Synchrotron X-ray Radiation in Medical Imaging

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Synchrotron X-ray radiation (SXR) has been widely studied to explore the structure of matter. Recently, there has been an intense focus on the medical application of SXR in imaging. Synchrotron X-ray radiation source provides many useful features (e.g., high intensity and collimation, a wide range of energy spectrum, option to use monochromator to select narrow beam of the desired energy, etc.). However, because of its high cost, it has still found limited applications in routine clinical and laboratory uses. With the advancement in other disciplines, specifically, the advancement in generating synthetic images from one modality to another modality using deep learning could be adapted to generate SXR images provided that a conventional X-ray image of the object is available. A photon-counting detector (PCD) can further improve the signal-to-noise ratio and soft tissue contrast by detecting scattered photons while using the monochromatic energy provided by the SXR. A combination of the computational advancement of different disciplines with the physical capabilities of the SXR can make high-resolution SXR-based medical imaging affordable and cost-effective, especially for in vivo microstructure and cellular level studies.

synchrotron X-ray radiation | medical imaging | deep learning

1. Introduction

Synchrotron X-ray radiation (SXR) has a variety of features that compete with conventional X-ray imaging in the field of research with direct and indirect clinical advantages, from having a tunable monochromatic beam to an inherent coherent self-collimated X-ray beam, over a wide range of energies [1].

The process of image formation in conventional radiology depends on the absorption and transmission differentiation of the primary X-ray beam, part of the X-ray beam is absorbed while the rest is transmitted through different organs and tissues. As the body consists of different tissues with different physical properties (e.g., thickness, density, atomic number, etc.), the beam is subjected to different attenuation as it travels, and an attenuation map is formed at the detector representing an image contrast of the anatomic area of interest [2]. The unavoidable limitation of this approach is the low flux available in the standard poly-energetic X-ray imaging system, poor detection of signals passing through the soft tissue. Because of these reasons, the poor soft tissue contrast provided by the system eventually affects the pathologic diagnosis and can only be conclusive with biopsy confirmation. Furthermore, the non-useful low energy of the conventional X-ray beam needs to be filtered out for two important reasons: (1) to reduce the amount of X-ray dose to the patient and (2) to reduce the scattering effect which is a prime source of reduction in contrast and signal to noise ratio (SNR).

On the other hand, synchrotron generates very high flux of SXR. Such high flux enables the selection of a narrow energy band from a full radiation spectrum, which allows researchers to characterize the structural and functional process of many diseases (e.g., breast cancer, lung disease, etc.) [3].

2. Breast Cancer

Breast cancer patients' survival rate highly depends on its early diagnosis. Breast cancer was found to be the second most common type of cancer-based on its fatality rate. This rate is expected to drop from second to fourth, based on a projected decline in fatality rates in 2017 [4]. The main reason for this expected decline in fatalities among breast cancer sufferers is the huge investment over the years in research and development in diagnostic technologies specifically targeting breast cancer. Conventionally, traditional imaging modalities such as X-rays, magnetic resonance imaging (MRIs), and ultrasounds have been the standard diagnostic tools utilized in detecting breast cancer. These imaging technologies obtain such high resolutions that accurately localize the lesion inside the tissue. For instance, 3T MRI machines are capable of resolving details as small as 1 millimeter, and that resolution can be improved to 0.5 millimeters in a 7-T machine. Emerging optical imaging techniques such as diffuse optical imaging and photoacoustic are noninvasive medical imaging techniques capable of providing functional information of the tissue [5][6]. However, the limited spatial resolution (around 1 cm) of these techniques is a challenge that usually is tackled by optical Imaging techniques with traditional X-rays, MRI, or ultrasound modalities [7][8].

New screening techniques which improve the sensitivity and specificity of current diagnostic modalities are needed to recognize women with early stage diseases. A recent study highlighted that propagation-based phase-contrast computed tomography (PB-CT) with synchrotron radiation (Australian Synchrotron (Clayton, Melbourne, Australia)) can provide significantly better breast cancer diagnosis accuracy with a similar level of exposure to the radiation [9]. A mastectomy sample from a 60-year-old woman was used for the investigation.

For breast cancer patients, different abnormal features of hair have been identified, such as the upgrowth of lipids and medulla loss of the patient hair are all potential biomarkers for screening of breast cancer. Hair samples from breast cancer patients were collected for determining diffraction patterns and results showed a new circular feature in a specific area of 4.6 angstroms. The observed samples were then identified ad positive and negative. The positive ones had a circular feature of 1.32

0.02. Synchrotron X-ray diffraction experiments were performed on the small-angle X-ray scattering—wide-angle X-ray scattering (SAXS-WAXS) beamline at the Australian Synchrotron, Melbourne. A MAR165 detector was used for the alignment of the sample and also for data collection. Diffraction patterns were analyzed using FIT2D and Saxs15ID. Synchrotron X-ray sources at the Advanced Photon Source (Argonne National Laboratory) were used on two beamlines BioCAT and ChemMatCARS. The beam size was 100 μm in the horizontal direction and 50 μm in the vertical direction. Two dimensional diffraction patterns were obtained investigating three or more samples of each species on each of these beamlines. The dimension of the pixel of the image plates was 0.1 × 0.1 mm [10][11].

Another group has utilized synchrotron X-ray nanoscopic 2D/3D imaging to investigate the structural variation for hair strands of breast cancer patients during cancerous progression and healthy individuals. Theoretically, a 30% efficiency was expected from this method. The first-order focal length was 40 mm at 6.78 KeV. The field of view was typically 110 lm diameter, with a resolution of 100 nm. A thin (18 lm) LSO: TB scintillator crystal (FEE, Germany) with a 10 lm diameter and a 203-lens handmade optical microscope make up the detector. A charge-coupled device with 203 objective lenses (Zeiss) made up the microscope. Each pixel on the CCD is 4096

4096 pixels of 9 lm size. A holed aluminum-film phase plate with a diameter of 3.78 mm was used for Zernike phase contrast. Data from nanotomography were collected using the same setup as previously described. Each specimen was rotated in place on a computer-controlled precision stage with an interval of 0.5 increments through 180, 0.5 s exposure duration per projection for data collection [12]. Nanoscopic projection and CT scanning of the hair samples were accomplished by a monochromatic synchrotron X-ray at the Pohang Accelerator Laboratory. There is a high correlation between the medulla loss demonstrated by the structural variations of the high-resolution synchrotron X-ray and the cancerous progression. The medulla loss is also age-dependent, which imposes a challenge to the accuracy of this technique. Recently, scientists have started looking for a more compact and cheap method to the high-resolution synchrotron X-ray imaging to image the internal structure of the hair. The healthy hair samples were undergone nanoscopic projection and CT scanning using a monochromatic synchrotron X-ray (6.78 keV) at the Pohang Accelerator Laboratory (PAL) 7C beamline. Reconstruction pictures of tomography data were created by utilizing the OCTOPUS software package to apply a filtered back-projection method on the projection image [13]. Notably, researchers developed cheap near-infrared microscopy (NIRM) to achieve a comparable high spatial resolution of the monochromatic synchrotron X-ray imaging. The developed NIRM was able to detect complete medulla loss (CML) per hair strand at (60.9 ± 10.2%) ($p < 0.001$) in the hair of all cancer patients than in the hair of either healthy individuals (less than 3.7 ± 7.5%) or those with benign disease (30.6 ± 5.9%). The method is based on photons scattering contrast between medulla and cortex tissue of hair.

3. Coronary Angiography

One of the approaches of synchrotron radiation in the field of cardiovascular studies is SR microangiography, which is suggested to be used as a substitute for conventional angiography. SR microangiography performs high contrast imaging of microvessels in milliseconds with an enhanced image resolution and clarity compared to conventional angiography. The two approaches that vary in using SR angiography include (1) K-Edge subtraction angiography (KES) and (2) single energy temporal subtraction angiography. These two approaches vary in the case of imaging area and the way of achieving optimization of the vessel image contrast. In KES, an iodine contrast agent is used in the blood which absorbs X-rays, and an image is produced subtracting the low energy image from the high energy image created from just below and above the K-Edge energy, respectively, using narrowly separated line detectors. In the second approach of single energy temporal subtraction, images are produced using single energy of SXR just above the K-Edge. An image without contrast is first subtracted, which helps to emphasize the contrast agent contained in blood vessels. Though it is well developed, complications and mortality (0.1–0.2%) are still there. Injection of the contrast agent into a peripheral vein could help in avoiding risks associated with arterial catheterization. However, the contrast gets diluted through the heart and lung before reaching the coronary arteries. The coronary arteries of rats were visualized with a big focal spot X-ray tube that delivered enough flux and exposure periods of 100 milliseconds with a finely tuned X-ray of 33.2 keV using a monochromator which is just above the iodine K Edge energy for maximum contrast. The absorbed X-rays in the pick-up tube's photoconductive layer are transformed immediately into electron-hole pairs, resulting in a video signal.

On the other hand, an SXR-based coronary angiography with intravenous injection and the KES method can provide details that can be suitable for diagnosing coronary disease. The advantage of SXR microangiography is the ability to study the microcirculation of small animals within their physical milieu as it can visualize the coronary and pulmonary microvessels within the intact chest wall of the animals. This approach was not possible before with conventional X-ray systems.

Another application of SXR in coronary angiography is transvenous angiography. In this method, chronography of iodine is used in which K-edge of iodine is enclosed by two monochromatic X-ray beams. The final image is produced by the logarithmic subtraction of the images created by the beams. The advantages of this method are that the signals arising from attenuation of iodine are enhanced and the signals arising from attenuation of soft tissue and bone are suppressed. The X-ray dose used during SXR angiography is comparatively less than conventional angiography and requires significantly less patient exposure. It is assumed that with additional experience, fewer frames will be needed to be recorded during transvenous angiography [14]. The electron beam which is used in the experiment for transvenous coronary angiography has a 3.0 GeV energy and a 40–80 mA current. The beamline IV-2, which was used in these tests, is lit by an 18 kg wiggler with eight poles (1 gauss = 1 × 10−4 Tesla). The transmitted X-rays impinge on the 300 sensitive elements of a Si (Li) linear detector after passing through the subject. The center-to-center spacing of detector components is 0.5 mm, and the beams' height is 0.5 mm, hence the system's pixel resolution is 0.5 mm × 0.5 mm.

4. Imaging Lung Ventilation

A recent study demonstrated that dual-energy KES CT imaging with SXR is capable of generating morphological and regional ventilation images along with quantitative regional maps of deposition of iodine-containing aerosol particles (after 5 and 10 minutes of aerosol administration) [15]. Acquisition of lung morphology, regional ventilation along with the quantitative information of regional aerosol particle deposition using single modality was never achieved before. The study was carried out on six rabbits with normal lung (n = 6) and six rabbits with asthma model (methacholine (MCH)-induced bronchoconstriction).

5. Bone and Joint Imaging

SXR has been used in bone research to analyze bone aging, disease, and factors that affect bone fragility and resistance. SXR micro CT is considered powerful as it features both biological mechanisms and control of bone quality. It can quantify thousands of lacunar volumes in 3D, which is followed by quantification and visualization for controlling matrix mineralization. All of these result in a change in bone quality and toughness. SR micro CT has shown effective results in the following bone-related studies.

5.1. Microstructural Features

Bone cells osteocytes, connected with one another and with the vascular network with the dendritic process, are studied using SXR micro CT. The parameters investigated in these studies are vTMD of bone and lacunar volume, density, and orientation [16]. The mechanical characteristic of the bone metal implant interface has been investigated using SXR. When compared to lab X-ray sources, synchrotron radiation with a high flux photon beam allows for higher resolution and faster imaging times. Shorter exposure times are particularly appealing for in situ loading investigations that require multiple repeated scans because they reduce the total duration of the test. This reduces the amount of drying of the test specimen (maintaining mechanical qualities) and sample relaxation during each scan (thus enabling tests that are more comparable to standard tests)

With a 3.6 m isotropic voxel size, samples were subjected to in situ pullout utilizing high-resolution synchrotron X-ray tomography at the Tomcat beamline (SLS, PSI, Switzerland) at 30 keV with a 25 ms exposure duration, resulting in a total acquisition period of 45 s per scan. Screws were pushed out at 0.05 mm increments using a custom-made loading mechanism positioned inside the beamline, acquiring several images until the sample ruptured. The field of view (FOV) of the detector was 2.8 × 7.2 mm^2 (height × width) [17].

5.2. Crack Propagation

The 3D images found from synchrotron radiation micro CT show the size and distribution of Haversian canals, which are significantly higher in aged bones. Different bone diseases affect crack deflection and toughness. SXR micro CT, in combination with other methods, is used to analyze the mechanism of toughness. Crack-tip stress field determined at the center of a 12 mm-thick CT test piece by synchrotron X-ray diffraction at $K_{I,max}$ (13.2 MPa√ m) for an ultrafine-grained (<1 µm) AA5091 Al alloy. A 25 × 25 µm gauge cross-section was used [18].

5.3. Mineralization

In an analysis of the SR micro CT bone research data, a shift in the peak of vTMD is considered a change in mineralization. The mineralization parameters provide effective information about the disease and genetic modification of the bone matrix. SRnCT is a strong technology for 3D visualization of bone ultrastructure, with an exceptional resolution of 30 to 100 nm. However, the FOV, and thus the sample size, are reduced. For example, a 0.15 × 0.15 mm^2 area FOV is implied by an SRnCT scan, equating to a 0.15 mm (height) 0.15 mm (diameter) cylindrical volume. Synchrotron light sources commonly attain resolutions of 30 nm to 0.5 m using visible light optics or X-ray optics such as zone plates and compound reflective lenses. [19].

5.4. Incudostapedial Joint

Synchrotron-radiation phase-contrast imaging (SR-PCI) was used in visualizing the ultrastructure of the incudostapedial joint (ISJ) of the middle ear at submicron voxel size. For each sample, a total of 900 projections spanning 180° of rotation were acquired, covering a total 3.6 mm × 2.4 mm field of view throughout the sample. Total scan time per sample was 2 h with exposure times ranging from 400 to 600 milliseconds per frame and four-frame averaging for a projection using X-ray energy of 30 keV. Each sample was placed 0.16 m away from the detector and the source-to-sample distance was 55 m [16].

5.5. Organ to Cellular Scale Imaging

A hierarchical phase-contrast tomography (HiP-CT) has recently been proposed. The technique is based on the X-ray phase propagation and carried out using the European Synchrotron Radiation Facility (ESRF)'s Extremely Brilliant Source (EBS) [20]. HiP-CT made it possible to image the excised intact human organ (brain, lung, heart, kidney, and spleen) from organ to the cellular scale with a minimum of 1.3 μm voxel size.

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