

PHASE-SENSITIVE X-RAY IMAGING

The basic principles of x-ray image formation and interpretation in radiography have remained essentially unchanged since Röntgen first discovered x rays over a hundred years ago. The conventional approach relies on x-ray absorption as the sole source of contrast and draws exclusively on ray or geometrical optics to describe and interpret image formation. This approach ignores another, potentially more useful source of contrast—phase information. Phase-sensitive techniques, which can be understood using wave optics rather than ray optics, offer ways to augment or complement standard absorption contrast by incorporating phase information.

Clinical and biological studies stand particularly well poised to benefit from the development of phase-sensitive techniques. Absorption contrast works well in distinguishing between hard and soft tissue: Heavier elements—like calcium in bones and teeth—have a much higher absorption cross section than the lighter elements that constitute soft tissues. However, in many clinical situations, such as mammography, there is a need to distinguish between different kinds of soft tissue—between tumors and normal tissue, for instance. Because the absorption is small to begin with, and differences in density and composition are slight, standard x-ray imaging is not as successful at this task.

According to radiologist Etta Pisano (University of North Carolina), who is part of a collaboration working to develop diffraction-enhanced imaging—one of the phase-imaging approaches—mammography currently has a very high rate of false positives and false negatives. In a population of undiagnosed women advised by their doctors to have regular diagnostic screening, only five women out of 1000 will actually have breast cancer. But for that same population, the rate of positive mammograms will be 10%—the ratio of false positives to true positives is nearly 20:1. And for about 10–20% of women who have palpable abnormalities, the mammograms won't show anything. There is thus a driving need to improve breast cancer detection technology.

The behavior of x rays as they travel through a sample (such as a patient) can be described using a complex index of refraction, just as in conventional optics. In the x-ray region, the index of refraction, n , deviates only slightly from unity; it can be written as $n = 1 - \delta - i\beta$, where β describes the absorption of x rays and the phase-shift term δ incorporates refractive effects. At typical mammography x-ray energies of 15–25 keV, the phase-shift term can be up to 1000 times greater than the absorption term—on the order of 10^{-7} , compared to 10^{-10} . Thus it may be possible to observe phase contrast when absorption contrast is undetectable. X rays passing through regions of differing δ pick up different relative phases, which corresponds to being refracted and produces a distorted wave front. These phase differences

New approaches that can detect x-ray phase shifts within soft tissues show promise for clinical and biological applications.

Richard Fitzgerald

are detected by the various phase-contrast techniques. absorption, and so imaging can be done at higher energies where the absorbed radiation dose can be less, thereby reducing potential damage to tissues.

Phase contrast may also prove useful in biological and medical studies because it falls off less quickly at higher energies than absorption contrast: $\delta \propto E^{-2}$, whereas $\beta \propto E^{-4}$. Phase contrast relies only on refraction of x rays, not on Several research groups are exploring ways of exploiting phase information as a source of image contrast. These approaches fall into three broad categories: interferometry, diffractometry, and in-line holography. "At a fundamental physics level, these three modes may be associated with directly measuring φ , $\nabla\varphi$, and $\nabla^2\varphi$, respectively," notes Stephen Wilkins of Australia's Commonwealth Scientific and Industrial Research Organisation (CSIRO). Here, φ is the phase change introduced in the incident x rays on passing through the sample.

X-ray interferometry

X-ray interferometry methods were pioneered by Ulrich Bonse and Michael Hart 35 years ago¹ (see *PHYSICS TODAY*, August 1970, page 26). In recent years, Atsushi Momose (now at the University of Tokyo), Tohoru Takeda (University of Tsukuba), and colleagues have been refining techniques for application in clinical and medical settings.^{2,3}

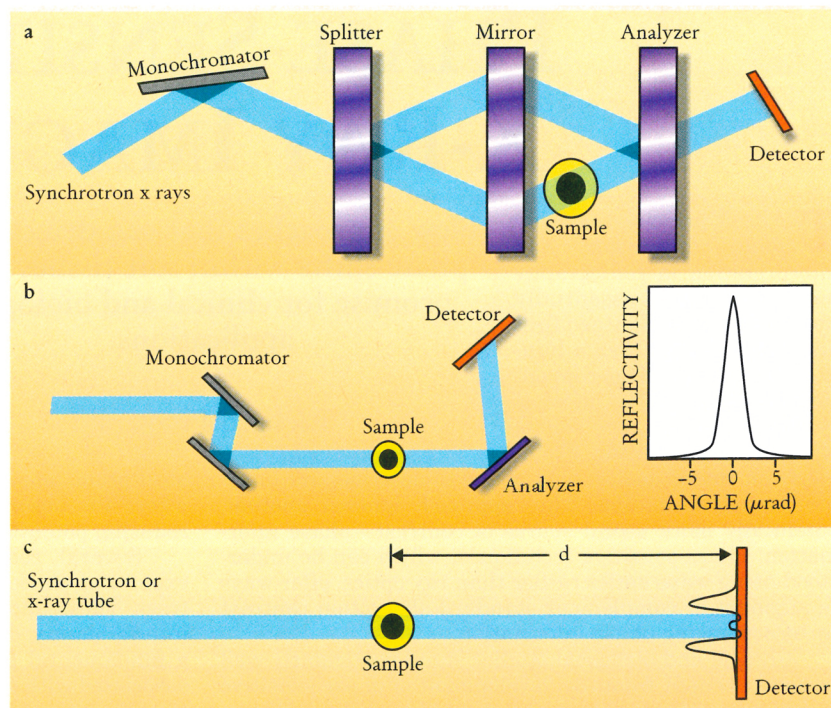
Three matching perfect crystals, arranged in parallel as in figure 1a, function as an x-ray interferometer. The first crystal splits the incident x-ray beam after it has been filtered by a monochromator—which typically consists of additional one or more crystals oriented so that only the x rays of the 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.

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.

Momose and company have incorporated this x-ray interferometry technique into computed tomography (CT).² By taking several interferometry images at different rotational orientations of a sample, they are able to reconstruct a three-dimensional map of the refractive index inside the sample. With this technique, they have studied a rat cerebellum and rabbit cancer lesions as well as cancerous tissues of human breast, liver, and kidney (see figure 2) using synchrotron radiation at the Photon Factory in Tsukuba. Their results illustrate the potential advantages of phase contrast and its sensitivity to minute density variations—on the order of 10^{-9} g/cm³. The researchers have recently shown that their phase-

RICHARD FITZGERALD is an associate editor at *PHYSICS TODAY*.

FIGURE 1. EXPERIMENTAL SETUPS for phase-sensitive imaging. **(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.



contrast CT results are similar to the images obtained with low-magnification ($\times 20$) optical microscopy, but without the need to generate contrast through staining.³

Because of its extreme sensitivity, the x-ray interferometer requires almost perfect crystal alignment and stability—on the order of 10^{-2} nm. The best results are obtained from a monolithic device in which all three x-ray mirrors are made from a single large crystalline silicon ingot. Although this technique provides inherent alignment and good stability, ingot sizes limit the potential field of view to about $3\text{ cm} \times 3\text{ cm}$. Clinical applications such as mammography require a $10\text{ cm} \times 10\text{ cm}$ field of view. Momose and coworkers are exploring the use of a two-piece interferometer that will allow the imaging of larger samples. Sub-nanoradian stability of the orientation between the two blocks will be needed, however, to prevent blurring of images.

The x-ray interferometry technique works best for small or smooth phase gradients. The fringe spacing is inversely proportional to the beam deflection, and the larger the fringe spacing, the easier is fringe detection. “All other phase-sensitive techniques benefit from larger beam deflection,” comments Momose. “Too steep a phase gradient may cause problems: When fringes become fine, it is hard to resolve them.”

Diffraction-enhanced imaging

A second approach to phase-sensitive imaging—first explored at the X-Ray Laboratory in St. Petersburg, Russia, by Viktor Ingal and Elena Beliaevskaya⁴ and at CSIRO by Wilkins and colleagues⁵—also uses perfect crystals, but as very sensitive angular filters that produce diffractometric images. A US collaboration has expanded on this technique, termed phase-dispersion introscopy or diffraction-enhanced imaging (DEI), to provide detailed images of the gradient of the refractive index in a sample.^{6,7} The physics side of this effort has been led by Dean Chapman (Illinois Institute of Technology), William Thomlinson (now at the European Synchrotron Radiation Facility in Grenoble, France) and Zhong Zhong

(Brookhaven National Laboratory); their colleague Pisano has been spearheading medical applications of it.

A typical DEI setup is shown in figure 1b. 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 (termed the analyzer), they can be absorbed, scattered coherently or incoherently (by milliradians or more), or refracted through very small angles (microradians) due to the tiny variations in the refractive index. X rays emerging from the sample and hitting the analyzer crystal will satisfy the conditions for Bragg diffraction only for a very narrow window of incident angles, typically on the order of a few μrad . X rays that have been scattered in the sample will fall outside this window and won't be reflected at all. Refracted x rays within the window will be reflected, but the reflectivity depends on the incident angle. This dependence, called the rocking curve, is shown in the inset of figure 1b.

If the analyzer is perfectly aligned with the monochromator, it will filter out any x rays that are scattered or refracted by more than a few μrad . The resulting image at the x-ray detector will resemble a standard x-ray radiograph but with enhanced contrast due to the scatter rejection.

If, instead, the analyzer is oriented at a small angle with respect to the monochromator—say by the half-width at half-maximum of the rocking curve—then x rays refracted by a smaller angle will be reflected less, and x rays refracted by a larger angle will be reflected more. Contrast is therefore established by the small differences in refracted angle of x rays leaving the sample. The cover of this month's issue shows an x-ray image of a mouse taken at the Elettra synchrotron (Trieste, Italy) with an analyzer crystal that has been offset by a small angle. The resulting contrast reveals soft tissue features such as the skin, whiskers, and lungs.

An image obtained with a detuned analyzer crystal will include both absorption and refraction effects. But by combining images taken on either side of the rocking curve, the effects can be separated. Images of pure refraction and of so-called apparent absorption (which also

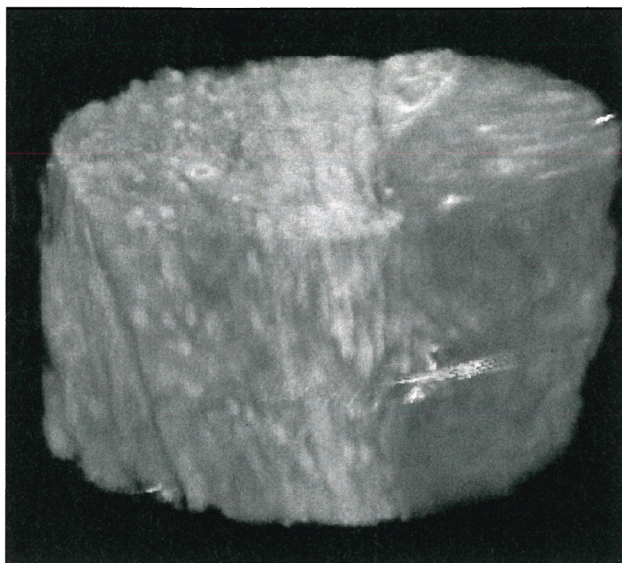


FIGURE 2. COMPUTED TOMOGRAM of a human kidney sample (5 mm in diameter) obtained with phase-contrast x-ray interferometry. The image maps the difference in the refractive index between the sample and water. The darker region on the right is cancerous. The density difference between the normal and cancerous tissues is calculated from the image to be 10 mg/cm^3 . (From A. Momose *et al.*, SPIE Proc. **3659**, 365 [1999].)

includes losses due to scattering) can thereby be produced,⁶ and because they rely on different contrast mechanisms, they can provide complementary information. The refraction image, being sensitive to the gradient of the refractive index, shows dramatic edge enhancement and provides a map of the boundaries between regions with differing refractive indices (see figure 3).

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 and company have recently demonstrated the improved cancer detail visualization that is possible with synchrotron-based DEI,⁷ and the team has also shown that DEI can be used for CT,⁸ which could increase the clinical potential for this technique. A European collaboration led by Ralf Menk (Elettra) that is bringing together researchers at synchrotrons (Daresbury in the UK, DESY in Germany, Elettra, and ESRF), universities (Bremen and Siegen), and industry (Siemens AG) has also begun exploring the medical potential of DEI. Ingal and Beliaevskaya, meanwhile, have continued to explore the use of commercial x-ray tubes.⁹

Phase-contrast radiography

If just a detector, and no analyzer crystal, is in the beam path (figure 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, one will get a conventional absorption image. If the source is very highly coherent and the detector is placed very far behind the sample, one will observe a fringe pattern as different components of the beam, having been diffracted by the sample, interfere with each other on further propagation through space. This regime corresponds to Fraunhofer or far-field diffraction. The interference pattern contains useful phase information, but extracting that information is an ongoing

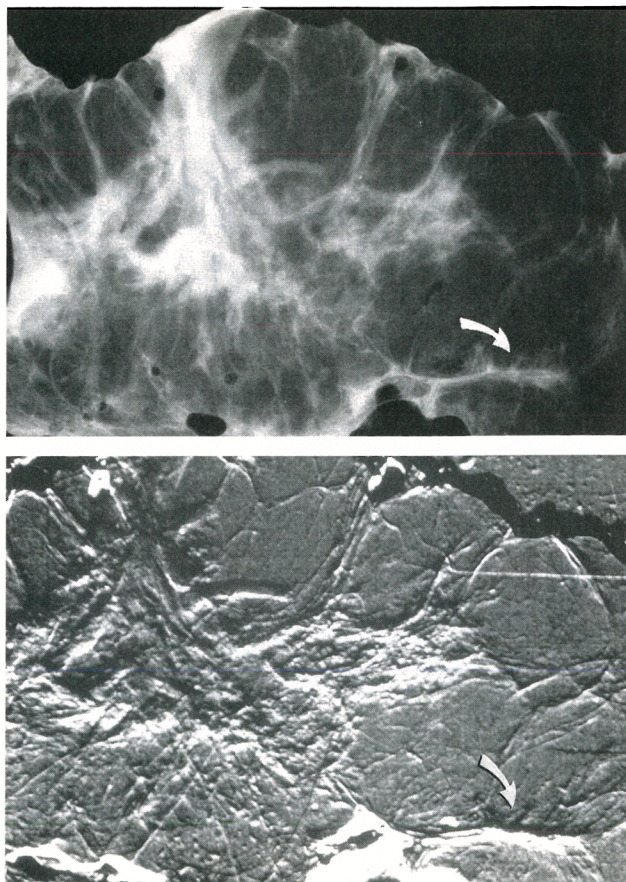


FIGURE 3. HUMAN BREAST CANCER SPECIMEN, imaged *in vitro* with conventional absorption (top) and diffraction-enhanced techniques (bottom). The DEI technique is sensitive to variations in the refractive index, which are greatest at the boundaries between different regions. Because of the resulting edge enhancement, spiculations (thin lines of cancerous growth) that are barely discernable in the top image (arrow) are more clearly visible in the DEI refraction image. (From ref. 7.)

computational and physics challenge.

With the detector placed at an intermediate distance, one gets Fresnel or near-field diffraction. Here, a combination of imaging and diffraction effects is found, typically involving interference fringes at the edges of features. These fringes improve edge visibility (see figure 4). The optimum positioning of the detector for best enhancement effects varies from sample to sample, depending on the x-ray wavelength and the size of the features of interest.

This “in-line” phase-sensitive technique, exploiting Fresnel diffraction and dubbed phase-contrast imaging (although it is distinct from optical phase-contrast imaging), was first explored by Anatoly Snigirev and coworkers at ESRF¹⁰ and by Wilkins and colleagues at CSIRO.¹¹ It is very similar to the original techniques for holography developed by Dennis Gabor in 1948.

In the absence of absorption, the contrast depends on the Laplacian of the phase shift φ in the sample. “Interpretation of the measured $\nabla^2\varphi$ or φ in terms of object properties becomes more difficult for thick objects due to the effects of multiple scattering within the sample,” says Wilkins. X rays that have been scattered through large angles will miss the detector altogether, which improves the signal-to-noise ratio of the image.

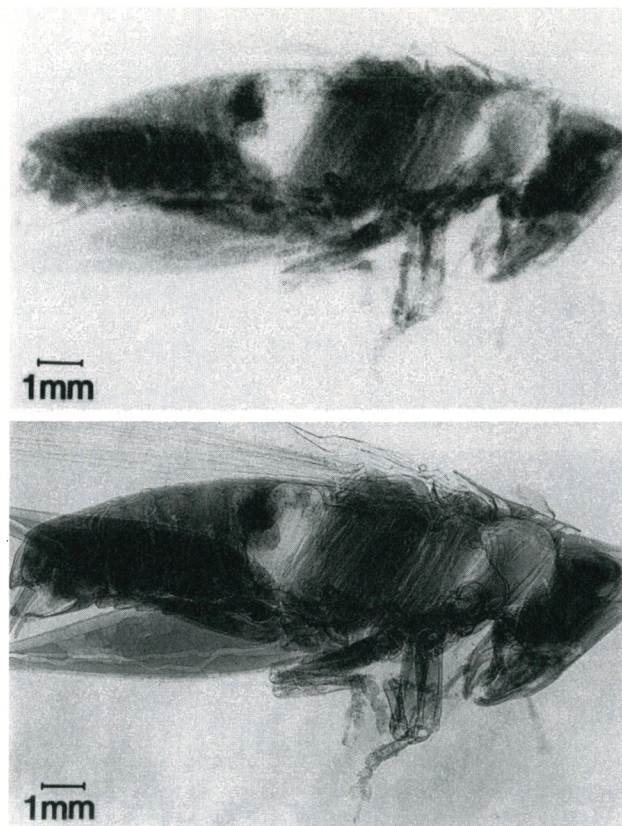


FIGURE 4. IN-LINE PHASE-CONTRAST imaging of a locust (bottom), compared to a conventional radiograph (top). Both images were taken using a microfocus x-ray tube source (with a nominal size of $10\ \mu\text{m}$). For the absorption image, the detector was placed 1 cm behind the object; for the phase-contrast image, the detector was 1 m away. The increased object-image distance allows interference fringes to develop from the phase distortions in the x-ray beam wavefront, producing the observed edge enhancement. (Images by Dachao Gao, CSIRO.)

In order for the interference between different parts of the x-ray beam not to be washed out, a source with high spatial coherence—that is, one that has a very small apparent angular source size—is needed. The ideal would be a point source. The latest generation of synchrotron radiation sources, such as Elettra and ESRF, produce x-ray beams that are on the order of $100\ \mu\text{m}$ or smaller. With samples typically placed 20 m or more away, the source closely resembles a point source when viewed from the sample, and the small angular divergence keeps most of the x-ray flux from being lost. Researchers at Elettra and at ESRF are using synchrotron radiation, filtered by a monochromator, for phase-contrast radiography. Much of the work being done at ESRF is on phase-contrast tomography,¹² a technique that researchers there have employed to study small plants and animals as well as minerals and ash particles from Chernobyl. A team at Elettra has recently compared synchrotron-based phase-contrast imaging, DEI, and conventional absorption images of phantom and *in vitro* full breast specimens, and found that both phase-sensitive techniques provide significantly improved feature detection¹³. Fulvia Arfelli (University of Trieste) adds, “For both techniques, the applied dose is comparable to or less than the clinical dose.”

The same spatial coherence available at synchrotrons can also be obtained with a so-called microfocus x-ray tube—which has a very small source size, about $10\ \mu\text{m}$ —placed 1 m away from the sample, notes Wilkins. Surprisingly, as shown by his team, a monochromatic beam is not necessary—spatial coherence is much more important than spectral coherence.¹¹ All the energy dependence falls neatly into a multiplicative factor, and the actual spatial pattern of the image is independent of the x-ray energy to first order. Giorgio Margaritondo and Guiliana Tromba (Trieste) have reached a similar conclusion.¹⁴

A monochromator throws much of the x-ray flux away, and, when used with an x-ray tube source, would make the time needed to record an image unacceptably long for clinical uses. (Studies of *in vitro* samples and inorganic materials don't have such exposure-time limitations.) The ability to use the polychromatic output of an x-ray tube is therefore important for potential clinical applications. The large beam divergence from such a source has the additional advantage of providing inherent magnification, with a corresponding increase in spatial resolution. The spreading beam also allows the imaging of large areas in a single step.

Into the clinic?

Phase-sensitive imaging techniques are beginning to find use in industrial and scientific applications, but none of these techniques is yet at the clinical stage. Obtaining a suitable x-ray source is one obstacle. For the approaches currently relying on synchrotron radiation, efforts are being made to develop a laboratory-sized source that can provide the needed intensity at the appropriate energy to get acceptable exposure times—without sacrificing spatial coherence in the case of in-line phase-contrast imaging. The microfocus x-ray tubes used by the CSIRO team appear to come close to being suitable for clinical radiography, and several companies are pursuing technical advances aimed in that direction. Continued advances in x-ray detector technology will also be helpful, both in terms of improved detection efficiency, which would yield lower exposure thresholds—and thus reduced flux requirements—and better spatial resolution.

Optimizing the techniques for obtaining the most useful information from the images is also still under way. For instance, the question of the appropriate x-ray energy for the various techniques—and various tissues and body parts—remains to be answered.

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