New Light Emission Detection Method Enables High Resolution Optical Imaging of Biological Tissue.

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PATENT STATUS

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United States Of America	Issued Patent	8,692,998	04/08/2014	2011-030

BRIEF DESCRIPTION

Researchers at the University of California, Irvine have developed a novel method for capturing cellular resolution images of biological tissue at depths of up to several millimeters.

Conventional fluorescence detection methods utilize microscope objectives for emission light collection, a less effective approach that is only capable of imaging up to one millimeter deep.To improve upon this standard, the UC researchers minimized light losses by optimizing the system's excitation and detection optics.

This new novel method increases the ability to capture cellular resolution images of biological tissues at depths 3x that of previously used methods. The improved method is capable of imaging up to 3 millimeters deep, while previous methods were only capable of depths up to 1 millimeter.

FULL DESCRIPTION

Biological tissue is by nature a turbid media, with optical properties characterized by a strong multiple scattering and inhomogeneity of the refractive index. As a result, most of the excitation light focused inside the turbid media is scattered before reaching the focal area, limiting imaging depth. Conventionally, fluorescence photon excitation and fluorescence detection are performed using the same microscope objective. However, this is an inefficient process due to the objective’s narrow light acceptance angle and limited sample area. For these reasons, two-photon induced fluorescence, the turbid media imaging standard, is localized in a small (micron scale) focal area inside the sample and is only capable of capturing images at depths of up to one millimeter.

In this novel approach, UCI researchers have developed an imaging system to enable a more efficient collection of fluorescence and enhance the potential imaging depth to several millimeters.

The invention is an apparatus and method for in-depth fluorescence imaging using two-photon fluorescence imaging in turbid media. The invention separates the excitation and detection optics, which allows for a more efficient collection of fluorescence and enhances the image depth.

The current invention provides an apparatus for in-depth imaging of a turbid sample. The apparatus includes a source of an excitation beam, excitation optics optically coupled to the excitation beam for optically processing the excitation beam, and a microscope optically coupled with the processed excitation beam. An objective is coupled to the microscope and is disposed on a first side of the turbid sample for directing the coupled excitation beam onto the first side of the turbid sample. A detector assembly is disposed on a second side of the turbid sample, wherein the detector includes detection optics and includes means for producing an

OTHER INFORMATION

KEYWORDS

Two-photon microscopy, Turbid media, Multiple scattering, Imaging depth, Fluorescence detection

CATEGORIZED AS

- **Agriculture & Animal Science**
  - Animal Science
  - Devices
  - Other
- **Biotechnology**
  - Health
  - Other
- **Imaging**
  - Medical
  - Molecular

in depth image from detected fluorescence coupled to the detector.

The objects of current embodiments of the invention are achieved by utilizing a wide cathode area photomultiplier tube coupled to a waveguide for detection and a shutter with index matching compounds. The detector assembly is placed directly on the specimen. The index matching compounds eliminate or reduce losses due to light reflection at optical component boundaries between the optical elements in the detector assembly. Unlike conventional detection methods that utilize microscope objectives for emission light collection, this method provides for the collection of multiply media-scattered photons from a wide area of the sample surface with minimum light losses (e.g. an area 25 mm in diameter or greater), because all photons, which reach the sample surface and enter the detector at any angle are directed to photocathode and detected. This cannot be achieved by use of conventional microscope objectives, which have limited light acceptance angle and area.

A primary purpose of the invention is to create a practical imaging system that is capable of obtaining cellular resolution images of biological tissues in depth of more than few millimeters. The invention uses a detector to help achieve this end. The advantage of the invention is the ability of the detector to collect multiply scattered photons from a wide area of the turbid media at any entering angle and direct them to PMT photocathode without losses or at least disabilitating losses. In addition to high detection efficiency, the detector is simple in construction and does not require any focusing optics. Using this detector in a two-photon microscope, allows for imaging depths of tissue samples can be expended to few millimeters (1-3 mm), compared with conventional detection that allows imaging only up to 1 millimeter.

The detector significantly enhances the apparatuses capability of efficiently collecting scattered fluorescence photons from a wide area of the turbid sample. By using this detector it is possible to perform imaging of turbid samples, simulating brain tissue at depths up to 3 mm, where the two-photon induced fluorescence signal is too weak to be detected by previous means used in conventional two-photon microscopy. The detector separates the excitation and detection optics which allows for more efficient collection of fluorescence and enhances the possible imaging depth.

The detector can also be combined with a scanning endoscope in the single imaging head to make an imaging device for noninvasive diagnostics and imaging of brain, breast, skin tumors and other disease states.

SUGGESTED USES

The invention is intended to be used in two-photon microscopy for the imaging of biological tissues.

In future applications, the detector could potentially be coupled with a scanning endoscope to produce an invasive imaging and diagnostic device. It could be used as a non-invasive diagnostics of imaging of the brain, breast, skin tumors and other disease states.

ADVANTAGES

Conventional detection allows imaging for sample depths of up to 1 millimeter. The advantage of this method is the ability of the detector to collect multiple-scattered photons from a wide sample area without significant losses. Using this detector in two-photon microscopy, the imaging depth of tissue samples can be significantly increased to up to 3 millimeters.

STATE OF DEVELOPMENT

A prototype has been developed.

TESTING

Tested using biological tissue samples.

RELATED MATERIALS

» Luca Lanzanò, Iván Coto Hernández, Marco Castello, Enrico Gratton, Alberto Diaspro, and Giuseppe Vicidomini. “Encoding and decoding spatio-temporal information for super-resolution microscopy.” Nat Commun. 2015; 6, 6701. PMCID: PMC4384168 - 04/02/2015

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