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Pushing the frontiers of x-ray imaging

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ABSTRACT One of the major challenges in x-ray imaging is to reveal microstructural information from high-contrast and high resolution images. In this article both x-ray microscopy and phase-sensitive x-ray imaging will be introduced. X-ray microscopy or microradiography have been providing information complementing that obtained from optical and electron microscopy. Phase-sensitive x-ray imaging that can detect x-ray phase shifts within soft tissues show promise for biological and clinical applications. Three approaches to phase-sensitive x-ray imaging, namely interferometry, diffraction enhanced imaging and phase-contrast imaging will be reviewed. With the concomitant development in flat panel detector technology, real-time fluoroscopic imaging of live specimens for functional study becomes a reality. The frontiers of x-ray imaging are being pushed further.

(X-ray microscopy, Microradiography, Phase-sensitive x-ray imaging, Diffraction enhanced imaging, Flat panel detector)

INTRODUCTION

One of the major challenges in x-ray imaging is to reveal microstructural information from high-contrast and high resolution images. This is especially demanding for the inherently low contrast biological specimens. Another goal is to image the specimen in its living state.

New x-ray microfocal sources have been developed to push the limits of x-ray microscopy. Novel x-ray imaging techniques have been developed that explore the phase information as another useful source of contrast. [1] The development of monochromatic synchrotron radiation sources has opened up new applications in material science, biological science and medicine. [2]

SOFT X-RAY MICROSCOPY (MICRORADIOGRAPHY)

X-ray microscopy is a method of studying the microstructure of materials and biological tissue using microfocal x-ray source. This technique can provide information complementing that obtained from optical and electron microscopy. [3-5]

The technical advances in x-ray microscopy have been due to two factors: (i) development of microfocal x-ray source to produce low energy x-ray and monochromatic synchrotron x-ray source; (ii) high resolution detector (photographic emulsion of 2000 lines pairs/mm).

Typically microradiography is performed using low photon energy of less than 10 keV (correspond to wavelength ~ 0.1 nm). This is particularly important when radiographing biological specimens since specimen contrast is enhanced by the low-energy x-rays.[3] The setup for contact mode of x-ray microscopy is shown in Fig. 1.[6]

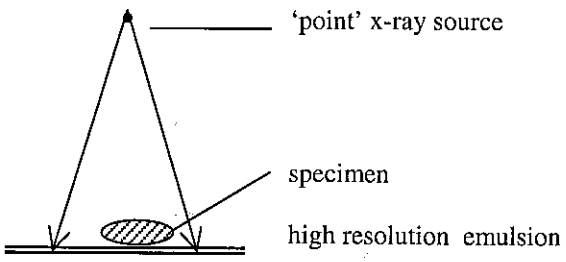

Figure 1. Contact mode x-ray microscopy.

X-ray microscopy is an ideal method of studying the internal morphology and development

changes in insects *in vivo*.[7] Some applications in entomology and botany are shown bellow. [8]

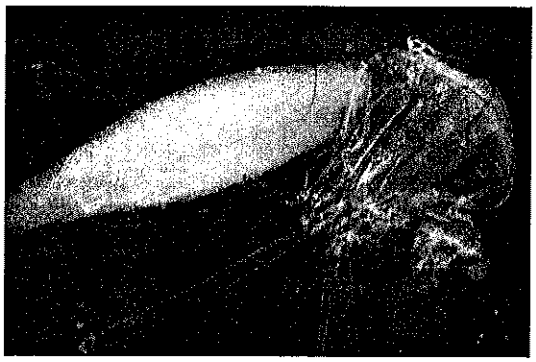

Figure 2. Microradiograph of Aedes Aegypti. (Courtesy Ng and Ng)

Figure 3. Microradiograph of an ant showing musculature morphology beside *Ascaris lumbricoides*. (Courtesy Ng & Ng)

Figure 4. Optically magnified section of an x-ray microscopic image from a shrub leaf *carmona retusa*. (15 kV, 15 mA, 30 min) x200 mag. (Courtesy of Ng & Ng)

X-ray microscopy of breast specimen has provided further insight into pathology. [3,6]

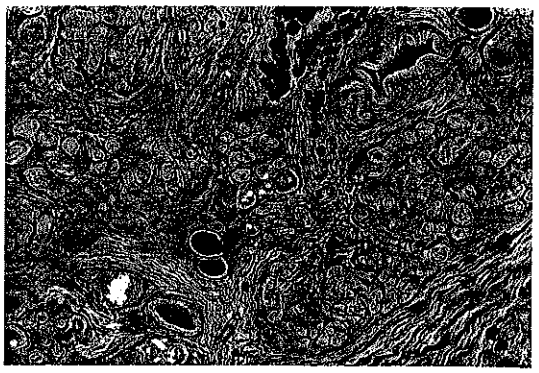

Figure 5. A freeze dried section of breast tissue 50 μm thick microradiographed in a helium atmosphere. x138 mag.

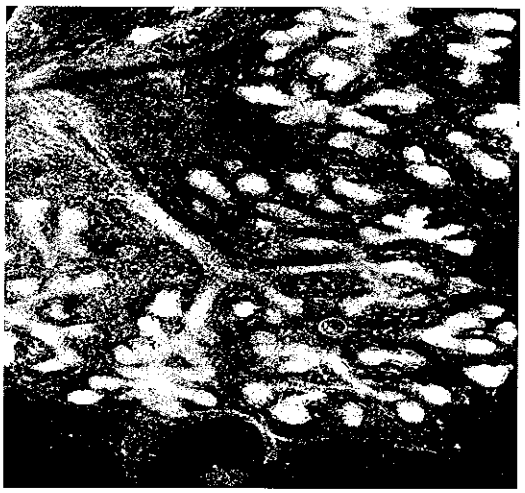

Figure 6. 100 μm thick moist breast tissue section of a terminal ductal lobular unit. [3]

Soft x-ray microscopy can deliver 30-nm resolution images of hydrated cells up to approximately 10 microns thick, and efforts towards obtaining higher resolution are under way. Although living specimens cannot be studied readily except in single exposures, fixed samples can be imaged at high resolution, and flash-frozen specimens can be studied without chemical modification and without significant radiation damage. Tomography is being developed for 3-D imaging, and spectro-microscopy offers unique capabilities for biochemical mapping of unlabelled structures beyond those of gold and fluorescent labels. [4]

PHASE-SENSITIVE X-RAY IMAGING

The basic principles of x-ray image formation and interpretation in conventional radiography

depends on x-ray attenuation as the main source of contrast. However phase-sensitive information offers another more useful source of contrast. Biological and medical research, especially for soft-tissue, will benefit from the development of phase-sensitive techniques. [1]

As x rays traverse through an object it can be described by the index of refraction $n = 1 - \delta - i\beta$, where β describes the absorption of x rays and the phase-shift term δ includes refractive effects. Note that n deviates only slightly from unity. We are exploring the use of phase-shift properties in x-ray imaging.

There are three approaches to phase-sensitive x-ray imaging: interferometry, diffraction enhanced imaging and phase-contrast imaging. Fig. 7 shows the schematic of these three approaches (courtesy of Physics Today).

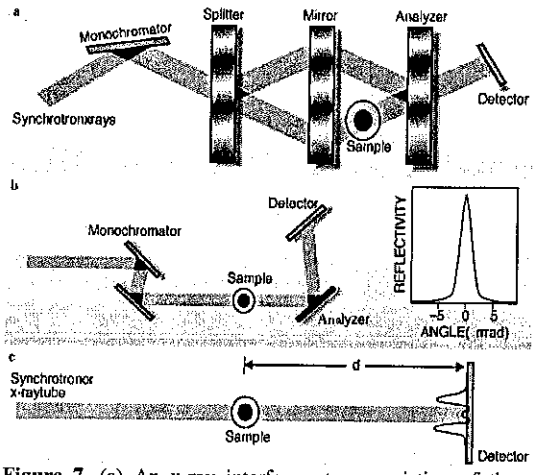

Figure 7. (a) An x-ray interferometer, consisting of three perfect crystals that serve as phase-coherent beam splitters and mirrors, generates interference fringes that reflect the phase changes produced in a sample placed in one of the beam paths. (b) In diffraction-enhanced imaging, variations in the refraction of x-rays in the sample produce contrast because the intensity of the beam that is reflected by the analyzer crystal depends on the relative angle of the incident beam with respect to the Bragg angle (inset). (c) In in-line phase-contrast imaging, the detector is placed sufficiently far behind the sample that wavefront distortions generated by the sample produce interference fringes at the detector. At an appropriate object-image distance d, these fringes yield edge enhancements in the image. [1]

X-ray Inteferometry

This old technique has recently been applied in clinical and medical settings. [9] Three matching perfect crystals, arranged in parallel as in Fig. 1a, function as an x-ray interferometer. The first crystal splits the incident x-ray beam after it has been filtered by a monochromator so that only the x rays of the desired energy are Bragg reflected toward the interferometer. The middle crystal acts as a mirror, sending the beams back toward each other. The beams meet at the third, analyzer crystal, which recombines them. [1]

A sample placed in the path of one of the beams between the mirror and analyzer will introduce phase shifts in that beam and distort its wavefront. Consequently, the recombined beams will generate interference fringes at an x-ray detector placed behind the analyzer. The fringe pattern will be sensitive to the phase shifts the probe beam experiences in the sample.

Because of its extreme sensitivity, the x-ray interferometer requires almost perfect crystal alignment and stability of the order of 10^{-2} nm. This poses limitation for imaging larger specimen.

Diffraction-enhanced imaging

Another approach uses perfect crystal to produce diffractometric images. [10] The technique was expanded as diffraction-enhanced imaging (DEI), to provide detailed images of the gradient of the refractive index in a sample.[11,12]

A typical DEI setup is shown in Fig. 1b above. Synchrotron radiation that emerges from a monochromator is essentially parallel. As the x rays traverse a sample placed between the monochromator and the angular filter (analyzer), they can be absorbed, scattered coherently or incoherently, or refracted through very small angles due to the tiny variations in the refractive index. The resulting image at the x-ray detector resembles a standard x-ray radiograph but with enhanced contrast due to the scatter rejection.

DEI requires an intense monochromatic x-ray beam for reasonable exposure times. Synchrotron sources have a definite advantage in this respect, but are not practical for clinical applications. Pisano et al [12] have recently demonstrated the improved breast cancer detail visualization that is possible with synchrotron-based DEI (Fig. 8). Many synchrotron centers are working with the industry to explore the clinical potential of DEI.

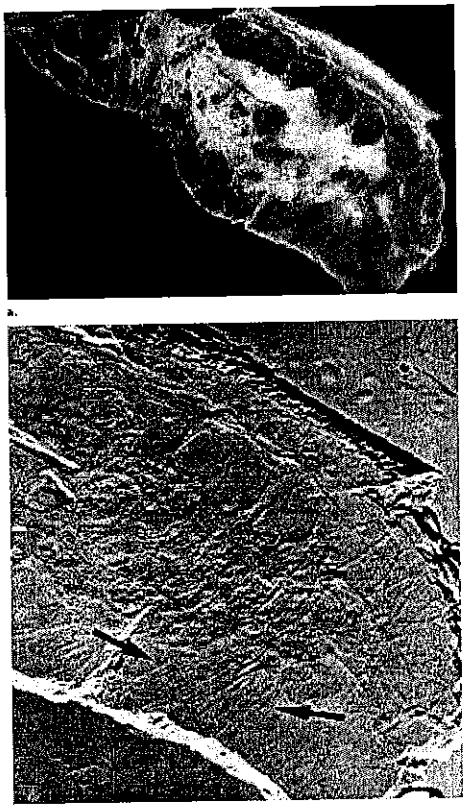

Figure 8. (a) Digital radiograph of a specimen of infiltrating ductal cancer. (b) Diffraction-enhanced image shows fine speculations on the surface of the lesion, between the two arrows, that are see in (a). This pathologic feature is a frequent cause of speculations and architectural distortion on mammograms.

Phase-contrast imaging

If just a detector is placed in the beam path (Fig. 1c) the x rays emerging from the sample at their various angles will propagate through free space until they reach the detector. With the detector immediately behind the sample, a conventional absorption image is obtained. Both Fraunhofer (far-field) and Fresnel (near-field) diffraction imaging have been experimented. The image formed is a combination of imaging and diffraction effects, typically involving interference fringes at the edges of features. One example of the superb enhancement in edge visibility is shown in Fig. 9.

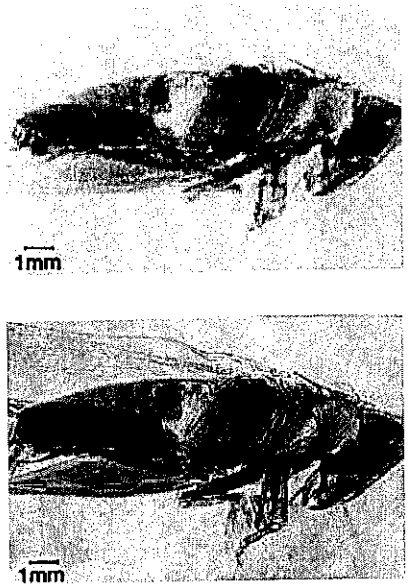

Figure 9. A conventional radiograph (top) of a locust, compared to a phase-contrast image (bottom). Both images were taken using a 10 μm microfocus x-ray tube source. For the conventional image, the detector was placed 1 cm behind the object; for the phase-contrast image, the detector was 1 m away. The increased object-image distance allows interference fringes to produce the edge enhancement. (courtesy of Physics Today; images by Dachao Gao, CSIRO, Australia.)

Researchers at Elettra and European Synchrotron Radiation Facility are using the latest generation of synchrotron radiation sources to produce x-ray beams that are on the order of 100 mm or smaller for phase-contrast radiography. Phase-contrast tomography, have been used to study small plants, animals as well as minerals. [13]

The same spatial coherence available from synchrotrons can also be obtained with a microfocus x-ray tube with a very small source size, about 10 μm placed 1 m away from the sample.

REAL-TIME IMAGING USING FLAT PANEL DETECTOR (FPD)

A great deal of research activity has been focused on development of new x-ray detectors to achieve fully digital imaging. The flat panel detector can be considered as one of the most important technological breakthrough in the history of radiology. The conventional film/screen system has limitations in linearity, noise, definition, detection efficiency and dynamic range. Both indirect conversion (x-ray

→ light → image) and direct conversion (x-ray → image) types of image formation have been developed. [14,15]

The latest generation of digital detector is the direct conversion type semiconductor (amorphous selenium) detector that converts x-ray energy into electrical signals and creates x-ray images. [14,15] Comparison of the physical principle and spatial frequency characteristics between these two types is illustrated in Fig. 10 and 11.

Currently FPD has superior spatial resolution characteristics (Modulation Transfer Function= 0.8 at 2 line pairs/mm spatial frequency) compared with film/screen system. Dynamic image is produced at more than 30 frames per second with no lag. One advanced structure of a direct conversion type FDP is shown in Fig. 12. [16]

An innovative real-time digital fluoroscopy imaging of a small animal using FPD is illustrated in Fig. 13.

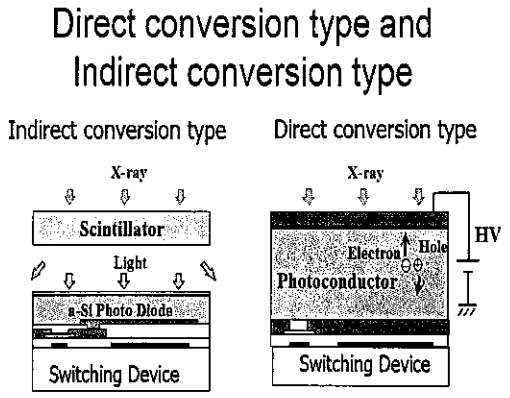

Figure 10. Comparison of physical principle between indirect and direct conversion type detectors.

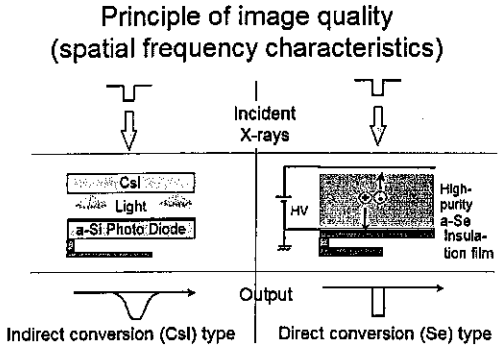

Figure 11. Comparison of the spatial frequency characteristics between indirect and direct conversion detectors.

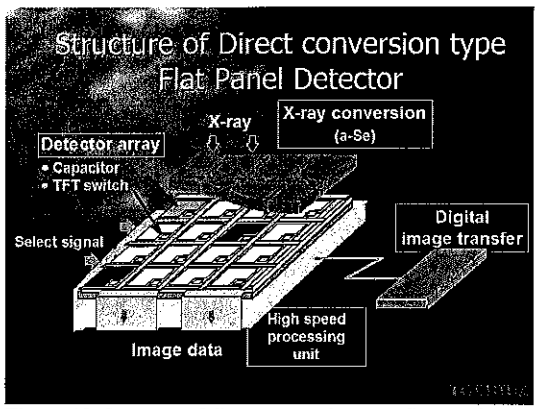

Figure 12. Structure of direct conversion type flat panel detector (Courtesy of Toshiba Medical System) [16]

Figure 13. Real-time x-ray imaging of a moving mouse (Courtesy of Toshiba Medical System)

PUSHING THE FRONTIERS OF X-RAY IMAGING

Phase-sensitive imaging techniques are spearheading applications in industrial and scientific research, but they have yet reached the clinical stage. Obtaining a suitable x-ray source

is one obstacle. Synchrotron radiation facility is too bulky and expensive, thus a laboratory-sized source that can provide the needed intensity at the appropriate energy is being developed. X-ray microscopy continues to attract more novel applications in the material and life sciences shedding more light in microstructure information.

Continued advances in x-ray detector technology will stimulate digital real-time imaging of live specimens facilitating structural and functional studies. With improvement in image quality, medical application will become a reality very soon.

The frontiers of x-ray imaging are being pushed further to unravel more useful information in science and medicine.

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