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# An Innovative Concept of 3D X-Ray Imaging Systems for Painless Breast Cancer Detection

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Additional information is available at the end of the chapter

## Abstract

Breast cancer is a life-threatening disease and considered one of the most common forms of cancer among women worldwide. Early and accurate detection with mass screening programmes helps improve a woman's chances for successful treatment. The current and the most effective technique used for screening and diagnosis of breast cancer is the X-ray mammography. The photon transport detection of such technique is mostly based on a forward scattering mechanism as well as makes use of attenuation and penetration coefficients. The painful compression and the double X-ray exposure of both patients' breasts carried out during the imaging process remain unavoidable. In addition, the conventional 2D mammography has two major limitations: sensitivity in detecting breast cancers (~ <80%) and the high recall rate (~10%). It suffers from certain limitations, most important of which is tissue overlap and false diagnoses arising thereof. To overcome this and as an alternative, a new 3D imaging method for breast cancer screening and diagnosis, namely, tomosynthesis, has recently been used. In such method, a limited number of low-dose 2D projection images of a patient are used to reconstruct the 3D tissue information. Tomosynthesis systems incorporate an X-ray source that moves over a certain angle to acquire images. This tube motion is a major limitation because it degrades image quality, increases the scan time and causes prolonged patient discomfort. Therefore, the goal of this work was to overcome all of the above limitations by developing an innovative proof of concept for painless 3D X-ray mammography to be hopefully used as a screening and as diagnostic methods for breast cancer detection by utilizing the scattered X-ray photon information. Most imaging modalities required a wide spectrum of capabilities, which span biomedical sciences, physical sciences and clinical medicine; thus, the ongoing methodology aims to establish a collaborative cross-disciplinary research engaging together with scientists in universities and clinicians in hospitals. Consequently, we hope that this work provides the potential to score some successes in clinical imaging science. In order to do this and since it is generally not possible or feasible to use real components to build and optimize a system repeatedly, a Monte Carlo simulation was used. The first phase focused on realistic computer simulation of the proposed imaging system to find the optimum setup as well as to aid in the analysis of the effect of various factors on the system performance. Thus, the main

focus was on 3D mammography imaging simulation setup. Five main steps have been carefully checked and successfully produced: (a) the production of X-ray radiation or source after careful and detailed physics check. This includes the interaction between the X-ray photons and the object (the 3D breast phantom) that is used on scan as well as the detector system and its associated electronics modelled. (b) Next is the realistic modelling of anthropomorphic breast phantoms to check if the effectiveness of prediction of the simulation is successfully achieved. A computer simulation model is developed to estimate the radiation dose to the breast that would be incurred using mammography. Mono-energetic normalized glandular dose coefficients, DgN(E), were computed for energies 11–120 keV using breast phantoms of various sizes and compositions.

**Keywords:** mammography, breast cancer detection, 3D imaging

# 1. Introduction

Breast cancer is one of the most common cancers in Saudi Arabia [1] and, thus, is an important health problem [2]. In the Western world, it is the second most frequent cause of cancer death in women (after lung cancer) [3]. Statistics show that a large number of women in Europe, North America, Australia and many Latin-American countries suffer from this life-threatening disease [4]. Worldwide, in the year 2005, the number of new cases exceeded 1.2 million [3]. Breast cancer is rare in women below the age of 20 years and less common below the age of 30 years, but it is more aggressive and thus has a lower survival rate. The incidence rate, however, rises dramatically over the age of 50 years. This could be due to several risk factors such as family history, genetics, early menstruation, late menopause and other factors that have not yet been identified. Breast cancer can also occur in males and often fatal, but it is extremely rare. The above problems have prompted global governments to put constant efforts to increase patient's recovery level against this disease. Early and accurate detection with mass screening programmes helps improve a woman's chances for successful treatment. It also minimizes pain, suffering and anxiety that surround patients and their families.

The current and the most cost-effective technique used for screening and diagnosis of breast cancer is X-ray mammography. It is the state of the art for earlier detection to improve both prognosis and survival rate [5]. This may be due to its good availability, high sensitivity and relatively low cost/patient. Despite the above efforts, the mortality rate of breast cancer still remains high and in the UK, for example, accounts for ~17% of all female deaths [6, 7]. This is due to some limitations of the current mammographic procedures. As a result, a large number of cases with positive mammography results undergo invasive surgical breast biopsies. Breast biopsy is still widely used and thus is the only fail-safe method to determine whether a lesion is malignant. Of all biopsy cases, only about 25% prove to be malignant. Moreover, a majority of the diagnosed women below the age of 50 have a dense breast tissue. This is a problem as it obscures lesions and results in false-negative mammography.

In addition, the size, shape and appearance of the female breast are not constant but undergo a number of changes during the lifetime of women. For instance, changes occur during

the menstrual cycle and more pre-/postmenopause. In addition, the age of the subject not only influences the shape but also parenchymal density of the breast. Thus younger women tend to have denser breasts (more fibro-glandular tissue), whilst postmenopausal women have breasts containing a larger adipose component. This makes the X-ray mammogram far more effective in older women as the fat content is more radio-translucent (appears darker) than glandular tissue (appears underexposed) in younger women [8].

The above discussion suggests that both the shape and parenchymal density of the breast impose particular constraints on the choice of imaging modality. The imaging technique should be powerful for initial detection and subsequent follow-up of the diseases. At present, no single technique can be used for all cases of breast cancer detection without showing certain clinical or technical limitations. This implies necessity to address the specific needs that can help for breast tumour imaging to overcome these limitations. For instance, breast compression is often needed as it holds the breast still and enhances the spatial resolution. It also evens out the breast thickness and reduces scatter in X-ray or gamma-ray imaging in case of scintimammography (SM) [9], thus increasing image sharpness. Moreover, it spreads out the tissue so that small abnormalities will not be obscured by the overlying breast tissue. Since the breast is an external organ and extends to the chest wall, it requires appropriate views to be taken. For instance, in X-ray mammography a lateral (from the side) view of the breast allows separation of the chest wall from lesions deep within the breast.

Furthermore, mammography involves the radiological examination of the breast using equipment specifically designed for, and dedicated to, imaging breast tissue. This equipment is primarily used for the detection of breast cancer at an early stage. It is widely used in screening programme involving healthy populations of women. Early detection of breast cancer in a healthy population places particular demands on radiological equipment as high-quality images are required at a low dose. Symptomatic patients may also benefit from the development of mammography equipment that produces high-quality images for breast screening. Perhaps because of the exacting demands of mammography, acceptability criteria and suspension levels are well developed [10, 11]. It has been an accepted practice that mammography should be performed on X-ray equipment designed and dedicated specifically for imaging breast tissue, due to the clinical imaging requirements for high-quality image. In practice, either film/screen or digital detectors may be used. Both qualitative and quantitative acceptability criteria have been published for X-ray mammography by considering the image quality needed clinically in screening programmed.

## 2. Literature review

Cancer is a disease that starts in a localized organ or tissue and then grows out of control. Breast cancer is an important health problem as in the western world; it is the second most frequent cause of cancer death in women (after lung cancer) [6, 7]. Statistics show that a large number of women in Europe, North America, Australia and many Latin-American countries suffer from this life-threatening disease [8]. Worldwide, in the year 2005, the number of new

cases exceeded 1.2 million [7]. Breast cancer is a heterogeneous disease as it has different cell types and different behavioural characteristics and appearances. Understanding the types of breast cancer and their growth pattern is important for imaging purposes. Breast cancer is usually categorized into two main types: invasive (infiltrating) and non-invasive (in situ) cancer. In situ means that the cancer cells are at early stage, i.e. remains localized to ducts (milk passages) or lobule (milk producing glands) with no micro-invasion to the surrounding fatty tissue. Once the basement membrane is penetrated, the cancer cells break into the surrounding tissue and are referred to as invasive breast carcinoma. Breast cancer is rare in women below the age of 20 years and less common below the age of 30 years, but it is more aggressive and thus has a lower survival rate. The incidence rate, however, rises dramatically over the age of 50 years. This is may be due to several risk factors such as family history, genetics, early menstruation, late menopause and other factors that have not yet been identified. Breast cancer can also occur in males and often fatal, but it is extremely rare. The above problems have prompted global governments to put constant efforts to increase patient's recovery level against this disease. Early and accurate detection with mass screening programmes helps improve a woman's chances for successful treatment. It also minimizes pain, suffering and anxiety that surround patients and their families. The current and the most cost-effective technique used for screening and diagnosis of breast cancer is X-ray mammography. It is the state of the art for earlier detection to improve both prognosis and survival rate [9].

Mammography is a low-energy (25–32 keV) X-ray examination of the soft tissues of the breast. It uses the variation in density between normal mammary features and abnormal tissue structures (lesion) to produce the image. The current widely used technique is based on screen-film technology. It is considered the gold standard in breast imaging as it is fast and available and has a lower cost than the scintimammography. It has two main applications: as a screening method in asymptomatic patients and as a diagnostic method in symptomatic populations. The former application is extremely important, and its introduction has significantly reduced the mortality rate of breast cancer in many countries [10, 11]. The American Cancer Society (ACS), the Department of Health and Human Services (HHS), the American Medical Association (AMA) and the American College of Radiology (ACR) recommend screening mammography every year for women, beginning at age 40. This is because the screening services accurately detect micro-calcifications and non-palpable soft tissue masses which until now have been beyond other imaging methods thanks to the high spatial resolution (50100 µm). Research has shown that annual mammograms lead to early detection of breast cancers, when they are most curable and breast-conservation therapies are available. The National Cancer Institute (NCI) adds that women who have had breast cancer and those who are at increased risk due to a genetic history of breast cancer should seek expert medical advice about whether they should begin screening before age 40 and about the frequency of screening. A recent review [12] estimated that screening leads to a reduction in breast cancer mortality of 15 and to 30% overdiagnosis and overtreatment. This means that for every 2000 women invited for screening throughout 10 years, one will have her life prolonged. In addition, 10 healthy women, who would not have been diagnosed if there had not been screening, will be diagnosed as breast cancer patients and will be treated unnecessarily. Furthermore, more than 200 women will experience important psychological distress for many months because of false-positive findings. Normally, screening is achieved

by exposing the breast to X-rays after being gently compressed between two plates and then taking two views for each breast. A craniocaudal (imaging from above to below) and lateral views are generally taken. A lead grid is used to reduce scattering photons that reach the film. Diagnostic mammography is used for assessing the size of the lesion, for pre-surgical localization of suspicious areas of breast and in the guidance of needle biopsies.

The reported sensitivity (the fraction of patients actually having the disease and correctly diagnosed as positive) in lesion detection varies between 69 and 90% [13] depending on the breast density. The specificity (the fraction of patients without the disease, correctly diagnosed as negative) is the major drawbacks of conventional mammography. A variation in specificity between 87 and 97% and a low positive predictive value as low as 15% have also been reported in Ref. [14]. This 'less than perfect' performance may be due to several confounding factors, e.g. poor mammographic technique, observer error, the lesions are non-palpable or at a cellular level and/or the lesions are obscured by the normal breast tissues. In addition, the presence of scars or tissue distortion may hide true small tumours on the mammogram. Moreover, in mammography the ultimate challenge with regard to X-ray image quality and, thus, improving the reliability of screening and early diagnosis, requires better epidemiological understanding of breast tissues, improved diagnostic tools, enhanced quality control, continuous training and efficient management of data and records. Nevertheless, conventional mammography remains the most valuable and cost-effective technique for breast tumour diagnosis.

Over the last two decades, considerable efforts have been carried out to improve the current screen-film mammographic technique. These improvements include image quality, acquisition techniques and interpretation protocol in order to reduce some of the mammographic limitations [15]. Furthermore, a new research effort started 5 years ago focusing on 'digital mammography' (DM) as a possible future direction in breast imaging. Digital mammography, also called full-field digital mammography (FFDM), is a mammography system in which the X-ray film is replaced by solid-state detectors that convert X-rays into electrical signals. These detectors are similar to those found in digital cameras. The electrical signals are used to produce images of the breast that can be seen on a computer screen or printed on special film similar to conventional mammograms. This technique offers many advantages compared to the conventional screen-film-based method [16, 17]. For instance, processing with digital systems increases dynamic range (two to four times the dynamic range of typical film screen) and improved quantum efficiency and storage and display mechanisms. In addition, the use of computer-assisted image interpretation is claimed to be helpful for the physician. This may enhance different features such as computer-aided diagnosis which may further improve the visibility of lesions and improve mammographic sensitivity [18]. Therefore, repeated exposures (which are sometimes needed when using conventional mammography) are not required, and this may reduce the radiation dose. Moreover, it does not need either cassettes or dark rooms or processors and thus allegedly saves space and time in archiving and retrieving DM images. However, DM requires large disk space for saving image data.

Despite several advantages, DM does not yet replace screen-film mammography in many centres. However, with continuous technical improvements of the digital system, it is gradually taking over the conventional systems. Both conventional and DM systems suffer

from substantial technical and clinical limitations. For instance, these systems are unreliable in imaging patients with dense parenchyma tissue especially in the younger female population due to more glandular tissue. Breast implants can also impede accurate mammogram readings because both silicone and saline implants are not transparent on X-rays. Thus, it blocks a clear view of the tissues behind them. This is true especially if the implant has been placed in front of, rather than beneath, the chest muscles. This issue requires an experienced technologists and radiologists to carefully compress the breasts to improve the view without rupturing the implant. All the above limitations and problems of imaging need to be dealt with to enhance detection efficiency and overcome the drawback. One of the methods that recently employed is the computer-aided detection (CAD) systems. Such systems use a digitized mammographic image that can be obtained from either a conventional film mammogram or a digitally acquired mammogram. The computer software then searches for abnormal areas of density, mass or calcification that may indicate the presence of cancer. The CAD system highlights these areas on the images, alerting the radiologist to the need for further analysis. Despite that mammographic findings are non-specific (cannot always differentiate benign from malignant disease) and often underestimate the size of the detected lesion, X-ray–based imaging is also not useful for breast diagnosis following surgery or radiotherapy as the patient's breasts in these cases have architectural distortion. Mammography is not recommended for women with breast implants and is also not useful following hormonal replacement therapy due to the increase of breast density. It is worth mentioning that X-ray mammography is not always useful for non-palpable tumours. Another group of women—close carrying a mutation in BRCA1 (human gene called breast cancer 1, early onset) or BRCA2 (breast cancer 2) genes—are at high genetic risk of cancer, some even having opted for preventative bilateral mastectomy. It is preferred not to repeat scan this group due to X-ray dose, and thus, a more sensitive diagnostic test would be advisable.

Moreover, the size, shape and appearance of the female breast are not constant but undergo a number of changes during the lifetime of women. For instance, changes occur with pregnancy, breast feeding and during the menstrual cycle. In addition, the age of the subject not only influences the shape but also parenchymal density of the breast. That is why young women tend to have dense breasts (more fibro-glandular tissue), creating a rounded appearance. On the other hand, postmenopausal women have breasts containing a large amount of fat. This makes the X-ray mammogram far more effective in older women as the fat content is more radio-translucent (appears darker) than glandular tissue (appears underexposed) in younger women [19]. The above discussion suggests that both the shape and parenchymal density of the breast imposes particular constraints on the choice of imaging modality. The imaging technique should be powerful for initial detection and subsequent follow-up of the diseases. At present, no single technique can be used for all cases of breast cancer detection without showing certain clinical or technical limitations. This implies necessity to address the specific needs that can help for breast tumour imaging to overcome these limitations. For instance, breast compression is often needed as it holds the breast still and enhances the spatial resolution. It also evens out the breast thickness and reduces scatter in X-ray or gamma-ray imaging [20], thus increasing image sharpness. Moreover, it spreads out the tissue so that small abnormalities will not be obscured by the overlying breast tissue. Since

the breast is an external organ and extends to the chest wall, it requires appropriate views to be taken. For instance, in X-ray mammography a lateral (from the side) view of the breast allows separation of the chest wall from lesions deep within the breast. On the other hand, in single photon-ray emission imaging, one needs to separate the breast from the heart by employing an appropriate prone (face down) position. However, it has been claimed that with prone imaging view, there is a possibility of missing a small low-intensity medial lesion because of attenuation. This implies that another image is needed but with the camera positioned in the lateral view. In addition, shielding the camera from the background cardiac flux is very useful in tumour detection in terms of contrast and resolution [21, 22].

Having discussed the golden diagnostic technique for breast tumour imaging, the following section will describe the complementary imaging techniques of the breast. The image reconstruction techniques will be then discussed. Section 3 will be closed by presenting some preliminary results and a description of the design details.

## 3. Complementary diagnostic techniques

From the previous discussion, it is clear that there are some clinical situations where there are significant limitations to use mammography in isolation. In such cases, there is a great need to use sensitive tests to achieve a high confidence and accurate diagnostic decision. The use of breast biopsies is necessary if breast cancer is indicated or suspected in such cases. Of the performed breast biopsies, about 60–80% [23] are negative breast cancer or have benign lesions. In these cases, breast biopsies are considered unnecessary. This has led many breast cancer experts to propose complementary imaging modalities to provide additional diagnostic information and reduce unnecessary breast biopsies.

Ultrasonography (US) uses high-frequency acoustic waves that reflect at boundaries with different acoustic properties. It is a non-invasive technique, easily available and relatively cheap. Breast US provides unique information in assessing both palpable and non-palpable breast abnormalities. For instance, it clearly differentiates between solid masses and cystic lesions [24]. It is also considered to be useful in cancer staging, measuring tumour sizes, easy accessing lesions located in peripheries and reducing the number of unnecessary biopsies. It allows accurate needle placement during biopsy and is very useful for aspiration of cysts. The members of the European group for breast cancer screening recommended using US as a complementary method to X-ray mammography. In addition, the use of high-frequency transducers has improved spatial resolution and thus claimed to be useful in axillary node evaluation. However, breast US technique is time-consuming and operator/observer dependent. It has also a number of other limitations that may be due to overlapping in sonographic characteristics. For instance, it cannot detect calcifications (micro-calcifications or macro-calcifications) in DCIS. It could also miss solid lesions especially in a fatty breast and if detected cannot determine whether a solid lump is benign or malignant. For these reasons, US is not used as a screening technique for asymptomatic breast cancer as it is difficult to ensure that the entire breast has been scanned.

Magnetic resonance imaging (MRI) images are created by the recording of signals generated after radio-frequency excitation of nuclear particles exposed to strong magnetic field. Breast MRI is a non-ionizing tomographic functional technique that may be used when the diagnosis is uncertain with mammography [25]. The technique is valuable for specific clinical indications such as patients with (1) axillary adenopathy (enlargement or inflammation of the lymph gland), (2) possible tumour recurrence after surgery or radiotherapy, (3) lesions overlying implants or (4) those requiring staging of multifocal carcinoma (two or more discrete lesions in one breast) [26]. Breast MRI with dedicated breast coil has excellent soft tissue resolution that enhances the ability to both identify the location and in some cases determine the full extent of the lesion. The use of intravenous contrast agent, gadolinium, which accumulates in tissues with a dense blood vessel network, has also increased the sensitivity of breast MRI [13]. However, the reported specificity (ability to determine if lesion is benign or malignant) is 56–72% [27]. This technique has a limited application in patients with implanted metal devices or other metallic materials inside the body. MRI cannot also differentiate between inflammatory breast cancer and abscesses. In addition, several clinical limitations have been reported in the literature suggested not to use MRI in premenopausal women. For example, changes that do occur in the T1 value of the breast tissue during the menstrual cycle [13] mean that patients should be scanned between the 6th and 16th days of the cycle. In summary, researchers have concluded that breast MRI is limited by lack of availability and inconsistent quality, and the technique is too expensive for routine use in breast cancer screening.

The need to improve the breast cancer detection and to reduce the unnecessary invasive breast biopsies has stimulated researchers to investigate functional imaging modalities. These techniques produce a range of different imaging approaches such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), planar imaging and dedicated imaging instrumentation with and without breast compression. These imaging techniques of the breast potentially over additional information in breast cancer diagnosis. This is because these imaging methods rely on the physiological and biochemical characteristics of a lesion. Thus, they are considered as the best hope to differentiate between benign/normal and malignant diseases. These functional techniques have also been used to assess and monitor the effect of cancer prevention drugs. The current radionuclide imaging techniques used for breast tumour imaging are briefly discussed.

In PET a small amount of positron emitter radio-tracer, 18fluorodeoxyglucose (FDG), is administered intravenously to the patient [27]. It is then distributed in the body, and as it decays, the radionuclide emits a positron in any random direction. If the positron whilst travelling interacts with an electron within the body, the two particles then annihilate and produce two rays of 511 keV each. Either a whole-body scanner or a breast-specific positron emission mammography (PEM) camera [28] is used to detect the two gamma-rays in coincidence (two events that are detected within ~ 12 ns). PEM is increasingly used in North America not only in cancer diagnosis but also in staging, planning and monitoring anticancer therapy. This information can be helpful not only in eliminating unnecessary axillary dissection [29] and biopsies but also in determining the appropriate treatment. The diagnosis of viable tumour tissue following chemotherapy is another application of PET [30, 31]. Imaging with 18F-FDG has shown considerable promise in breast cancer imaging, but the exact role is

still in evolution. Wahl [32] recommended that it is best applied to solve difficult clinical cases in specific patients rather than routinely. There are a number of reasons that limit the wide use of PEM for routine cancer diagnosis: (1) the high cost (over \$2 million) of PET coincidence imaging equipment, i.e. cyclotron, scanner and radiochemistry facility [27]; (2) the difficulty of producing and labelling the short half-life PET radionuclides [28]; (3) the lack of centres with the required experience to develop more advanced methodology appropriate for breast oncology—in particular, more data are needed about the metabolism of different PET radio-pharmaceuticals in breast tumours—and (4) the lack of oncologists with a high knowledge of PET methodology [32].

Scintimammography (SM) is a promising non-invasive functional imaging technique. It has been proposed to complement X-ray mammography and to improve patient selection for biopsy. This single-photon imaging of the breast involves injecting the patient in the arm vein with a small amount (555–740 MBq [33]) of radiopharmaceutical. The most commonly used radiopharmaceutical for SM is $^{99m}$Tc labelled Sestamibi. After a period of time, the tracer distributes in the breast tissue as well as in the body organs. It accumulates more in the target object (lesion) with uptake ratio nearly 9:1 tumour-to-background ratio (TBR) [43]. A standard full-size clinical gamma camera is then used to scan the patient and thus measure the 3D distribution of the radioactivity. SM imaging using full-size clinical camera includes a range of different imaging approaches such as planar (2D) imaging or SPECT technique. The latter technique gives a 3D representation image but is not widely used because it is difficult with this technique to accurately localize the lesion [40]. In contrast, planar SM is the technique that is more widely used in clinical practice because it provides better lesion localization particularly the prone images with lateral views [34]. In this case the gamma camera is usually equipped with a LEHR parallel-hole collimator, and two views (prone and supine) are taken to the diagnosed breast. Since the energy imaged is 140 keV representing the photo peak, 20% energy window (symmetric ~10%) is often used and thus centred over the photo peak.

In brief, SM with a general-purpose camera has been introduced to evaluate patients with dense breast prior and in a least case after breast biopsy [35]. The technique may also be considered valuable for many clinical applications such as evaluating the axillary lymph nodes, investigating patients with microcalcifications [36], assessing multifocal and multi-centric breast cancer diseases [37]. It is also useful for imaging patients following surgery, chemotherapy, hormonal replacement therapy and radiotherapy as well as for patients with breast implants [34]. The technique may also assist in the differentiation of benign and malignant breast abnormalities by measuring radio-tracer uptake in the lesions as compared with surrounding breast tissues. Studies such as [38, 39] suggested that SM may be used as a second-line diagnostic test in cases where the sensitivity of mammography is decreased or there is doubt about the presence of lesion. In summary, SM using conventional camera may be considered as a useful complementary imaging modality to aid the diagnosis and the detection of breast cancer [40]. It may also help to assess in patient selection for biopsies, and this may reduce the number of unnecessary or negative breast biopsies. However, the major drawback of the current standard clinical gamma camera SM imaging systems is the use of mechanical collimator. This causes the camera imaging system to utilize a very small fraction, ~0.01%, of the total number of the emitted photons. This limits the statistics

and hence the quality and diagnostic value of the observed images. The collimator sensitivity and resolution are a trade-off, and the camera is also limited by its intrinsic spatial resolution. As a result, these factors make it difficult to practically image cases of smaller, non-palpable, lesions (<1 cm) that may be deep seated or those close to the chest wall. These have stimulated the development of new dedicated (breast specific) instrumentations that are used for breast tumour imaging applications.

Recent years have seen considerable interest by scientists in developing new compact medical imaging detectors. These instruments were proposed for different clinical applications with the aim to improve image quality by building cameras of suitable size and shape for the part of the body under investigation. Among these designed detectors is the small dedicated gamma camera for functional breast tumour imaging. The justification for this development is that a standard full-size clinical gamma camera is designed for whole-body imaging and, thus, has not been optimized for breast tumour imaging. In other words, there are a number of shortcomings with such general-purpose gamma camera such as the limiting sensitivity (on average 50% [41]) for lesions <1 cm such as DCIS particularly the medially located tumours. In addition, several studies have pointed out that due to the large FoV of the camera and the bulky collimators, it is difficult to position the camera close to the breast, and thus, imaging breast tissue adjacent to the chest wall may not be possible. This may, ultimately, decrease the spatial resolution of the camera imaging system and thus affect the diagnostic value of the test in detecting such a small lesion size.

To overcome some of the limitations offered by conventional gamma camera on breast imaging, Gupta and colleagues [42] reported the first preliminary clinical data that are performed with breast-specific detectors and then compare it with the data obtained from standard full-size camera. A limited number of patients were investigated in this study but interestingly reported a higher sensitivity for the dedicated camera. Following this and due to the large research activities, new generation of detectors has been designed and developed for breast tumour imaging, for instance, the position-sensitive photo-multiplier tubes (PSPMT), semiconductor arrays and scintillation crystals coupled to an array of solid-state photo detectors.

The commercially available dedicated breast camera has two detectors and is designed and optimized to image only the breasts. It possesses a high intrinsic spatial resolution, and the camera is also equipped with ultra-high-resolution parallel-hole collimator and thus optimized for high-resolution SM. The main advantage of such cameras is the ability to separate the breast from the chest wall by positioning the camera close to the breast. Thus, the camera can be used in areas with limited space (e.g. medial view can be possible), where the use of a full-sized camera is impractical or impossible. The use of moderate breast compression capabilities may improve both the signal-to-nose ratio (SNR) and the spatial resolution [43] and thus increase the sensitivity for detecting smaller lesions. The proposed clinical indications for such dedicated cameras are similar to the full-size clinical gamma camera SM. There are some recent clinical studies associated with using these dedicated gamma cameras. For instance, a clinical preliminary study by Brem et al. [44, 45] using dedicated breast camera demonstrated a slight improvement in resolution and tumour sensitivity particularly for lesions~ 1 cm. Rhodes and colleagues reported [46] on SM performed on 40

women with small mammographic abnormalities (<2 cm) scheduled to undergo biopsy. The SM examination identified (33/36) malignant lesions confirmed at biopsy. The authors concluded that this preliminary study suggested an important role for the dedicated SM camera in women with dense breasts. In another study Brem and colleagues [47] evaluated 94 women (median age 55 years) presented with normal mammographic and physical examination results but all considered at high risk of developing breast cancer. Of these women 35 had a history of previous breast carcinoma or atypical ductal hyperplasia. The authors concluded that with this camera, they can depict small (8–9 mm) non-palpable lesions in women at high risk of breast cancer.

In summary, whilst these studies using breast-specific cameras are promising, all are considered preliminary in nature because they based on very few cases. Additional studies with a larger sample size are needed to accurately assess and reach scientific conclusions concerning these proposed cameras. They also need to be cost competitive with the general-purpose gamma cameras in order to be widely used in breast tumour imaging applications. In addition, the smallest lesion sizes that can be detected with these cameras claimed to be 3–3.3 mm [48] compared to 4–5 mm [49] with conventional camera. However, the evidence published to date did not demonstrate a statistically significant difference in lesion detection. The spatial resolution of these proposed cameras may further improve by increasing the pixel size, but there are however practical limitations in the development of cameras with small pixel sizes, including cost and detector design. More importantly due to the use of collimator, these dedicated cameras suffer from low detection efficiency. Nowadays, the latest revolution in the mammography field was announced by Dr. Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health, said on Friday, February 11, 2011 "Physicians can now access this unique and innovative 3-D technology that could significantly enhance existing diagnosis and treatment approaches". In addition, the US Food and Drug Administration approved on Friday the first X-ray mammography device that provides three-dimensional images of the breast for cancer screening and diagnosis.

### 3.1. Image reconstruction techniques

Screening and diagnostic mammography suffers from the limitation that the complex 3D breast structure is projected into a plane. Thus, lesions can be obscured by overlaying and underlying tissue structures which could cause a false negative, or dense overlapping tissue can mimic lesions, leading to an unnecessary recall of a patient. The proposed solution is 3D breast tumour image reconstruction techniques such as digital breast tomosynthesis (DBT) which is an emerging modality that produces 3D breast images. In DBT, lesion conspicuity is improved, which could potentially lead to earlier cancer detection and a more accurate diagnosis. In tomosynthesis, a volume image is created from a sequence of projection views acquired over a limited arc. Reconstruction from this data is challenging because the data is inherently incomplete. One-shot algorithms such as filtered back projection (FBP) have been developed for DBT image reconstruction. Though efficient, they tend to yield conspicuous artefacts. Iterative algorithms such as expectation maximization (EM) have also been employed with DBT. Such algorithms sacrifice efficiency but yield images with fewer

artefacts. An additional drawback for EM, however, is that in general some form of regularization is needed which tends to reduce resolving power necessary for calcification detection.

## 3.2. Design details and preliminary results

### 3.2.1. Design details

The experimental system consists of a general radiography tube pointing at a given distance from the central axis of the breast. Four flat-panel digital detectors will be used to collect all the photon information (energy, flux, position) scattered by the phantom breast covering all possible area around it. The patient would lie on a table in the prone position with one breast drawn downwards through an opening to allow the X-ray tube and detector flat panels to be safely placed beneath the table (**Figure 1**).

During one irradiation of such phantom, we will investigate all the collected data to reconstruct the image in a 3D framework.

### 3.2.2. Preliminary results

As an illustrative example to indicate whether the proposed idea will work, we simulated a semi-spherical breast phantom including two air-filled cavities, irradiated with $10^8$ photons. The photon energies imitate the standard spectrum of the commonly used X-ray source in mammography case studies. Monte Carlo sampling of the X-ray generator (30 kVp, Mo anode, filter 0.03 mm Mo and 1 mm Be) was carried out using the inverse cumulative method
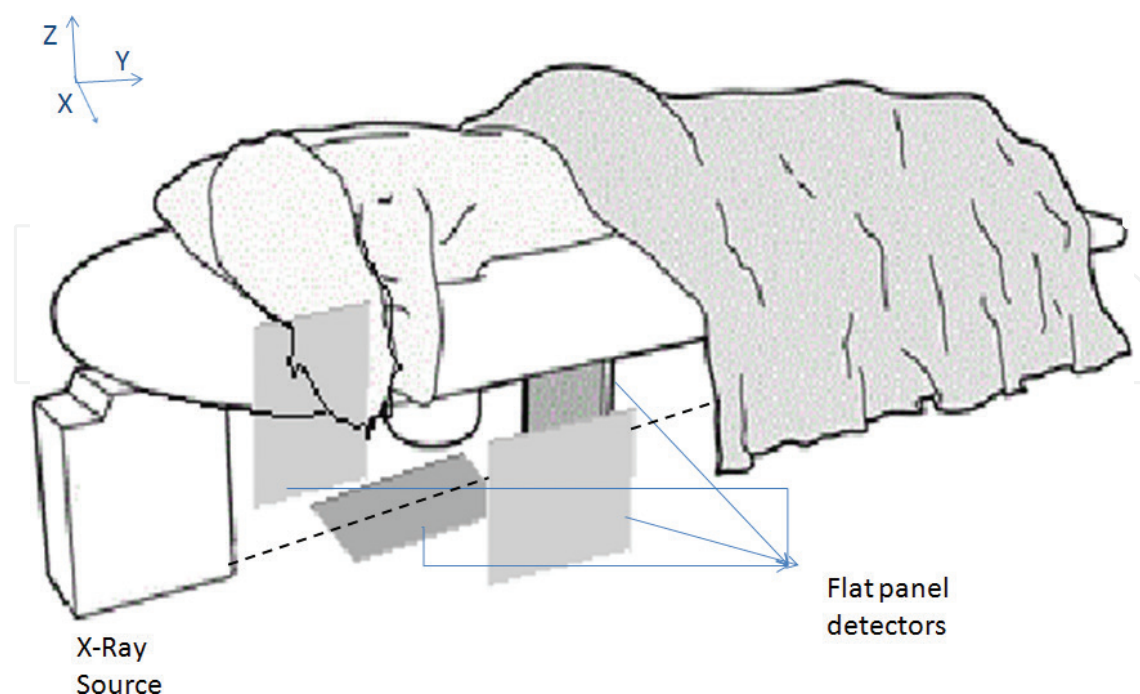


**Figure 1.** Schematic view of proposed setup design. Patient lies prone with one breast drawn downwards through opening in scanning device.

starting from experimental data sets. **Figure 2** shows the phantom (magenta colour) including two cavities (yellow) and surrounded with four flat-panel detectors (white). The two other faces contain the chest and the source beam zone.

The important data given by the scorers (flat-panel detector) numbers 2, 3 and 4 will contribute significantly on the final 3D image reconstruction process. **Figure 3** demonstrates how important the scattered photon statistics are for the given simulated setup.
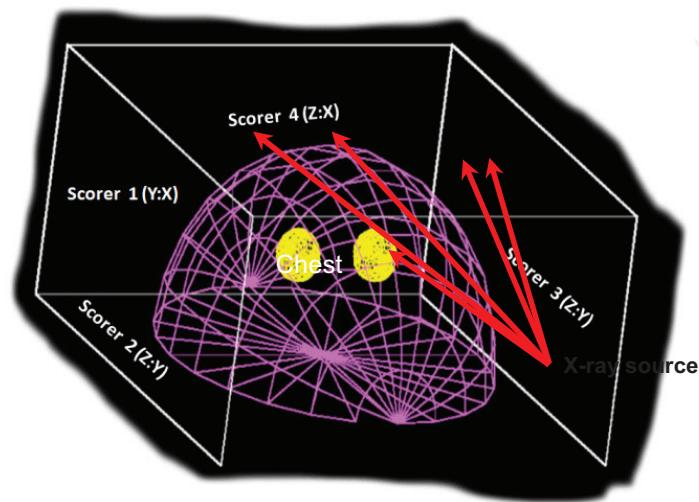


**Figure 2.** Simulated setup including the breast phantom (magenta), air cavities (yellow), X-ray photon (red) and the four scorers.
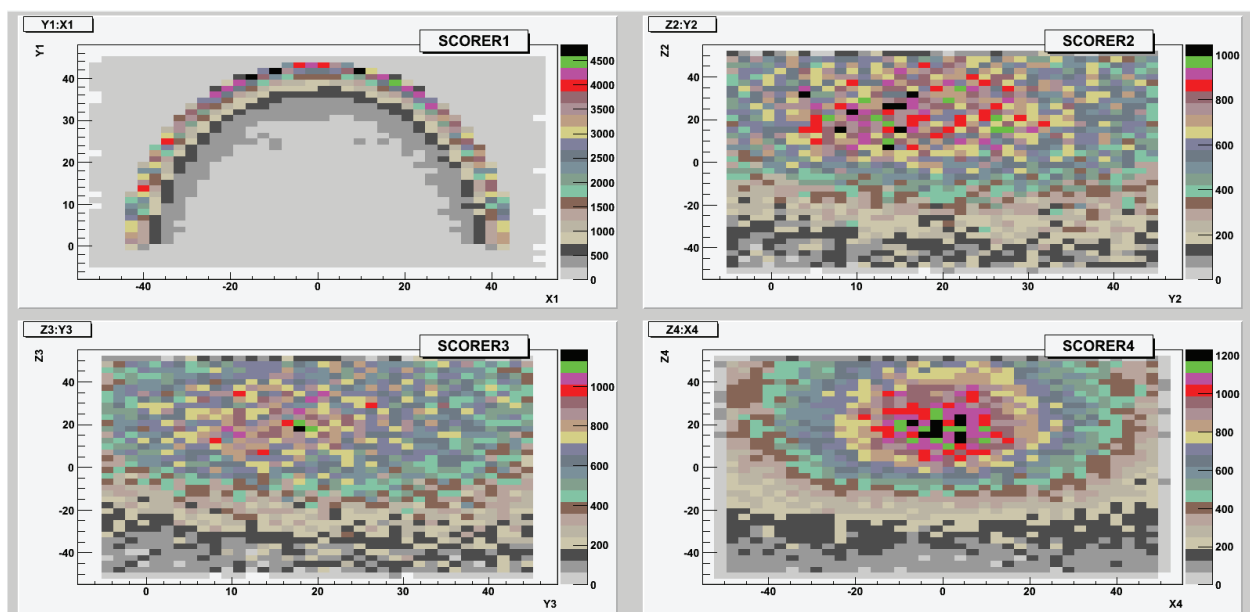


**Figure 3.** Simulated deposited energy using Geant4 Monte Carlo simulation toolkit for the four scorers. Bar scale indicates the specific magnitude of deposition.

Therefore, the goal of this project is to overcome all of the above limitations by providing a proof of concept for painless 3D mammography to be used as a screening and as diagnostic methods after commercialization. The proposed prototype includes (1) the detection system, which will be a set of semi-conductor arrays spatially distributed around each breast; (2) the X-Ray source; and (3) the convenient patients' test bed for painless exposition to X-rays. For that purpose, the first phase of the proposed project will focus on a versatile and widely used Monte Carlo simulation tool, Geant4, to optimize the detector arrays' chemical composition (CdZnTe, GaAs, etc.), spatial positioning around patient, source characterization (energy, spatial localization) and also the test-bed geometry to mainly fulfil the two conditions of radiation protection and painless positioning.

Secondly, we will use an iterative reconstruction algorithm to reconstruct the images of a mathematically breast phantom using the cluster network technique. Then, the experimental construction of the overall design will be carried out. Finally, the use of anthropomorphic breast phantoms to check the effectiveness prediction of the simulation will resume the project phases. Since most imaging modalities required a wide spectrum of capabilities which span biomedical sciences and physical sciences and clinical medicine, thus this project will be a collaborative cross-disciplinary research engaging together with scientist in universities and clinician in hospitals. Consequently, this proposal has the potential to score some successes in clinical imaging science. The project outputs will include the creation of a numerical platform able to more understand the breast disease problems and the development of an innovative prototype for painless breast imaging within a 3D framework. These allow the large communities of researchers and doctors to improve the breast imaging process and to build and to share some knowledge and experiences within that context. As a result, some international and national publications will be submitted to well-recognized journals.

Based on the assessment of current prevalence and projected incidence of diseases, cancer has been selected as medical and health-priority area for strategic intervention by the National Medical and Health Research Strategic Priorities (NMHRS) for the Kingdom. It is classified as a non-communicable disease [1]. Within that context, breast cancer is the second leading cause of cancer deaths in women today. About 1.3 million women are diagnosed annually worldwide, and about 465,000 will die from the disease. Incidence and mortality have reached a plateau and appear to be dropping in both United States and parts of Europe [1]. This decline has been attributed to several factors, such as the early detection. Despite the relatively low incidence in Saudi Arabia compared to other countries, breast cancer has been the most common cancer among Saudi females for the past decade (Saudi Cancer Registry, 1994–2005). The most concerned patients were aged between 40 and 50 years old. For that, a breast cancer screening programme will help all the female population, including the young one (having dense breast), for early detection and prevention advices.

So, the potential positive impacts on the economy and society of the current project are well defined in terms of decreasing the enormous burden to the healthcare-utilization costs.

Furthermore, the expertise to be developed through this project will be applied to the review of new digital radiographic imaging systems, the development of amendments to the diagnostic X-ray performance standard, the development of an advisory pertaining to national

public breast cancer screening programmes and the joint planning of a consensus development conference on the 3D X-ray imaging modality with the King Saud University.

Also, investigating the computer-assisted diagnosis devices will provide the Kingdom with the scientific basis to effectively regulate this fast-growing field. In addition, this project may provide powerful tools of a commercial value for X-ray imaging application, especially with the development of such prototype, including the detectors, the source and the patient bed, that will meet to a 3D painless mammography.

Another benefit of such project concerns the supervision of two master's students and to create a locally competent talent capable of conducting novel medical and health sciences research. The creation of an infrastructure that supports and enables further research, in such medical field, will be an extra added benefit to the College of Applied Medical Sciences and to the King Saud University. The development and the setup of cooperative agreement by establishing collaborative research with advanced institutions such as the CERN and the University of Surrey will contribute to the technological opportunities transferred from over the world. Finally, the proposed project should participate in increasing national scientific discovery and productivity through promotion by publishing in peer-reviewed and reputable journals.

## 4. Valuable to the Kingdom

Based on the assessment of current prevalence and projected incidence of diseases, cancer has been selected as medical and health-priority area for strategic intervention by the National Medical and Health Research Strategic Priorities (NMHRS) for the Kingdom. It is classified as a non-communicable disease [1]. Within that context, breast cancer is the second leading cause of cancer deaths in women today. About 1.3 million women are diagnosed annually worldwide, and about 465,000 will die from the disease. Incidence and mortality have reached a plateau and appear to be dropping in both United States and parts of Europe [1]. This decline has been attributed to several factors, such as the early detection. Despite the relatively low incidence in Saudi Arabia compared to other countries, breast cancer has been the most common cancer among Saudi females for the past decade (Saudi Cancer Registry, 1994–2005). The most concerned patients were aged between 40 and 50 years old. For that, a breast cancer screening programme will help all the female population, including the young one (having dense breast), for early detection and prevention advices. So, the potential positive impacts on the economy and society of the current project are well defined in terms of decreasing the enormous burden to the healthcare-utilization costs.

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