chromosome in Escherichia coli by bacteriophage lambda-based recombination. Nat Methods. 2005 Feb;2(2):95–97.

Patent Status: U.S. Patent No. 7,494,813 issued 24 Feb 2009 (HHS Reference No. E–355–2001/2–US–02).

Licensing Status: Available for licensing.

Licensing Contact: Sue Ano, PhD; 301–435–5515; *anos@mail.nih.gov*.

Dated: December 23, 2009.

Richard U. Rodriguez,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. E9–31075 Filed 12–30–09; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, HHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of Federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7057; fax: 301/402–0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Fourier X-ray Scattering and Phase-Contrast Imaging: Enhanced Contrast and Sensitivity of X-ray Images

Description of Technology: The invention offered for licensing is broadly applicable to medical diagnostic imaging, biological imaging, industrial non-destructive testing, security screening, and other routine x-ray inspections. The invention provides a method and apparatus that can significantly improve and enhance the contrast and sensitivity of x-ray images. More specifically, the method described in the invention provides a technique to obtain in a single shot x-ray diffraction, differential phase-contrast, as well as the conventional absorption images. X-ray diffraction reveals information about microscopic structures in the imaged object from nanometer to micrometer scales which enables detection of specific materials and disease pathologies that are invisible in conventional x-ray images. The main advantage of the invention over prior art is the single-shot capability without the need to scan an analyzer crystal or grating, and without the need for any hardware beyond standard radiography equipment. It also offers flexibility in hardware configuration to target specific materials by their diffraction signature. For this reason the invention is highly adaptable and well suited for day-to-day applications of x-ray radiography and computed tomography.

In one of the embodiments of the invention for example, a scattering imaging method uses a transmission grid to modulate the intensity of a beam of an x-ray radiation source. A detector captures a raw image from the modulated intensity pattern. A diffraction image can be automatically generated from the detected modulated intensity pattern.

In yet another embodiment, both a diffraction image and a differential phase-contrast image are obtained in a single exposure. Advantageously, commercially available x-ray grids and radiography machines can be used for this method, and exact positioning of the grid is unnecessary, as the method works for any non-zero distance between the grid and the detector. Thus, the speed and ease of implementation makes it suitable for both planar radiography and 3D computed tomography. In addition to its medical diagnostics significance, the invention can be utilized in other, non-medical applications such as non-destructive inspections and security screening.

Applications

- Medical diagnostic radiography and computed tomography. For example, imaging blood vessels, imaging of bones (*i.e.,* osteoporosis, fractures).
- Non-invasive characterization of material microscopic structures by planar radiography or 3D computed tomography implementations of the invention.
- Detection of materials by their diffraction signature in x-ray inspections and security screening.

Advantages: Although x-ray diffraction and phase-contrast imaging can detect materials and structures that are invisible by conventional absorption images, current techniques remain difficult to implement due to requirements for specialized x-ray optical components and/or brilliant sources, and lengthy scanning of analyzer components such as perfect crystals or high-density gratings. A recent publication (US2007/0183563 A1) mentioned that by using a detector with elements less than ⅓ of the pitch of an analyzer grating, it is possible to obtain differential phase-contrast images in one measurement without the need to scan. US2007/0183580 A1 further elaborates on this technique and specifies that the detector elements are an integer fraction of the grating pitch so that sub-groups of the detectors can report x-ray intensities of different portions of a grating period, from which the phase shift of the grating pattern is measured. Such detectors are highly challenging to realize, and are not able to cope with varying pitches or patterns of x-ray beam modulation.

It is additionally known in the art to remove the effects of scattering with the use of grids, gratings, or other masks of periodically arranged opaque areas. Specifically, a mask or multiple masks of periodically arranged opaque areas are placed in the x-ray path, such that periodic dark shadows are created on a recorder surface either by direct geometric shadowing or by wave-interference effects. The shadow areas only receive x-ray which is scattered in the object. The signals of these shadow areas are subtracted from the raw image to yield an image free of the effects of scattering.

Nonetheless, the above variations require exacting procedures or are expensive, making the prior art ill-suited for today's routine x-ray imaging applications, including non-destructive testing (*e.g.,* component inspection without damage), security screening, and medical diagnostic exams.

The present technology overcomes the drawbacks of the prior art by allowing the acquisition of x-ray diffraction, differential phase-contrast and absorption images all in a single exposure without the need for scanning or any hardware beyond commercial radiography equipment.

It is particularly flexible when compared to prior art in that the number of transmission grids, their patterns and their positions can all be adjusted to selectively detect or enhance specific materials, such as contrast agents in medical diagnostic imaging or explosive materials in security screening.

Development Status: The invention is fully developed.

Market: The market for medical imaging equipment industry is approximately $9.0 billion dollars now and has been growing by approximately 7.6% annually. X-ray imaging and related instrumentation constitutes a significant portion of this market.

• X-ray radiography is the most common and widely available diagnostic imaging technique. Even when a diagnostic testing requires more powerful or sophisticated tests, an x-ray imaging may many times be needed first before other more sophisticated tests are applied.

• X-ray angiography currently provides the best visualization of blood vessels in the body. The ability of this technology to selectively enhance contrast agents can eliminate difficulties associated with subtraction angiography and improve angiography exams.

• The advent of Computed Tomography (CT) and other digital x-ray technologies have enhanced the capabilities of x-ray imaging and have resulted in the tremendous growth of x-ray imaging. CT combines x-rays with computer technology and can produce a highly detailed, cross-sectional image of the body and organs, tissues or tumors inside the body. CT scans are now routinely used to diagnose problems with small, bony structures or in cases of severe trauma to the brain, spinal cord, chest, abdomen, or pelvis. Furthermore, the introduction of multi-slice CT has been one of the most significant enhancements ever brought to the market, and the technological innovations that have been made within the realm of CT in recent years are revolutionary and should be the primary drivers for future industry growth. Electron Beam Technology (EBT) for example is a CT technology that created opportunities in cardiac diagnostics. CT requires fast and robust image acquisition, thus the present invention is uniquely able to enhance CT with diffraction and phase contrast.

• The United States market for computed tomography (CT) scanning systems is estimated to touch $3.6 billion by the end of 2009. The U.S. accounts for over 50.0 percent of the worldwide market. Cardiac imaging is a fast expanding CT application due to its utility in emergency medicine, perfusion studies and CT angiography. While hospitals started out as the original care site where scanning was done, independent imaging centers and physician's offices offering scanning have become widespread in the U.S. over the last decade. With the advent of portable and mobile CT scans, access and availability of this imaging modality has increased significantly. Currently it is estimated that about 25% of scanning stations are in private practices and imaging centers that are not part of a hospital. Most hospitals have a range of scanners from low-slice to high-slice. The overall trend is towards acquiring high-slice scanners which can be similar in terms of capital costs but far superior in function.

• One of the fastest growing applications is CT angiograms, currently at an annual rate of about half a million in the U.S. Pediatric usage is also growing. An estimated 6 million CT scans per year are done for pediatric cases. Of these, about 600,000 are done for head and abdominal examinations. The ability of the present technology to highlight certain contrast agents against background tissue and bone signal can significantly enhance CT angiography.

• The women's mammography segment of x-ray imaging is poised for a major new phase of growth fueled by the availability of new technology coming out of the computer and digital areas and the higher interest of individual patients and general healthcare consumers to take charge of their own health status. Continuous improvements in technology are resulting in a growing number of new imaging diagnostic tests that combine high levels of accuracy with rapid, easy-to-use product formats. Digital mammography is driving more screening programs.

• X-ray inspection in product quality control and in security screening. The present technology offers the ability to detect and target materials based on their x-ray diffraction signatures. It may significantly enhance the sensitivity and specificity of the inspection.

The present technology provides enhancement in x-ray imaging, thus its application in x-ray instrumentation, offers excellent commercial opportunities given the size of the industry.

Inventors: Han Wen (NHLBI).

Related Publications

1. Wen H, Bennett EE, Hegedus MM, Rapacchi S. Fourier X-ray scattering radiography yields bone structural information. Radiology 2009 Jun;252(3):910–918.

2. Wen H, Bennett E, Hegedus MM, Carroll SC. Spatial harmonic imaging of X-ray scattering—initial results. IEEE Trans Med Imaging 2008 Aug;27(8):997–1002.

Patent Status: PCT Application No. PCT/US2009/051642 filed 24 Jul 2009 (HHS Reference No. E–248–2009/0–PCT–01).

Licensing Status: Available for licensing.

Licensing Contacts: Uri Reichman, PhD, MBA; 301–435–4616; *UR7a@nih.gov;* or John Stansberry, PhD; 301–435–5236; *stansbej@mail.nih.gov.*

Collaborative Research Opportunity: The National Heart, Lung, and Blood Institute, Laboratory of Cardiac Energetics, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize single-shot x-ray diffraction and phase-contrast imaging. Please contact Denise Crooks at 301–402–5579 or *crooksd@nhlbi.nih.gov* for more information.

Non-Contact Total Emission Detection Methods for Multiphoton Microscopy: Improved Image Fidelity and Biological Sample Analysis

Description of Technology: The technology offered for licensing and for further development is in the field of multiphoton microscopy (MPM). More specifically, the invention describes and claims optical designs that can enhance and extend the capabilities of MPM in spectral imaging of biological samples. The unique design of the light collection and the detection optics maximizes the collection of emitted light, thus increasing the signal and hence the signal-to-noise ratio (SNR). Improvement in image fidelity will result in improved analysis of biological samples and thus will favorably impact medical research and possibly clinical diagnosis. The present technology is a further improvement on the TED (Total Emission Detection) technology, first disclosed by Dr. Robert Balaban *et al.* at the NIH in 2006 and claimed in U.S. patent application 11/979,600, now allowed (Patent Publication US–2008–0063345 A1, March 13, 2008). The earlier NIH TED technology proposed an optical design based on enveloping the entirety of a small sample in a parabolic mirror/condenser combination so light emanated by a sample in all directions is redirected to the detector. The present technology further expands the capabilities of TED as its unique design employing parabolic, toric and conic mirrors ensures maximum light collection from large samples in cases where there is only access to one side of the tissues (*e.g., in vivo* or *ex vivo*). This is accomplished by the redirection of all attainable light (*i.e.,* light escaping the tissue or a whole animal in the epi and sideway directions) to the detector.

Applications

• Tissue and cell analysis in biomedical research.

• Potential applications in clinical diagnostics.

Advantages: The advent of multiphoton microscopy (MPM) provided several advantages in comparison to single-photon confocal microscopy. In particular the nonlinear optics used with this technology, combined with the elimination of a confocal pinhole aperture, led to direct sectioning and the use of lower energy photons. This approach preserves the integrity of the observed object (i.e. tissue) thus improving imaging results. The technology presented here further enhances the capabilities of MPM by providing the following advantages:

- Increased signal-to-noise ratio.
- Enhanced image resolution due to SNR.
- Improved analytical capabilities.
- Non-contact.
- May readily be adaptable to commercial microscopes.

Development Status: The invention is fully developed. Prototype microscope has been built. May need further validation by rigorous in vivo testing under a variety of different conditions. Also need to build the smaller prototype that could screw into normal objective turrets. Alternative realizations with 'integrated optic' structures are also planned.

Market: Multiphoton microscopy (MPM) has found a niche in the world of biological imaging as the best noninvasive means of fluorescence microscopy in tissue explants and living animals. Coupled with transgenic mouse models of disease and 'smart' genetically encoded fluorescent indicators, its use is now increasing exponentially. Properly applied, it is capable of measuring calcium transients 500 μm deep in a mouse brain, or quantifying blood flow by imaging shadows of blood cells as they race through capillaries. One of the great advantages of optical microscopy is its ability to let scientists peek beneath the tissue surface and study cellular processes at work. Over the last two decades, the use of multiphoton microscopy has spread to all major areas of biological research. As researchers are finding more and more applications for this powerful technique the need for enhanced performance and enhanced capabilities is also increasing. The improvements provided in the present technology are simply added to existing MPM and therefore present excellent commercial opportunities.

Inventors: Jay R. Knutson (NHLBI).

Related Publications

1. U.S. Patent Application Publication US–2008–0063345 A1, March 13, 2008.

2. Presentation, 7th EBSA European Biophysics Congress, July 11–15, 2009, Genova, Italy (*http://EBSA2009.org*).

3. CA Combs, AV Smirnov, JD Riley, AH Gandjbakhche, JR Knutson, RS Balaban. Optimization of multiphoton excitation microscopy by total emission detection using a parabolic light reflector. J Micros. 2007 Dec;228(Pt3):330–337.

Patent Status: U.S. Provisional Application No. 61/224,772 filed 10 Jul 2009 (HHS Reference No. E–236–2009/0–US–01).

Related Technology: U.S. Patent Application No. 11/979,600 filed 06 Nov 2007, now allowed (HHS Reference No. E–257–2005/0–US–04).

Licensing Status: Available for licensing.

Licensing Contacts: Uri Reichman, PhD, MBA; 301–435–4616; *UR7a@nih.gov;* or Michael Shmilovich, JD; 301–435–5019; *shmilovm@mail.nih.gov.*

Collaborative Research Opportunity: The NHLBI Laboratory of Molecular Biophysics is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize an enhanced method of multiphoton microscopy that is suitable for the spectral imaging of biological samples. Please contact Brian W. Bailey, PhD at *bbailey@mail.nih.gov* for more information.

Dated: December 24, 2009.

Richard U. Rodriguez,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. E9–31074 Filed 12–30–09; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, HHS.

ACTION: Notice.

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Device and Method for Direct Measurement of Isotopes of Expired Gases: Application in Research of Metabolism and Metabolic Disorders, and in Medical Screening and Diagnostics

Description of Technology: The technology offered for licensing and for further development concerns a novel device for intervallic collection of expired gas from subjects and subsequent measurement of the isotopic content of such expired gases. The device is specifically designed for medical research and clinical applications, and in particular in the area of metabolic disorders. The device may facilitate the development and testing of new therapies for such disorders and may be used for medical screening and diagnostics of metabolic diseases. The unique design of the device includes a constant volume respiratory chamber equipped with a series of valves and stopcocks to allow precise and repetitive removal of expired gases, and addition of air or other gas to maintain the chamber at a constant volume. Also included is a vacuum tube adapter linked to a port on a three-way stopcock to allow facile transfer of the chamber gases to vacuum tubes for subsequent chemical analyses. The device also includes gas sensors operably linked to detectors and inserted to the chamber through airtight ports; this allows the operator to independently and directly measure the carbon dioxide production rate and oxygen consumption of the test subject while the expired gases are removed for study.

The experimental subject (*e.g.* mammal) is first contacted with a substrate (*e.g.* amino acid, fatty acid, organic acid) containing an isotope (*e.g.* ^{13}C) and placed in the chamber. The unique design allows easy gas removal and addition while maintaining a constant chamber volume. Precisely measured air samples are collected from the chamber by the syringe and subsequently transferred to a self-sealing vacuum tube which is then removed for analysis. Subsequent sampling is accomplished in the exact