator obtained from Richardson extrapolation. A 50% "factor of safety" over the Richardson error estimator would be achieved with the value '1.5', or the naive value of '2' might prove to be a neat and reasonable compromise.

The value '3' is probably too conservative. However considering practical complications such as rapidly varying coefficients from strong grid stretching in the breast model domain, nonlinear systems, nonmonotonic convergence, nonuniform behaviour of various error norms, experiment4 determination of spatially varying p , we need to consider retaining '3' as the coefficient as "factor of safety".

7.3 Analysis of Variance (ANOVA Yates' Method)

It was decided to analysis the factors that affect the breast's surface potential difference and their order of importance. We consider a three-dimensional model of the breast with tumour kept in the fats region; which is the outer most layers. The factors considered are probes' source strength, tumour's size, tumour's conductivity and tumour's location along the fats region. A 2^n factorial design was used where each factor would have two levels of low and high with a total of 16 runs.

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The 4 probes' source strength is set at 1mA for low value and 10mA for a high value. The tumour sizes are 5mm in diameter for low and 17mm in diameter for high. The tumour's conductivity is fixed at 850V and 1236V. The low and high values are summarised in Table 7.1. For tumour's location, its low point is located 70° away from the y-axis along the outer layer. And its high point is at the tip of the breast (0°) in the centre of the y-axis, as denoted in Figures 7.1 and 7.2. The factors are denoted in upper case and the runs in lower case by convention.

The runs conducted are as Run: (1), a, b, c, d, ab, ac, ad, bc, bd, cd, abc, abd, acd, bcd, abcd. Run (1) corresponds to simulation conducted where all the factors are at low level. A presence of a lower case letter in the run signifies that the simulation is conducted by fixing the value corresponding to that factor (denoted in upper case) at the high level and the rest at low level. Such combination of high and low levels would yield a total of 16 runs for 4 factors.

The observation is taken at the breast surface. The ANOVA results are tabulated in Table 7.2 using Yates' method [Natr1996]. We used pooling and pooled all sum of square (SS) of 3rd and higher order interactions (abc, abd, acd, bcd, abcd) to provide estimation of error variance. SS in the table denotes sum of square which is given by $g^2/n = g^2/16$, n is the number of data points, DOF is the degree of freedom, mean square which is given by SS / DOF , also equals to the estimates of variance effect, error of the method is defined by variance error, which is given by $(g_{abc} + g_{abd} + g_{acd} + g_{bcd} + g_{abcd}) / 5$ and finally F is the variance effect divided by variance error, gives SS / error . From the F-Table at 5% level of significance, we tabulated that $F_{0.05; 1, 16} = 4.49$. As shown in the above Yates' table, factors A, B and D are greater than 4.49 thus have significant effect on the surface potential field.

7.4 Taguchi Method

Taguchi separates factors into two main groups; control factors and noise factors. Noise factors are those over which we have no direct control but which vary with the breast environment [Tagu1986]. The control factors that may contribute to reduced variation (improved quality) can be quickly identified by looking at the amount of variation present as a response. It is our aim to be able to capture the signal from the tumour rather than that from those three more significant factors (A, B and D). We apply an analysis based on the Taguchi method [Tagu1986] widely used in quality engineering to build in robustness in the experimental set up.

In Taguchi method, quality is measured by the deviation of a characteristic from its target value. A loss function is developed for this deviation. Uncontrollable factors known as noise, cause such deviation and thereby lead to loss. Since elimination of noise factors is impractical and often impossible, the Taguchi method seeks to minimise the effect of noise and to determine the optimal level of the important controllable factors based on the concept of robustness. In this method, the controllable factor is separated from the uncontrollable factors and the analysis is carried out to find the best setting for the controllable factors that would yield the optimum result irrespective of the variation in magnitude of the uncontrollable factor. Taguchi has created a transformation of the repetition data to another value which is a measure of the variation present. The transformation is the signal-to-noise (S/N) ratio. The S/N ratio consolidates several repetitions (at least two data points are needed) into one value that reflects the amount of variation present.

7.5 Results and Discussion

Two sets of results were recorded in Figures 7.3 and 7.4. Both test 1 and test 2 used longest mesh refinement method, sampling was done at (0.0, 0.0, 0.7) and (-0.15, -0.15, 0.6) respectively. The magnitude of the Richardson Extrapolation error estimator of the normal grid solution for both

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tests is about 0.10%. The normal grid value of the GCI is around 0.30% referred to Figure 7.3 and Figure 7.4. Our result complied with the theory of Richardson Extrapolation error estimator, in which, E_1 is not conservative, whereas GCI is conservative and quite so in the spirit of a $2\text{-}\sigma$ error band. If the coarse grid solutions were to be used, the Richardson Extrapolation error estimates would be increased to $|E_1| + |\epsilon| = 0.4\%$. The GCI would be increased by $3|\epsilon|$ to $GCI [coarse\ grid] = 1.25\%$. Once again E_1 is not conservative and GCI is conservative with higher error percentage. As we reduced the grid resolution from coarse to coarser to extremely- coarser, the error percentage for both methods increase exponentially, eventually it achieved asymptotic range [Ngwk2005]. The theory of Richardson Extrapolation and GCI depends on the assumption that the Taylor series expansion is valid asymptotically, and that the two grids are within the asymptotic range. If an exact solution is known to a model problem, we can monitor $E_p = error / h^p$ as grid spacing, h is refined. Then the (approximate) constancy of E_p is a faithful verification of the order p and an indication that the asymptotic range is achieved. Extensive studies had been done in the area [Rich1927] [Roac 1990] [Roac 1994] [Ste1985]. In our case wherein the exact solution is not known, we performed five grid solutions and calculated two GCIs, from fine grid to normal (GCI_{12}) and from normal to coarse grid (GCI_{23}) and so on. Then the (approximate) constancy of

$$E_p \approx GCI / (3h^p) \text{ or} \quad (7.8)$$

$$GCI_{23} \approx r^p GCI_{12} \quad (7.9)$$

indicate that the asymptotic range is achieved.

The aim is to maximise the signal (i.e. surface potential from the tumour size and location) to the noise (i.e. associated from tumour conductivity). Table 7.4 summarizes the surface potential field predicted with respect to the interaction of the parameters A, B, C and D. We are using the non-dynamic output response application: nominal-the-best method to get the Taguchi table above. It is seen that a non-dynamic approach is useful for a specific test with a fixed output.

The nominal-the-best ratio is described as

$$\begin{aligned} S/N &= \text{desired output} / \text{undesired output} \\ &= \text{effect of the average} / \text{variability around the average} \end{aligned}$$

Calculations for a nominal-the-best S/N ratio are as follows. There are n pieces of data:

$$y_1, y_2, y_3, \dots, y_n \quad (f = n) \quad (7.10)$$

The total variation S_t is

$$S_t = y_{21} + y_{22} + y_{23}, \dots + y_{2n} \quad (7.11)$$

The average variation S_m is

$$S_m = (y_1 + y_2 + y_3, \dots + y_n)^2 / n \quad (f = 1) \quad (7.12)$$

The error variation S_e is

$$S_e = S_t - S_m \quad (f = n-1) \quad (7.13)$$

The error variance V_e is the error variation divided by its degree of freedom:

$$V_e = S_e / (n-1) \quad (7.14)$$

The S/N ratio is given by

$$S/N = 10 \log \frac{(1/n) (S_m - V_e)}{V_e} \quad (7.15)$$

For an example, to calculate the S/N value of interaction between parameters A(low), B(low): We have 4 data values: 7.27217E-04, 7.25691E-04, 7.27217E-04, 7.25640E-04

$$S_t = (7.27217E-04)^2 + (7.25691E-04)^2 + (7.27217E-04)^2 + (7.25640E-04)^2 = 2.1108700E-06$$

$$S_m = (7.27217E-04 + 7.25691E-04 + 7.27217E-04 + 7.25640E-04)^2 / 4 = 2.1108676E-06$$

$$S_e = S_t - S_m = 2.1108700E-06 - 2.1108676E-06 = 2.4084527E-12$$

$$V_e = S_e / (n-1) = 2.4084527E-12 / (4-1) = 8.0281758E-13$$

$$S/N = 10 \log \frac{(1/n) (S_m - V_e)}{V_e}$$

$$= 58.1778$$

Table 7.5 summarizes the effect and the signal to noise for various factors. The effect is computed by taking the mean T_{avg} which represents a particular condition. For example effect of Factor A at low level is computed by taking the two T_{avg} corresponding to A at low level and divided by 2.

$$A_{LOW} = (7.26441E-04 + 6.92388E-04) / 2 = 0.0007094 \text{ similarly,}$$

$$C_{HIGH} = (0.004002 + 0.003809) / 2 = 0.0039055$$

7.6 Conclusion Remarks

We draw a conclusion that fairly agreed with Roache, that Richardson Extrapolation method is in fact oblivious to the equations being discretized and to the dimensionality of the problem. This method can easily be applied as a postprocessor to solutions on two grids with no reference to the codes, algorithms or governing equations which produced the solutions, as long as the original solutions are indeed second-order accurate. The error estimate E_I itself does not provide a very good confidence interval. One might expect that it is equally probable that E_I be optimistic as conservative. It is just as likely that the actual error A_I be greater than E_I or less than E_I . The extrapolation must be used with considerable caution, since it involves the additional assumption of monotone truncation error convergence in the mesh spacing h . This assumption may not be valid for coarse grids. Also the extrapolation magnifies machine round-off errors and incomplete iteration error.

Studies made earlier by Yates' method shows that the probes source strength A, tumour size B and location of the tumour D have significant effect on the breast surface electropotentials.

Signal-to-noise ratio, often written S/N or SNR, is a measure of signal strength relative to background noise is calculated above using Taguchi method. The tabulated result shows that, in

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order to receive the effect of tumour's conductivity on the breast's surface, factors A, B and D have great influences on the effect.

Both methods used proved that probes' source strength, tumour size and location of tumours have great effect on the surface potential field. For best results on the breast's surface, the probes' strength should be low while having the tumour's size and location high. While tumour with higher conductivity would have better detection on the breast surface however this also means that it would produce slightly higher background noise.

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Figure 7.1: Tumour location (high)

Figure 7.2: Tumour location (low)

Figure 7.3: Percentage Error vs. Refinement Method for Test 1.

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Figure 7.4: Percentage Error vs. Refinement Method for Test 2.

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Factor	Description	Low	High	Units
A	Probes' source strength	1	10	mA
B	Tumour Size (diameter)	5	17	mm
C	Tumour conductivity	850	1236	V
D	Location of tumour	70.0	0.0	degree °

Table 7.1: Variables Properties

1 Parameters Combination	2 Response (Yield)	3	4	5	6 g	SS	DOF	Mean Square	F
(1)	7.25839E-04	4.35832E-03	8.72186E-03	1.74260E-02	3.37887E-02	-	-	-	-
a	3.63248E-03	4.36354E-03	8.70414E-03	1.63627E-02	2.25277E-02	3.17185E-05	1	3.17185E-05	14021.931
b	7.26257E-04	4.33976E-03	8.20085E-03	1.16221E-02	-5.60173E-04	1.96121E-08	1	1.96121E-08	8.670
ab	3.63728E-03	4.36438E-03	8.16183E-03	1.09056E-02	-3.77359E-04	8.89997E-09	1	8.89997E-09	3.934
c	7.23545E-04	4.25143E-03	5.81767E-03	2.98384E-05	-5.67353E-05	2.01181E-10	1	2.01181E-10	0.089
ac	3.61622E-03	3.94942E-03	5.80440E-03	-5.9001E-04	-3.79369E-05	8.99505E-11	1	8.99505E-11	0.040
bc	7.26324E-04	4.22492E-03	5.46514E-03	2.34460E-05	3.34093E-05	6.97611E-11	1	6.97611E-11	0.031
abc	3.63806E-03	3.93692E-03	5.44046E-03	-4.0080E-04	2.85740E-05	5.10298E-11	1	-	-
d	7.07594E-04	2.90664E-03	5.21823E-06	-1.7714E-05	-1.06331E-03	7.06645E-08	1	7.06645E-08	31.239
ad	3.54384E-03	2.91102E-03	2.46202E-05	-3.9021E-05	-7.16471E-04	3.20832E-08	1	3.20832E-08	14.183
bd	6.60264E-04	2.89267E-03	-3.02010E-04	-1.32617E-05	-6.1985E-04	2.40134E-08	1	2.40134E-08	10.616
abd	3.28916E-03	2.91173E-03	-2.88002E-04	-2.4675E-05	-4.2425E-04	1.12493E-08	1	-	-
cd	7.03980E-04	2.83624E-03	4.38287E-06	1.94020E-05	-2.1306E-05	2.83714E-11	1	2.83714E-11	0.013
acd	3.52094E-03	2.62889E-03	1.90631E-05	1.4007E-05	-1.1413E-05	8.14163E-12	1	-	-
bcd	6.56706E-04	2.81696E-03	-2.07349E-04	1.46802E-05	-5.3947E-06	1.81892E-12	1	-	-
abcd	3.28021E-03	2.62350E-03	-1.93455E-04	1.38938E-05	-7.86453E-07	3.86568E-14	1	-	-
error							5	2.26206E-09	
Total	3.37887E-02								
SS	1.03240E-04								

where $SS = \text{sum of square} = g^2/n = g^2/16$

$n = \text{number of data points}$

$DoF = \text{degree of freedom}$

$\text{Mean square} = SS / DOF = \text{estimates of variance effect}$

$\text{Error} = \text{variance error} = (g_{abc} + g_{abd} + g_{acd} + g_{bcd} + g_{abcd}) / 5$

$F = \text{variance effect} / \text{variance error} = SS / (DoF * \text{error})$

Table 7.2: Analysis using Yates Method

Parametric Optimisation for Tumour Identification

	A(LOW)		A(HIGH)		Tavg	Total Variation St	Average Variation Sm	Error Variation Se	Error Variance Ve	S/N
	B(LOW)	B(HIGH)	B(LOW)	B(HIGH)						
C	D(LOW)	7.27217E-04	7.26257E-04	7.25211E-03	3.98839E-03	1.0618275E-04	6.3629131E-05	4.2553621E-05	1.4184540E-05	- 0.5976
(LOW)	D(HIGH)	7.25691E-04	6.60264E-04	7.24510E-03	3.80990E-03	9.7126851E-05	5.8061314E-05	3.9065537E-05	1.3021846E-05	- 0.6314
C	D(LOW)	7.27217E-04	7.26324E-04	7.25156E-03	4.00239E-03	1.0699665E-04	6.4076511E-05	4.2920139E-05	1.4306713E-05	- 0.6063
(HIGH)	D(HIGH)	7.25640E-04	6.56706E-04	7.24393E-03	3.80864E-03	9.7101835E-05	5.8023000E-05	3.9078834E-05	1.3026278E-05	- 0.6370
Tavg		7.26441E-04	6.92388E-04	7.24818E-03						
Total Variation St		2.1108700E-06	1.9222071E-06	2.1014422E-04						
Average Variation Sm		2.1108676E-06	1.9176032E-06	2.1014416E-04						
Error Variation Se		2.4084527E-12	4.6039178E-09	5.4418100E-11						
Error Variance Ve		8.0281758E-13	1.5346393E-09	1.8139367E-11						
S/N (dB)		58.1778	24.9434	64.6184						
				25.0894						

Table 7.4: Analysis using Taguchi Method

FACTOR		LOW	HIGH
Probes' source strength A	Effect	0.0007094	0.0070952
	S/N	41.5606435	44.8538685
Tumour Size B	Effect	0.0039873	0.0038174
	S/N	61.3980957	25.0164163
Tumour Conductivity C	Effect	0.0038991	0.0039055
	S/N	-0.6144788	-0.6216672
Location of Tumour D	Effect	0.0039954	0.0038093
	S/N	-0.6019523	-0.6341937

Table 7.5: Effect and S/N Ratio for Various Factors

Chapter 8

Conclusions & Recommendation

8.1 Conclusions

From the literature review, it was observed that the use of biofield diagnostic system (BDS) as a detection tool is feasible more particularly: (a) as a risk marker; (b) as an adjunct tool with mammography; (c) for continuous follow-up of patients with false positive results as they are at a higher risk; (d) for younger patients whose dense breasts yield poorer sensitivity to mammogram; and finally, (e) for those who are afraid about the carcinogenic effects due to mammographic radiation and pain due to breast compression. A systematic review also showed that a delay of 3-6 months in symptomatic patients was associated with lower survival. Duijm et al concluded that, due to those presence inadequacies in screening and diagnosis of breast cancer, the workup of patients with a positive screening needs improvement to prevent unnecessary diagnostic delay [Duij 2004]. Biofield Diagnostic System (BDS) manifests of the bulk spatial inhomogeneities in the complex dielectric constant that represent the various tissues types. The basic idea lies in the notion that tissues differ in their dielectric properties. Potential distribution between the preliminarily classified as an abnormal breast is then mapped with a controlled probe placed on the palm of the patient. BDS injects small electrical currents through arrays of probes placed on

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the surface of a patient's body and measure the voltages needed to maintain these current. Then the inverse problem is to be solved to approximate the electrical conductivity changes inside the solution domain given the applied currents and equipotential lines on the surface. Once the conductivity is known, the underlying material could be predicted, in particular the possible presence of water as in water cysts, or mineral deposits. Hence, we argue that BDS has great potential to be used successfully in breast cancer diagnosis.

In the early two-dimensional analysis, simulation results confirmed that there is a relationship between the presence of tumor and surface potential distribution. It was found that the biopotential equation, in spite of the limitations, was able to provide numerical results consistent with experimental results, and therefore suitable for the present simulation. The model was further benchmarked, both with other numerical models published and also on-the-field data to obtain conclusive results. For a small malignant area of 13mm^2 (Diameter = 2mm), the surface potential only decreases slightly about 0.5%. For the largest malignant area of 615mm^2 (Diameter = 14mm), examined in this study, the decreased of surface potential was 16.4%, indicating that realistic sizes of tumours result in profound reduction of surface potential, following relationship of a polynomial of 4th order.

The 2-D model was then extended to three-dimensional realistic model to capture a more close-to-actual change in electropotential when there is a bulk inhomogeneity underlying. Breast was considered as a hemisphere in supine condition where the various layer were of unequal thickness. Optimisation was also done on the mesh of the FE model by using the standard h_2 Richardson Extrapolation for grid invariance test. Again, the author confirmed, that the existence of tumour, its type and location influenced the surface potential contour profoundly. The test closely agreed with the clinical trial, in which the tumour is easier to be detected when it is close to the surface. Therefore, the author suggested that detection probes to be placed as close to the predicted location of tumour as possible.

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In order to optimise the parameters for the identification of a tumour signal, a parametric optimisation was performed. The effects of the various parameters were analysed by performing an Analysis of Variance (ANOVA). The Taguchi method was further used to optimise the parameters in order to ensure the signal from the tumour is maximised as compared to the noise from the other factors. This step is of great importance in setting up a protocol and help in identifying the factor of interest that is the existing of tumour. Simulation results and conclusion were drawn in the previous chapter. The author would just want to stress again that, the final parameters used in the test must not violate the clinical protocol, but to optimise and help to build an intelligent algorithm and analytical tool for the diagnosis. Numerical simulation can aid as an adjunct tool to complement the data bank obtained. A multidisciplinary approach can bring out the best results.

8.2 Recommendation

Intelligent manifestation of surface potential with regard to the underlying breast abnormality could well enable one to make a good prediction. A bio-statistical error control based on the individuals such as age, race, and previous history with the device reading could help in providing an early non-invasive detection tool for breast cancer diagnosis. This is less expensive, non-invasive, and in certain cases can be at least a few years ahead of a mammogram in breast carcinoma detection. Further work is recommended to look into a normal breast as a starting point and then simulate the presence of a known significant malignant breast. It is also suggested to obtain field data from patients from the local hospital, for the different cancer classifications like ductal carcinoma, phyllodes and cyst etc., for validation of the model. This database could be used for developing an intelligent cancer diagnostic system.

8.3 Future Works

The author will not attempt to give a detailed discussion of any of the specific applications, but instead, point out several applications of Biofield in each field. It is noted that the numerical techniques discussed henceforth are pertinent to all the applications below but none of them deals with breast cancer detection in particular.

In the next phase, it is necessary to acquire as many field data as possible, with corresponding mammograms and biopsy results. The breast model should then be simulated for all possible combinations of parameters. With this database, an intelligent system should then be developed to help make both quantitative and qualitative analysis, thereby avoiding the subjective analysis by human that is prone to errors. Data base results from field data and selected output from numerical simulations could be used as an input to diagnosis using artificial neural network. Since the modelling of noise is of vital importance, extensive work can be done on the improvement of the hardware and software. For example, the current set up uses 16 electrodes for the data collection, but with the increase of channel to 32, we can perform a more thorough examination and produce higher quality images.

Furthermore, a new statistical method for BDS system based on an analogy to electrical-thermal circuit theory; referred to as electric-thermal analogy can be developed. The theoretical model can be developed by coupling the thermal and metabolic effect of the body, and their influence to the surface potential. The system will have high commercial value as detection of breast cancer at the early stage possible can reduce the likelihood of metastatic spread a quantitative analysis.

The state of BDS research is still encouraging. There are about 20 or 30 groups worldwide who are actively performing in the related research, and I think it is still seen as an exciting area of medical physics. In the past few years, there has been a breakthrough into clinical practice, with the implementation of BDS scanning hardware on a commercial basis for the adjuvant diagnosis of breast cancer. However, a major drawback is that it is not yet granted the FDA approval and

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accepted for routine clinical use in any other area, in spite of the existence of a score or so of good pilot studies.

Finally, the development of the expert system for quantification of the biopotential plots need not be restricted to the area of breast tumours alone. Biopotential or similar electrical impedance imaging are used vastly in various engineering applications, the simulation and model can find its place in the areas such as geology, petrochemical industry or even the structural engineering with non destructive testing without major alteration in the algorithm.

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PUBLICATIONS FROM THIS THESIS

Peer Review International Journal

Ng EYK, Ng WK, Ang WT and Sim LSJ, Simulation of biofield potential for early detection of breast tumour with a realistic 2D FE model. Journal of Medical Engineering and Physics, 2005. (Under second review)

Ng, W.K., and Ng, E. Y-K. Biofield Potential Evaluation as a New Modality for Early Diagnosing of Breast Lesions: A 3D numerical model, IEEE Transactions on Biomedical Engineering, 2005 (Under review)

Ng, W. K. and Ng, E. Y. K., Parametric Optimisation of the Biopotential Equation for Breast Tumour Identification using **ANOVA** and Taguchi Method, Journal of Engineering in Medicine, Proceeding of the Institution of Mechanical Engineers U.K. Part H (Under review)

International Conferences and Seminars

W. K. Ng, E. Y. K. Ng., Simulation of Biofield Potential for Early Detection of Breast Tumor with a Realistic FE Model. Multi-physics Modelling: Grid-Enabled FEMLAB. (Invited speaker)

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