Final Report

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K- Edge Subtraction Angiography with
Synchrotron X-Rays

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**Final Report for DOE Grant #DE-FG03-87ER60527-M011:
K-Edge Subtraction Angiography with Synchrotron X-rays
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The purpose of this project was to utilize dual energy, monochromatic X-rays produced from synchrotron radiation in order to obtain noninvasive medical imaging. The application of synchrotron radiation to medical imaging is based on the principle of iodine dichromography, first described by Bertil Jacobson of the Karolinska Institute in 1953. The imaging system described below was developed at Stanford University and the Stanford Synchrotron Radiation Laboratory (SSRL) in a collaborative effort involving members of the faculties of the Department of Physics, the Department of Applied Physics, and the Department of Medicine at Stanford University, faculties and students of the Department of Physics at the University of California Santa Cruz, and staff and scientists from the Lawrence Berkeley Laboratory and the National Synchrotron Light Source at the Brookhaven National Laboratory.

Background

Production of Monochromatized X-rays from Synchrotron Radiation

Charged particles traveling in curved trajectories at relativistic velocities emit synchrotron radiation. The emission of this electromagnetic radiation by ultra-relativistic charged particles of low mass is characterized by a Lorentz transformation, which results in the confinement of the beam of radiation (synchrotron radiation) within a forward-directed cone (Figure 1). The small solid angle (ϕ) of the cone is determined by the rest mass (mc^2) and the total energy (E) of the emitting particle

$$\phi = mc^2/E$$

With electrons or positrons as the emitting particles ($mc^2 = 0.51$ MeV) and a particle beam energy of 3.0 GeV, the angle is < 1 milliradian. The natural collimation of virtually all the radiation provides exceedingly high X-ray fluence in an essentially planar, fan-shaped beam. For example, at 3 billion electron volts of energy (3 GeV), the vertical divergence of the beam of synchrotron radiation is only about one-one hundredth of a degree. This means that the paths of the beams of photons are essentially parallel, and therefore the X-radiation can be efficiently monochromatized by diffraction. The energy of the diffracted beam can be selected by adjustment of the incident angle, as given by the Bragg equation

$$n\lambda = 2d \sin \phi$$

Synchrotron radiation is generated within an accelerator known as an electron storage ring, an evacuated annular pipe in which there are curved sections and straight sections. Electrons are preaccelerated in a linear accelerator, and then introduced into a straight section of the storage ring. The position and strength of the fields of a lattice of magnets surrounding the storage ring are adjusted so as to bend the trajectory of the electron beam into an orbital path which takes the shape of the ring. As the electrons accelerate through curved sections, they lose energy, which is emitted in the form of synchrotron radiation. This energy must be replenished as the electrons emerge from a curved section into a straight section. This is accomplished by applying radiofrequency energy provided in cavities by klystron tubes.

The intensity of the synchrotron radiation beam can be greatly increased by the use of an insertion device known as a wiggler. This consists of an array of magnets, with reversed polarity, positioned above and below a straight section of the ring. As electrons pass through the alternating fields of the wiggler, they are compelled to execute tight sine-wave excursions, the accelerations of which result in the emission of copious amounts of radiation downstream. The use of wigglers with high field strength make it possible to generate intense beams of radiation with the energy needed for xenon K-edge bronchography.

Figure 1. Schematic representation of generation of synchrotron radiation. An electron traveling at relativistic velocity is accelerated by a change in direction, which results in the production of a forward directed cone of polychromatic radiation. The radiation is pulsed and very nearly polarized and is of extremely high intensity.

Figure 2. Diagram of the SPEAR electron storage ring and the synchrotron radiation beam lines at SSRL. The positron injector is used for high energy physics colliding beam experiments.

The radiation leaves the storage ring through beryllium windows, which preserve the vacuum but are transparent to X-rays. The radiation propagates down a beam line and is monochromatized by diffracting elements. Polychromatic synchrotron radiation enters the crystal, and monochromatic radiation exits, its energy determined by the angle of the incident polychromatic beam with the plane of the crystal. Such diffraction is efficient only when the incident radiation consists of parallel beams. This is the reason that synchrotron radiation can be monochromatized. The widely diverging beams of photons emitted by an X-ray tube cannot be monochromatized by this process without an overwhelming loss of intensity.

The monochromatized radiation is continuously monitored for fluence and position by ionization chambers, passes through the subject and then impinges on a pair of segmented line detectors. The signals are amplified, computer-processed, and displayed electronically.

K-Edge Dichromography

The advantage of having monochromatic X-rays for medical imaging relates to being able to use the principle of K-edge dichromography in order to maximally enhance images containing certain materials. An example of this principle is shown in Figure 3. This is a graph demonstrating the K-edge of xenon. The horizontal axis is X-ray wave length in keV, and the vertical axis is a logarithmic scale of X-ray attenuation. For soft tissue and bone, there is a gradual increase in X-ray attenuation as wave length is decreased. However, for both iodine (the major constituent of the primary intravascular X-ray contrast agents used in clinical practice) and for xenon, there is a fairly abrupt increase in X-ray attenuation as the X-ray wave length diminishes. The X-ray attenuation is the sum of the Compton effect, and the photoelectric absorption from atoms in soft tissues, bones, and the iodine contrast agent. At the K-edge, the attenuation of X-rays due to the photoelectric absorption of iodine or xenon disappears, and the overall attenuation of X-rays drops by a factor of 6-9. This wave length, the K-edge, is 33.16 keV for iodine and 34.56 keV for xenon.

Polychromatic synchrotron radiation is monochromatized using a bent Laue geometry focusing crystal, which diffracts two monochromatic X-ray beams—one just above, and the other just below the K edge (Figure 4). The image formed by the higher energy beam contains information provided by Compton scattering and photoelectric absorption from atoms in soft tissues, bones, and the contrast agent; the image formed by the lower energy beam contains information provided by the same X-ray attenuating effects except for the absence of photoelectric absorption by iodine. The two beams cross at the position of the organ or structure being imaged, diverge and then impinge on the photosensitive elements of two solid-state line detectors. These detectors consist of lithium-drifted silicon, and produce images with a pixel resolution of 0.5 x 0.5 mm.. The two digital images generated are then subtracted logarithmically with a computer. The resultant image maximizes the contrast agent, while minimizing signals arising from other structures. The imaging suite is diagrammatically shown in Figure 6.

Figure 3. X-ray attenuation as a function of energy. The upper curve shows the attenuation by xenon, the middle curve the attenuation by soft tissue, and the lower curve the attenuation by bone. There is a six-fold stepwise increase in attenuation by xenon at 34.56 keV.

Iodine K-Edge Dichromography

The original experiments using monochromatized X-rays for medical imaging were pioneered by our group at Stanford University, and were directed toward noninvasive imaging of human coronary arteries following venous injection of an iodinated contrast agent. The first human images obtained by iodine K-edge dichromography were obtained at SSRL with a pair of Bragg-reflecting silicon crystals oriented to the (111) reflection, resulting in two horizontal line beams intercepting the patient and converging at a single position-sensitive detector. The beams were mechanically chopped with a rotating drum, so that at any given moment the patient and detector were exposed to monochromatic radiation, alternately below and above the K-edge of iodine.

In subsequent experiments at SSRL, images were obtained by means of a dual detector, which had the advantage that the effective flux was increased by a factor of 2.5, and that the beams intersected at the patient, resulting in superior cancellation of artifacts due to bone and soft tissue background. Nevertheless, the images fell short of clinical quality, owing to the statistical fluctuations in the pixel-to-pixel intensity.

The inadequate clinical quality of these images, owing to unacceptable signal:noise let to the development of a new optical imaging system utilizing the concept of Laue diffraction from a thin, bent crystal. This concept is illustrated in Figure 4. This design is superior to previous designs in that the monochromator is intrinsically focusing, thus making good use of the off-axis light, and it is a broad bandwidth, high throughput device. The latter effect can be understood if one considers that only 40 mm. of crystal is needed for efficient reflection of X-rays; a 500 mm. bent or curved crystal can be qualitatively regarded as a succession of roughly ten independently reflecting films, each tilted at a slightly different Bragg angle, and thus each reflecting a slightly different X-ray energy. Development of this instrument led to a 10-12 fold increase in X-ray fluence.

Figure 4. Diagram of Laue geometry, focusing monochromator currently utilized at NSLS.

Figure 5. Coronary arteriogram following venous injection of iodinated contrast in a patient with prior history of PTCA of the mid right coronary artery. Clearly visible are the three aortic cusps, the proximal left main, left anterior descending, and left circumflex coronary arteries. The right coronary artery is visualized throughout its entirety. This vessel terminates proximal to the expected takeoff of the right posterior descending coronary artery.

It is with this instrument that the best coronary angiograms have been obtained to date. Figure 5 is a representative image from a woman who had undergone a previous PTCA of her right coronary artery

Although the image clarity in this proposal is limited by printing a digital image, one can clearly see the aorta (with the individual sinuses clearly defined), the right coronary artery in its entirety, the left main coronary artery, and the proximal left anterior descending coronary artery. The proximal left circumflex coronary artery is visualized, but the more distal branches are not seen. The right coronary artery terminates prior to the expected takeoff of the posterior descending coronary artery. This image demonstrates clarity not seen in the other noninvasive imaging modalities.

Xenon Bronchography

Xenon contrast bronchography is based on this principle of K-edge dichromography. Two line-scan images are simultaneously recorded using monochromatic X-ray beams whose energies closely bracket the K-edge of xenon, 34.56 keV (Figure 3). As outlined above, the image recorded with the high energy beam includes signal attenuation arising from the photoelectric absorption of the K-shell electrons of xenon, Compton attenuation by electrons of xenon, and photoelectric and Compton attenuation from electrons of atoms comprising the soft tissues, bone, and air. The image recorded with the low energy beam includes virtually identical signal attenuation except that there is no attenuation by the K-shell photoelectric effect of xenon. Therefore the logarithmic subtraction of the two images results in an image of the contrast agent, and essentially eliminates all other signals.

In principle, the best images can be obtained when the highest concentration of xenon is present in the airway deadspace and the lowest concentration present in the alveoli, thus maximizing the contrast between airways and adjacent alveoli. Based on this principle, we have designed a xenon inhalation protocol to optimize airway contrast while simultaneously minimizing the alveolar xenon concentration and thus the absorption of soluble xenon gas into the bloodstream. This protocol limits the opacification of the pulmonary circulation and avoids the potential anesthetic effects of xenon. Aside from being a weak general anesthetic, the gas is otherwise nontoxic.

Medical-grade nonradioactive xenon gas (80 percent xenon, 20 percent oxygen; Praxair Inc., East Chicago, Indiana), is used as the bronchographic contrast agent in these studies. In preliminary studies, we have found that optimal large airway xenon concentrations were obtained when the subject inspired a gas volume (500 ml) which was slightly greater than the estimated anatomical dead space.

The Imaging System for Xenon Bronchography

The bronchography imaging system is similar to the system used in dichromographic coronary angiography at beamline X17B2 at the National Synchrotron Light Source, reconfigured for operation at the K-edge of xenon (34.56 keV). This system is shown schematically in Figure 6. In summary, an electron beam (200mA, 2.5 GeV) passing through a 3.0 T superconducting wiggler emits a horizontal fan beam of polychromatic X-radiation, which is split into an upper and lower pair of beams that fall onto a bent Laue monochromator. The dual beam monochromator is adjusted to produce two monochromatic fan beams that bracket the K-edge of xenon and are separated by 300 eV. The bandwidth at FWHM is 135 eV. The beams converge and cross at the patient forming a 125 mm wide and 0.4 mm high area of interrogation. The beams then diverge and are simultaneously measured by a 600-element Si(Li) dual beam line detector located 3.7 m behind the subject. The pixel resolution of this imaging system is 0.5 by 0.5 mm.

Using xenon gas, the monochromator is adjusted to the xenon K-edge. Exposure levels are determined by referencing a pre-run set of TLD (thermoluminescence dosimeter) calibrations. A patient positioning scan is performed using a low radiation dose, typically 0.16 rad, prior to the contrast studies. Aluminum filters are then adjusted on the basis of the subject's weight and girth

to determine the minimum radiation dose that produces the maximum contrast. The average radiation dose for each bronchographic image was 0.30 - 0.35 rad skin entry dose.

The patient is seated in a power-driven, computer-controlled chair and is scanned vertically through the fan beams of monochromatic radiation. The two monochromatic beams converge at the position of the subject's lung, diverge, and then impinge on a pair of lithium-drifted silicon line detectors, with pixel resolution of 0.25 mm by 0.25 mm. The output current of each detector (each X-ray photon gives rise to about 10,000 electrons) is fed into a two-stage amplifier, then into a voltage-to-frequency converter, and then into a scaler. The dynamic range of the electronic system is 40,000:1, in a readout time of approximately 2 ms. The images are recorded in line scan fashion and assembled by the computer. The exposure time for each line is 4 msec, and approximately 1.2 sec are required to complete an entire image.

These two images are then processed to produce a difference image of the xenon contrast agent, delineating the airways, and virtually eliminating signals from soft tissue and bone.

Figure 6. The optical system employing synchrotron radiation for xenon bronchography. The polychromatic radiation is monochromatized by diffracting elements that provide two monochromatic beams with energy closely bracketing the K-edge of xenon. The beams cross at the position of the subject's lung, diverge, and then impinge upon the dual detectors.

Preliminary Studies

Xenon contrast bronchograms were obtained in two healthy male volunteers. To optimize airway contrast, each subject inhaled room air to near total lung capacity (at which point the airways are optimally patent), then inhaled 500 ml of the xenon-oxygen gas mixture from a latex anesthesia reservoir bladder over a period of 5 sec. The subject then held his breath for 5 sec. The dead space of the xenon administration apparatus was less than 5 ml.

Figure 7a. Xenon bronchogram of the right lung in a normal subject. Third and fourth order bronchioles are visualized.

Figure 7b. Xenon bronchogram of the left lung in a normal subject. The bronchograms shown in Figures 5a and 5b, as well as the chest X-ray shown in Figure 6 are from the same patient.

The subject was seated in a motor-driven, computer-controlled chair, and was scanned while being moved vertically through the two monochromatic beams at a rate of 12 cm/sec. Each image (125 mm horizontal and 150 mm vertical dimension) was acquired during a period of 1.5 sec. Four sequential images of each lung were recorded for each subject. The first image was taken 2 sec after the onset of inhalation of xenon, the second at 4 sec after the onset, the third image after 1 sec of breath-holding, and the fourth after 3 sec of breath-holding.

Figures 7a and 7b are images of the right and left bronchial airways obtained in one of the normal volunteers. The recordings were made in the anteroposterior projection. Airways, ranging in size from the mainstem bronchi to fourth-order branches, can be seen. The xenon concentration at the level of the first bronchial bifurcation was 75 percent, as determined by X-ray attenuation measurements. The second subject's conventional chest X-ray is shown in Figure 8, for comparison. The X-ray dosage at the skin was measured at approximately 0.3 rad/image. However, these are very low intensity (34 keV) X-rays; thus, the total body radiation dose is substantially lower (1/10 to 1/100 of the skin dose).

Figure 8. Conventional chest X-ray of the subject whose xenon bronchogram images are shown in Fig. 5.

Limitations of K-Edge Dichromography

The initial studies performed by our group utilized a Bragg monochromator for coronary imaging studies. A limiting feature of this instrument was the relatively low flux of the monochromatized X-ray beams. Development and implementation of a focusing Laue monochromator was a significant advance in our ability to utilize monochromatic X-rays for medical imaging (Figure 4).

However, the image quality did not improve quantitatively as much as one would have expected from the increase in X-ray fluence. The pixel-to-pixel noise saturates at about 3% in human subjects for the high and low beams taken separately, even though studies on wedge absorbers show that the statistical fluctuations could be reduced to the 0.2% level at the same intensity, consistent with the statistics of the beam. From this we conclude that there is an inherent granularity in the absorbance of the human torso of about 3%, at a transverse dimension of 0.5 mm. This is equivalent to roughly a 1 mm fluctuation in the effective thickness of the patient, over an average thickness of 250 mm, which is not too surprising. From analysis of the difference

image we have shown that the fluctuations associated with this "granularity" do not perfectly cancel in the present geometry.

This lack of cancellation is the chief handicap of the Laue monochromator and occurs because of the parallax effect arising from the non-coplanarity of the beams falling on the patient. In practice, this angle is approximately 900 mrad, so there is a substantial non-overlap of the beams in front of, and behind, the patient's heart. Thoracic tissue is intrinsically granular, owing to, for example, the alveoli (200 μ m), bone porosity, and so forth. Thus, the present method does not adequately subtract the fluctuations arising from this granularity, resulting in a background noise that obscures the organs under examination.

Although this is the main handicap of the method, there are additional problems that compromise the image quality using the Laue monochromator at NSLS: poor harmonic rejection, broad bandpass, wide energy separation, and poor beam noise rejection. Poor harmonic rejection arises from the fact that in a single Laue reflection, the (333), (444), and (555) reflections are strongly allowed. The resulting harmonic contamination compromises the quality of the subtraction, giving rise to microscopic, as well as large-scale, artifacts. This problem has been largely overcome through reduction in the field strength of the superconducting wiggler magnet. This lowers the critical energy, and essentially eliminates harmonic contamination. The broad bandpass of the monochromator, as well as the wide energy separation of the beams, also compromises the integrity of the subtraction of bones, owing to the slight differences between the energy dependence of the absorption coefficient of tissue relative to bone. Whereas the bandwidth using Bragg diffraction was only 15-25 eV, it is much larger when using a Laue monochromator--approximately 150 eV. Furthermore, beam position shifts, either adiabatic, sudden, or oscillatory, can result in large relative intensity shifts between the two beams, giving a line-to-line flicker in the subtracted intensity.

To overcome the problems of spatial and temporal misregistration owing to non-coplanarity of the high and low energy beams with the current Laue monochromator, we proposed to develop a novel monochromator geometry which would utilize paired Laue-Bragg monochromators to produce a single beam of radiation of different wave lengths. After passing through the patient, these two beams would be separated by a single Laue crystal, and directed upon two linear position-sensitive detectors. This innovation would have the effect of reducing noise to its theoretical level of 0.2%, and would afford a significant improvement in signal:noise. The final result would be superior images obtained at a fraction of the radiation exposure to the patient. During preliminary studies we constructed and tested a model Laue-Bragg monochromator. The results validated the proof-of-principle concept, with elimination of the image degradation produced the misregistration of the two X-ray beams. We had hoped to construct a full-size model of the monochromator, which is depicted in Figure 9.

Figure 9. Proposed Laue-Bragg monochromator. Polychromatic synchrotron radiation is diffracted by a Laue crystal into a high and a low energy beam of monochromatic radiation. The beams are then directed by Bragg diffraction through another Laue crystal. This crystal exactly superimposes the two X-ray beams. Thus, the beams overlap exactly when passing through the imaging target, thereby eliminating misregistration. The beams are subsequently separated back into the high and low energy components following diffraction by another Laue crystal.

The basic principle would be to utilize a pair of Laue-Bragg monochromators to prepare a beam of radiation comprised of two horizontal, physically overlapping beams of distinct wave-lengths. Downstream of the patient, the two beams are resolved by a single Laue crystal, whereupon they impinge upon two linear position-sensitive detectors. A detailed dynamical diffraction calculation yields the following efficiency-bandwidth product for various possible sequences of crystals:

Reflection sequence	Efficiency x Bandwidth
Laue-Bragg-Laue	0.3×10^{-4}
Laue-Bragg-Bragg	0.5×10^{-4}
Bragg-Laue-Bragg	0.5×10^{-4}
Bragg-Laue-Laue	0.3×10^{-4}

Since the first Laue reflection may suffer modest distortion due to thermal loads, it would be most conservative to have the Laue-Bragg pair followed by a Bragg, rather than Laue, reflection. From the above table it can thus be seen that the optimum choice of reflection sequences would be Laue-Bragg-Bragg for the high energy beam (33160+e eV) and Bragg-Laue-Laue for the low energy beam (33160-e eV). The higher fluence is chosen for the high-energy beam because there is a slight signal-to-noise advantage, owing to the relatively greater opacity of the dye above the absorption threshold.

A feature of Laue-Bragg style monochromators is the need to compensate for the refraction of the X-ray wave in the Bragg crystal (an effect which is negligible in the Laue crystal). At 33160 eV in silicon this amounts to 7 mradian or 1.5 arc seconds. This compensation will be achieved by mounting a piezoelectric transducer onto the crystal, and cutting a slot in the material to allow for a weak link. This is an established technique and should have posed no problem.

A key feature of the proposed beam line would have been the inclusion of an X-ray mirror at the 12.5 m position, to provide an achromatic line focus of the radiation at the patient (see Figure 7). This mirror would be a 1.0 m long flat, platinum-coated fused quartz mirror, tilted at an angle of 2.0 mrad, and dynamically bent to provide 1:1 vertical focusing. This would result in a beam of less than 100 mm vertical size at the patient, yet would allow the collection of 2 mm of beam at the 12.5 m point, or about 160 mrad. Since the vertical opening angle of 33 keV radiation from the beam line IV wiggler magnet (intrinsic plus electron beam spread) is about 100 mrad, virtually all of the useful beam would be accepted.

Figure 10. Diagram of platinum-coated fused quartz mirror

These instrumentation developments would result in co-planar monochromatic X-ray beams, with elimination of beam misregistration. Importantly, because of the significant improvements in signal:noise, this would have allowed for additional reduction in X-ray dose, and should have provided the basis for obtaining funds for construction of a small, clinically suitable synchrotron storage ring.

SUMMARY

Medical imaging using synchrotron radiation and K-edge dichromography was pioneered at Stanford University under the leadership of Dr. Ed Rubenstein, and the late Nobel Laureate in Physics, Dr. Robert Hofstadter. With progressive refinements in hardware, clinical-quality images were obtained of human coronary arteries utilizing peripheral injections of iodinated contrast agent. These images even now are far superior to those being presented by investigators using MRI as an imaging tool for coronary arteries. However, new supplies and instruments in the cardiac catheterization laboratory have served to transform coronary angiography into an outpatient procedure, with relatively little morbidity.

We extended the principles learned with coronary angiography to noninvasive imaging of the human bronchial tree. For these images, we utilized xenon as the contrast agent, as it has a K-edge very similar to that of iodine. In this case, there is no true competing diagnostic test, and pulmonary neoplasm is an enormous public health concern. In early experiments, we demonstrated remarkably clear images of the human bronchial tree. These images have been shown internationally; however, funding difficulties primarily with the Department of Energy have not allowed for progression of this promising avenue of research.

One potential criticism of the project is that in order to obtain these images, we utilized national laboratories. Some have questioned whether this would lead to a practical imaging modality. However, we have shown that the technology exists to allow for construction of a miniature storage ring, with a superconducting wiggler magnet, which would occupy minimal space, and would be of a cost comparable with that of a clinical cardiac catheterization laboratory.

Much of the focus of this research is now shifting to Europe, where individual whom we have trained or with whom we have worked are now heading up extensive efforts in medical imaging and K-edge dichromography. This work is occurring mostly at DESY in Hamburg, and at the European Synchrotron Research Laboratory (ESRF) in Grenoble.