# Biological Imaging Based on X-ray Phase Measurement

## — Toward Applications in Cancer Diagnosis —

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*Overview: An X-ray beam is a powerful probe for investigating the inside of opaque objects, and it is extensively used especially in the field of medical diagnosis. However, X-ray images cannot always find early-stage cancer, which is an important subject of image diagnosis. This is because soft tissues only weakly absorb X-rays, so the contrast in conventional X-ray images cannot reveal structures in soft tissues satisfactorily. Hitachi is conducting research on generating contrast from X-ray phase information in collaboration with the University of Tsukuba. By mapping the difference in the velocities of X-ray waves instead of the difference in X-ray absorption, imaging sensitivity is improved by about a thousand times compared to that of the conventional method. It will therefore also be possible to provide a safer imaging system because the X-ray dose is correspondingly reduced. Moreover, this method provides high-spatial-resolution X-ray imaging and is expected to open up new areas of X-ray imaging.*

### INTRODUCTION

THE contrast in X-ray images in current clinical use is generated from the difference in the X-ray absorption from different parts of an object. That is, elements of higher atomic number absorb more X-rays. Soft tissues consisting mainly of hydrogen, carbon, nitrogen, and oxygen are therefore comparatively transparent to X-rays and generate poor contrast. Because localized areas of disease almost always appear in soft tissues, the sensitivity of X-ray imaging to soft tissues must be improved. Currently, contrast media containing heavy elements are used to enhance image contrast. However, suitable contrast media for all the diagnostic cases currently requested are not available.

An imaging method that produces contrast from the speed of X-ray waves can overcome the poor–contrast problem. When waves (X-rays) pass through an object, the relative position of the waves changes, and the amount of shift is called the "phase shift." The conventional imaging method produces contrast from the difference in the waves' attenuation of intensity. As mentioned above, this difference is small when imaging soft tissues. On the other hand, the difference in the X-ray phase shifts caused by soft tissues is comparatively large. It is estimated that the sensitivity is increased by a thousand times if this difference is used for imaging.[1] In general, the methods for forming an image by using the distribution of the phase shift are called "phase-contrast" methods. If such methods are used in the field of medical diagnosis, breakthroughs are expected in (1) finding small tumors, (2) distinguishing between cancerous and benign growths, (3) reducing X-ray exposure, and (4) improving reliability of diagnosis.

This paper describes the status of the present research on phase-contrast imaging using an X-ray interferometer.

### PHASE MEASUREMENT OF X-RAYS

#### X-ray Interferometer

One century has passed since the discovery of X-rays, but few measurements of X-ray phase have been attempted. In the visible-light region, light phase can be measured by an interferometer. Similarly, in the X-ray region, X-ray phase can be measured by an X-ray interferometer. However, because the wavelength of X-rays is smaller than one thousandth of the wavelength of visible light, extremely high precision is required in forming an X-ray interferometer. The development of an X-ray interferometer is therefore a key for measuring X-ray phase.

Making use of diffraction by a crystal, an X-ray interferometer that functions by comparatively simple procedures was invented more than thirty years ago.[2] X-rays that satisfy the condition for diffraction in the lattice plane perpendicular to a crystal wafer are split and emitted from the back surface of the wafer. Making use of this phenomenon, a crystal wafer is used as an X-ray beam splitter or an X-ray half mirror. An X-ray interferometer is formed by aligning such crystal wafers (see Fig. 1). X-rays split by the first wafer are split again by the second wafer. Behind the second wafer, the two beams overlap at the position of the third wafer, which mixes the beams. As a result, an interference pattern is observed in the outgoing beams from the third wafer.

The X-ray interferometer shown in Fig. 1 is monolithically cut from a crystal ingot. Diffraction by a crystal occurs because its atoms are aligned regularly. In the X-ray interferometer of Fig. 1, all atoms in the interferometer are regarded as regularly arranged. Therefore, diffraction occurs at every point at the same time, and two interfering beam paths are generated. An object is placed in one of the beam paths between the wafers, and the other beam is used as a reference beam. As a result, an interference pattern corresponding to the phase shift from that of the reference beam is produced.

## Observing Interference Patterns

The usefulness of an interferometer for phase-contrast X-ray imaging has been shown,[2, 3] and its high sensitivity to soft tissues has been experimentally demonstrated.[1] An interference pattern of a 1-mm slice of a rat cerebellum, which was obtained in collaboration with Prof. Fukuda at the National Defense Medical School, is shown in Fig. 2. The white matter and gray matter (granular layer and molecular layer) are differentiated in the interference pattern. In the absorption-contrast (i.e. conventional) image of this slice, no layer structure can be seen. This result thus confirms the high sensitivity of the phase-contrast method.

The image of the slice of a rat cerebellum was recorded on an X-ray film. For quantitative analysis, however, another step is required. This step is “a technique for measuring X-ray phase” and is described below.

X-ray phase measurement involves measuring interference patterns quantitatively with an X-ray image sensor and converting the interference patterns to an image that maps the distribution of the X-ray phase shift. This technique provides a variety of image analyses such as three-dimensional observation described below.

## Measuring X-ray Phase

Interference fringes are similar to contours on a topographical map, and phase measurement corresponds to the determination of a topography from contours. It is impossible to determine from the interference pattern whether the shape of the phase distribution is concave, convex, or a mixture of both. Similarly, mountains and basins cannot be distinguished only by contours. The aim of phase measurement is to resolve this fundamental problem.

Hitachi adopted an imaging method which determines an image that maps the phase shift (a phase map) from several interference patterns, which are obtained by changing the phase of the reference beam by a tunable phase shifter. This process is illustrated in Fig. 3. An interference pattern is shown on the far upper-left of Fig. 3. The remaining four interference patterns in the upper half of Fig. 3 show that the fringe pattern varies when the phase of the reference beam is changed. By analyzing the displacement of the fringes,

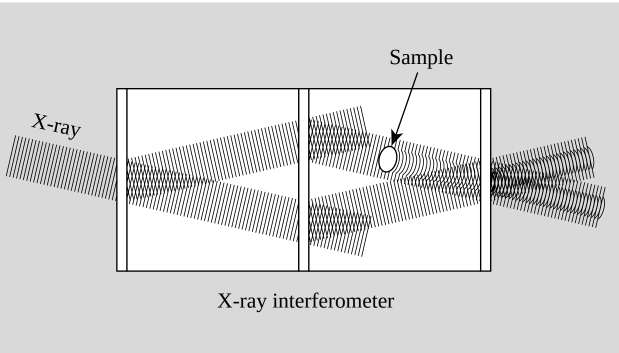


*Fig. 1— X-ray Interferometer and Generated Beam Paths.*
*By means of diffraction, X-ray beam paths are generated in an X-ray interferometer cut out from an ingot of a perfect silicon crystal.*

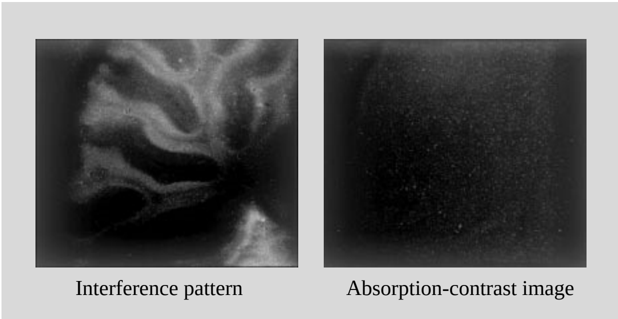


*Fig. 2— Interference Pattern and Absorption-contrast Image of a Rat Cerebellar Slice.*
*Contrast due to layer structures in a cerebellum appeared in the interference pattern while no contrast was obtained by the absorption-contrast image.*

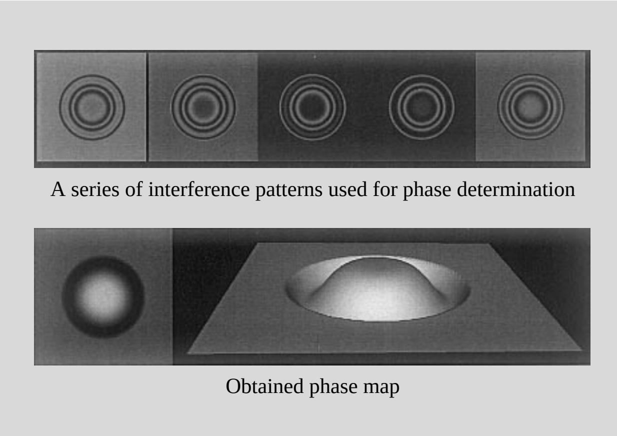


*Fig. 3— Schematic Diagram of the Determination of a Phase Map from Interference Patterns.*
*From interference patterns (upper half) obtained by changing the parameter of interference, a phase map (lower half) required for phase-contrast X-ray CT is determined.*

we can uniquely determine the phase map. The phase map shown in the lower half of Fig. 3 is produced by processing the series of interference patterns in the upper half of Fig. 3 according to a prescribed procedure.[4] This example shows a phase map which is concave at the edges and convex at the center. The X-ray phase is measured by using an X-ray interferometer with a tunable phase shifter for changing the phase of the reference beam.

Phase-contrast X-ray computed tomography (CT) described in the next section is a method for reconstructing the inner three-dimensional structure from X-ray phase maps produced by the procedure described above. And Hitachi is the first in the world to develop phase-contrast X-ray CT.[5]

## PHASE-CONTRAST X-RAY COMPUTED TOMOGRAPHY

### Principle

X-ray CT reconstructs an image on an imaginary sectional plane nondestructively from plural projection images. This technique has spread quickly, mainly in the medical field, and its applications are still being studied. However, because the mechanism of contrast creation always depends on X-ray absorption, the problem of low sensitivity to soft tissues has not been resolved. The phase-contrast X-ray CT aims at use of the phase-contrast method in X-ray CT which enables us to observe biological soft tissues because of its high sensitivity.

An X-ray transmission image is equivalent to a projection of X-ray absorption coefficient. As a result, conventional X-ray CT processes X-ray transmission images (strictly the logarithm of them) and reconstructs images which map the distribution of X-ray absorption coefficient. On the other hand, phase-contrast X-ray CT processes phase maps. And because a phase map is a projection of refractive index, sectional images that map the refractive index are produced by using a conventional reconstruction algorithm. This correlation is shown in Table 1.

Although the effects of absorption and refraction depend on materials, in the case of soft tissues, the effect of refraction is about one thousand times greater than that of absorption. Phase-contrast X-ray CT is therefore a thousand times more sensitive to soft tissues than conventional X-ray CT.

### Apparatus

The experimental setup of phase-contrast X-ray CT is shown in Fig. 4. A sample is put in a cell filled with water for observation in a wet environment. To enable a CT scan, the sample can be rotated in the cell. An X-ray sensing pickup tube is used to obtain interference patterns. For measuring the phase, a tunable phase shifter is placed on the other beam path. This apparatus is installed in the Institute of Materials Structure Science, High Energy Accelerator Research Organization to perform experiments using synchrotron radiation.

### Reconstructed Images

Biological soft tissues of a cancerous rabbit liver observed by phase-contrast X-ray CT are shown in Fig. 5.[6] The purpose of this observation is to clarify whether cancer lesions can be revealed by phase-contrast X-ray CT. As shown in Fig. 5(a), a tumor (center to left) is well differentiated from a normal tissue (right) in terms of gray level. Furthermore, structures in the tumor are depicted much clearer than

TABLE 1. The Correlation Between the Input Data and the Reconstructed Image in the Scheme of X-ray CT
*In conventional X-ray CT, X-ray attenuation is used as the input data to reconstruct an image which maps a distribution of absorption coefficients; and in phase-contrast X-ray CT, phase-shift is used as input data to reconstruct an image which maps a distribution of refractive indexes.*

| Type \ Item | Input data | Reconstructed image |
|---|---|---|
| Conventional | Attenuation | Distribution of absorption coefficient |
| Phase-contrast | Phase shift | Distribution of refractive index |

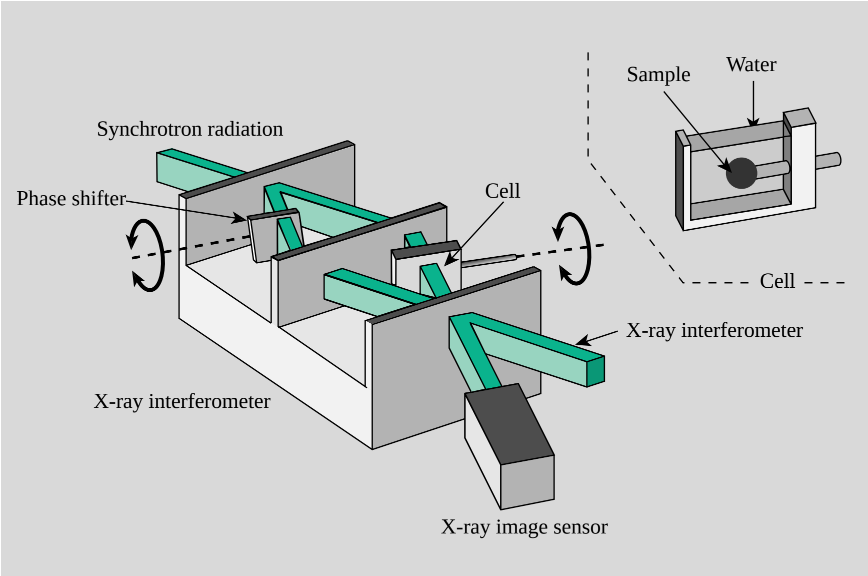


*Fig. 4— Experimental Setup of Phase-contrast X-ray CT.*
*A sample is placed on one of the beam paths generated in the X-ray interferometer, and a phase shifter is placed on the other beam path. X-ray beam paths are indicated with green color. Synchrotron radiation is used as an X-ray source.*

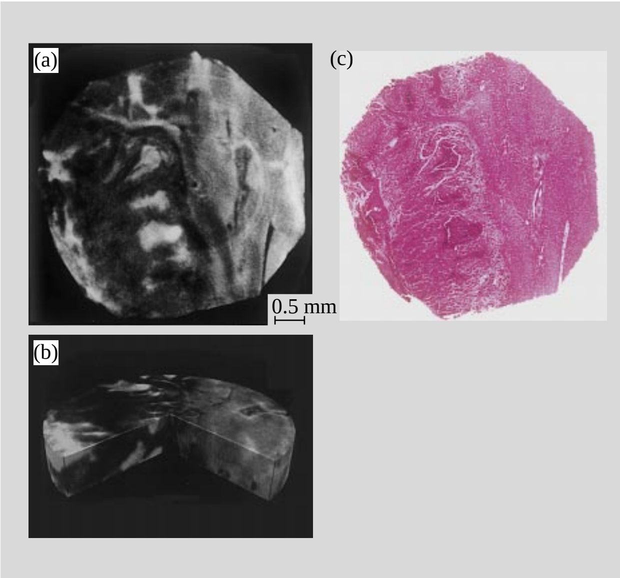


*Fig. 5— Images of a Tissue Piece Obtained from a Cancerous Rabbit Liver.*
*(a) phase-contrast X-ray CT image, (b) three-dimensional image where one quadrant has been cropped by a computer to show the inside, and (c) optical picture of a slice corresponding to (a), which was prepared after the X-ray measurement.*

we expected before the experiment. Fig. 5(c) is an optical picture of the slice shown in Fig. 5(a). Comparing (a) with (c) reveals that structures appearing bright are necrotic parts and the structures shown in the marginal part of the tumor are fibrous tissues. A three-dimensional image is produced by stacking all reconstructed images obtained in one scan. A three-dimensional image is shown in Fig. 5(b), in which one quadrant has been cropped by computer in order to show the inside.

A number of human tissues were also observed by phase-contrast X-ray CT.[7] Several examples are shown in Fig. 6. Fig. 6(a) is an image of a cirrhotic liver with hepatocellular carcinoma (upper half). Fig. 6(b) shows the structure inside a tumor of colon cancer metastasized to a liver. Necrotic parts appear bright as in Fig. 5. Fig. 6(c) is an image of a normal liver. However, the image indicates that this is a fatty liver because the dark pattern shows too much fat. Figs. 6(d) – (f) are images of breast tissues: (d) shows breast cancer, (e) shows a benign tumor (fibroadenoma), and (f) shows normal tissue. Characteristic contrast in each image suggests the possibilities of distinction between cancerous and benign tissues in addition to distinction between cancerous and normal tissues. For precise discussion, more observation results should be accumulated.

## THE FUTURE OF X-RAY IMAGING

The high sensitivity of phase-contrast X-ray imaging has been made clear at the experimental stage. However, a number of problems should be solved before an imaging technique based on the X-ray phase measurement can be practically developed. Applications of this technique to medical imaging would be the most useful because high sensitivity is achieved in imaging biological soft tissues. The following are the main problems to overcome: (1) increase the size of observable objects, (2) reduce scan time, and (3) develop suitable X-ray sources.

The size of observable objects (1) is limited by the

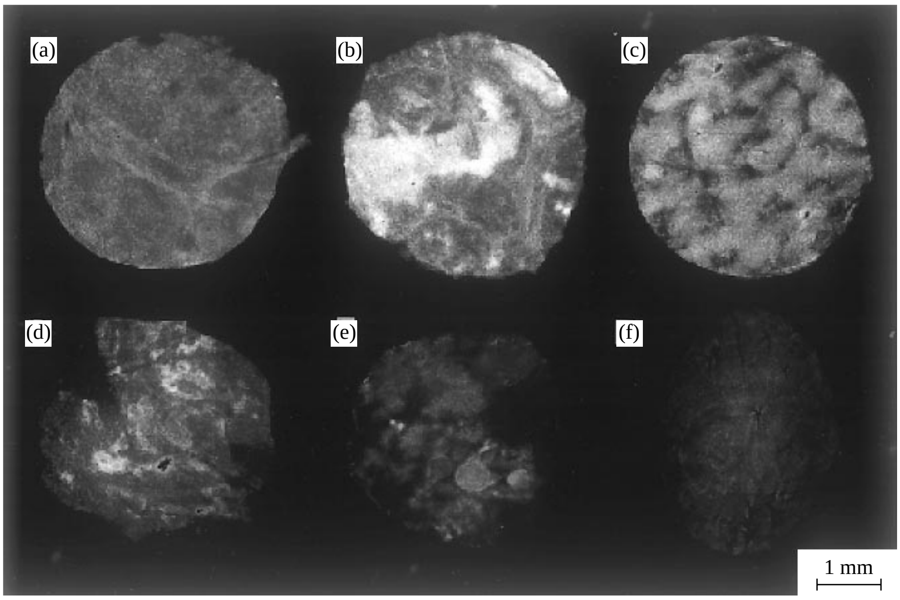


*Fig. 6— X-ray Images of Tissue Pieces Obtained from Human Organs.*
*(a) hepatocellular carcinoma (upper part) appeared in liver cirrhosis, (b) inside structure of a tumor in a liver caused by metastasis of colon cancer, (c) normal but fatty liver (regions with a dark level correspond to fat), (d) inside structure of a tumor due to breast cancer, (e) benign breast tumor (fibroadenoma), and (f) normal breast tissue.*

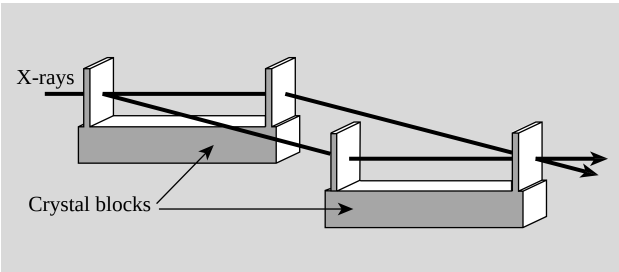


*Fig. 7— Separated-type X-ray Interferometer for Imaging Larger Objects.*
*Beam paths are generated by two independent crystal blocks.*

size of X-ray interferometer. Our present apparatus can observe tissue pieces smaller than 5 mm. To observe (a part of) a living body, a larger X-ray interferometer is needed. From a commercially available ingot of a high-quality silicon crystal, however, it is difficult to cut out a monolithic X-ray interferometer of satisfactory size. We have therefore developed a separated-type X-ray interferometer,[8] whose composition is shown in Fig. 7.

The function of this separated-type X-ray interferometer is fundamentally the same as that of the monolithic X-ray interferometer. In the former, however, the spacing of the two crystal blocks, of which the X-ray interferometer consists, can be selected depending on the size of an object. On the other hand, because we have to give up the advantage of the monolithic X-ray interferometer, in which no mechanical tuning is needed to generate interference, a stage for aligning and stabilizing the two blocks is additionally required. To generate an interference pattern of X-rays of wavelength shorter than 0.1 nm, the relative position of the blocks must be stabilized within 0.1-nm deviation along some tuning axis. Therefore, the influence of vibration and temperature drift must be reduced. At the experimental stage, generation of an observation field of $2 \times 2$ cm has been tried.

Regarding scan time (2), phase-contrast X-ray CT currently takes several hours. This is because pixel size is set to $12 \times 12$ µm and the narrow X-ray energy band-width in the X-ray interferometer reduces the X-Ray intensity. The scan time can be remarkably reduced by increasing the pixel size. However, because the time for phase measurement is not so long, clinical applications should be studied at the stage of phase measurement before phase-contrast X-ray CT. For example, if an observation field of $10 \times 10$ cm is created, diagnosis of breast cancer might be possible (see Fig. 8). In this application, the breast does not need to be rotated, and imaging can be performed with a 1-second exposure.

Finally, developing suitable X-ray sources (3) is also important for a practical use. In the experiments, synchrotron radiation was used because a highly collimated and brilliant X-ray beam is available. This kind of beam property is desirable in the optics using the X-ray interferometer where monochromatic X-ray beam is formed. However, a synchrotron radiation source is a huge system, so it must be down-sized and/or other X-ray sources must be developed in the future. In the meantime, research will be continued with a synchrotron radiation source.

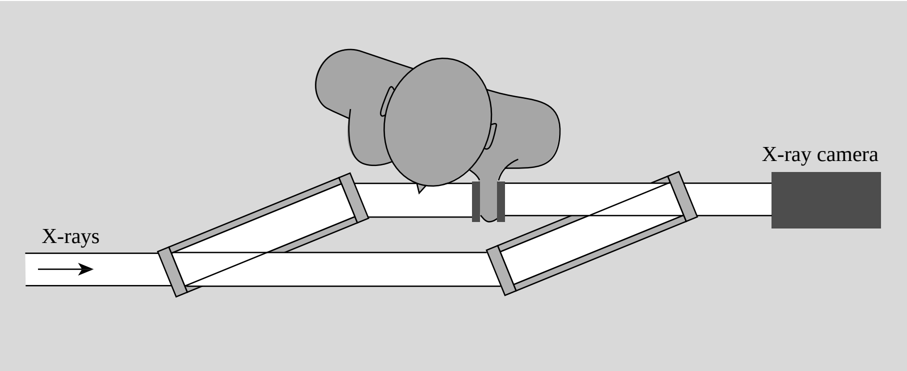


*Fig. 8— Schematic View of Diagnoses of Breast Cancer by Using a Separated-type X-ray Interferometer.*

## CONCLUSIONS

Phase-contrast X-ray imaging using an X-ray interferometer has been developed. X-ray phase has not been measured so far in spite of the useful information it can provide. X-ray imaging using X-ray phase information can improve sensitivity by a thousand times compared to conventional X-ray imaging. To attain this high sensitivity, however, an X-ray interferometer must be used. Therefore, all the conventional X-ray imaging techniques cannot be converted into phase-contrast ones. Hitachi will mainly concentrate on developing phase-contrast mammography and generate business by advancing the technique of phase-contrast X-ray imaging.

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