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(54) **QUANTITATIVE MULTI-SPECTRAL OPTO-ACOUSTIC TOMOGRAPHY (MSOT) OF TISSUE BIOMARKERS**

QUANTITATIVE MULTISPEKTRALE OPTOAKUSTISCHE TOMOGRAPHIE (MSOT) VON GEWEBEBIOMARKERN

TOMOGRAPHIE OPTO-ACOUSTIQUE MULTI-SPECTRALE QUANTITATIVE (MSOT) DE BIOMARQUEURS TISSULAIRES

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Description

Field of the invention

[0001] The present invention relates to a method and a device for quantitative three-dimensional sensing and imaging of target tissue biomarkers, in particular in clinical, small animal and small organism imaging applications using multiple-wavelength illumination.

Background of the invention

[0002] Non-invasive imaging of functional and molecular biomarkers *in vivo* is an emerging and important capacity in biological discovery, drug discovery and several clinical applications, which goes beyond anatomical imaging and retarded disease identification. Another important prospect of visualizing tissue biomarkers is the ability to examine and quantify treatment responses *in vivo* by monitoring specific primary molecules or downstream targets. Therapeutic efficacy could then be probed dynamically on timescales of hours to days. This ability is in contrast to the mainstay of today's healthcare with traditionally late end points of drug efficacy, a practice that often impairs prompt revision and exclusion of ineffective treatment strategies with potentially lethal results.

[0003] Similarly, while microscopy gives unprecedented insights into biology, it can only penetrate for a few hundred microns in tissues. Therefore the biological *in vivo* observation is limited by the microscopy penetration limit. Clearly methodologies that can penetrate deeper in tissue and visualize the microscopic contrast or utilize new contrast mechanisms are of immense importance in dynamic observations of biological phenomena, in developmental studies and in the drug discovery process.

[0004] Optical functional and molecular mesoscopic and macroscopic imaging of tissues has opened new pathways for study of many pathological processes *in vivo*. Indeed, optical wavelengths offer great variety of probing mechanisms that can be used for variety of interrogations, from intrinsic functional information on blood oxygenation to molecular sensing. The use of extrinsically-administered fluorescent optical agents has further advanced the noninvasive photonic imaging by allowing visualization of otherwise invisible cellular and subcellular processes. For instance, the use of contrast agents and fluorescent reporters with specificity to proteins and enzymes has shown a high potential to differentiate several diverse disease biomarkers, such as inflammation and tumor progression.

[0005] US patent 6,641,798 discloses tumor-targeted optical contrast agents useful for diagnostic imaging and therapy. The bioconjugates described include cyanine dyes with a variety of bis- and tetrakis (carboxylic acid) homologes. The compounds may be conjugated to bioactive peptides, carbohydrates, hormones, drugs, or other bioactive agents. The small size of the compounds allows more favorable delivery to tumor cells as compared to larger molecular weight imaging agents. These contrast agents are useful for diagnostic imaging and therapy, in endoscopic applications for the detection of tumors and other abnormalities, for localized therapy, for opto-acoustic tumor imaging, detection and therapy, and for sonofluorescence tumor imaging, detection and therapy. Fluorescence molecular tomography (FMT) is also capable of sensing picomole to femtomole quantities of fluorochromes in deep tissues at macroscopic scale, i.e. in whole animals with millimeter resolution. The technique shares tomographic principles with diffuse optical tomography and utilizes multi-projection illumination, combined with mathematical models that describe photon propagation in tissues, in order to reconstruct three-dimensional tomographic images of fluorochrome concentration.

[0006] US patent 6,615,063 describes a fluorescence-mediated molecular tomographic imaging system, designed to detect near-infrared fluorescence activation in deep tissues. The system can use targeted fluorescent molecular probes or highly sensitive activable fluorescence molecular probes. Such probes add molecular specificity and yield high fluorescence contrast, to allow early detection and molecular target assessment of diseased tissue, such as cancers, *in vivo*.

[0007] Recently, tomographic imaging of tissues using opto-acoustics (photo-acoustics) has also demonstrated the ability to achieve penetration depths from several millimeters up to centimeters range with ultrasonic resolution. Opto-acoustic imaging relies on ultrasonic detection of opto-acoustically induced signals following absorption of pulsed light. The amplitude of the generated broadband ultrasound waves reflects local optical absorption properties of tissue. Since scattering of ultrasonic waves in biological tissues is extremely weak, as compared to that of light, biomedical opto-acoustic imaging combines high optical absorption contrast with good spatial resolution limited only by ultrasonic diffraction. Photo-acoustic imaging was proven efficient in imaging vascular trees, tumor angiogenesis, blood oxygenation monitoring, as well as sensitive to tissue chromophores, light-absorbing nanoparticles and dyes, and chromogenic assays.

[0008] For instance, US patent 5,840,023 teaches a laser opto-acoustic imaging system, which utilizes time-resolved measurement of profiles of laser-induced transient pressure (acoustic) waves. The pressure waves are emitted by acoustic sources preferentially generated in absorbing tissues of diagnostic interest. This technique allows visualization of absorbed light distribution in turbid, layered and heterogeneous tissues irradiated by laser pulses in vivo. The laser opto-acoustic tomography can be used for the characterization of structure and properties of normal tissue, and for the

detection of tissue pathological changes. The optical heterogeneities that can be imaged with the laser opto-acoustic imaging system include abnormal tissues such as tumors, injured tissues, blood vessels and other layered tissues. Further, three dimensional images of organs and portions of organs can be obtained.

[0009] Therefore, multi-spectral detection is often applied, as a means to better discriminate spectral signatures of various objects of interest. For example, US patent 6,208,749 discloses a system for multi-spectral imaging of skin tissue that enables automatic characterization of the condition of a region of interest of the skin, based on direct digital imaging of that region or the digitization of its color photographic slides, when illuminating by appropriately filtered light. Parameters related to the texture, asymmetry, blotchiness and border irregularities are automatically estimated. The region of interest is automatically characterized by the digital processor, based on those parameters. The region of interest may include a skin lesion, in which case the characterization of the lesion as malignant or benign is enabled.

[0010] In US 6,760,609, a method for determining an arterial blood oxygen saturation level by measuring the light transmittance through tissue of light of a first wavelength and a second wavelength, is suggested. A steady-state component of the measured light transmission is used to select an appropriate calibration curve. A pulsatile component of the measured light transmission is used to determine the arterial blood oxygen saturation level using the selected calibration curves of oxy- and deoxy-hemoglobin spectral signatures. An oximetry system is further provided wherein a plurality of light transmission measurements are used to determine a blood oxygen saturation level.

[0011] In opto-acoustic spectroscopy, multi-wavelength methods were previously applied for differentiating blood chromophores (J. Laufer et al., "Phys. Med. Biol." vol. 52, p. 141-168, 2007, US 7 298 869).

[0012] US patent 6,498,942 also discloses an opto-acoustic apparatus which includes a radiation source of pulsed radiation and a probe having a front face to be placed in close proximity to or in contact with a tissue site of an animal body. The probe further includes a plurality of optical fibers terminating at the surface of the front face of the probe and connected at their other end to a pulsed laser. The front face of the probe also has mounted therein or thereon a transducer for detecting an acoustic response from blood in the tissue site to the radiation pulses connected to a processing unit which converts the transducer signal into a measure of venous blood oxygenation. Another method, disclosed in US patent application 2004/0127783, was suggested for imaging of dye markers by generating images with and without dye stimulation using two wavelengths (inside and outside the frequency band of fluorescence of the dye) and combining those for image enhancement.

[0013] A limitation of the above illumination techniques is that when operating with optically complex structures, such as tissue, the resulting images are a combined effect of the targeted chromophore and other native tissue chromophores. This complexity is particularly important in molecular imaging applications where molecular marker has to be resolved in the presence of many other non-specific tissue absorbers. In addition, opto-acoustic (or: photo-acoustic) observations so far have been limited to utilizing mono-directional homogenous illuminations, operating on the assumption that a similarly homogeneous illumination will occur as light propagates in tissue.

[0014] For example, WO 2007/084771 describes a method that delivers illumination which establishes "a homogeneous distribution of an energy fluence within any given plane or slice inside the body...". Such illumination field is very difficult to achieve in practice, since tissue heterogeneity is not known and can impose significant variations of light intensity at any given plane inside tissue. When cylindrical objects are considered, such as the mouse torso, the conversion of mono-directional illumination in polar co-ordinates results in the utilization of multiple illumination points, arranges so that light is directed towards the center of the object, in the longitudinal sense. In this case, in order to simplify the illumination and detection arrangements, it is required that the tissue of investigation is surrounded by water or a similar fluid.

[0015] B.T. Cox et al., Applied Optics, Vol. 45, No.8, 10. March 2006 disclose a method for two-dimensional quantitative photoacoustic image reconstruction of absorption distributions by use of a iterative method.

[0016] M. Zibulevsky et al., Blind Source Separation by Sparse Decomposition, ICA: Principles and Practice, Cambridge, 2001, disclose the use of spasse decomposition in a proper dictionary.

Objective of the invention

[0017] The objective of the invention is to provide an improved imaging method, in particular for clinical and preclinical imaging or laboratory search purposes, which is capable of avoiding disadvantages of conventional techniques. In particular, the objective is to provide an imaging method which enables three-dimensional localization in tissues and quantification of molecular probes with increased precision. Furthermore, the objective of the invention is to provide an improved imaging device in particular being adapted for conducting the inventive imaging method. The method and device are to be provided yielding in particular practical implementations and highly accurate discrimination of tissue biomarkers *in vivo.*

Summary of the invention

[0018] The above objective is solved by an imaging method and/or an imaging device comprising the features of the independent claims. Advantageous embodiments of the invention are defined in the dependent claims.

[0019] The present invention is based on the general technical teaching of quantitative three-dimensional sensing and imaging of tissue biomarkers, in particular in clinical, small animal and small organism imaging applications using multiple-wavelength illumination while accounting for photon propagation in tissue to achieve accurate knowledge of the multi-spectral photon excitation field, which in turn generates acoustic pressure waves.

[0020] The Method of multi-spectral opto-acoustic tomography (MSOT) imaging or a target tissue including a target tissue biomarker according to the invention, comprising the steps of:

- illuminating the target tissue with an illumination device emitting at least one pulsed illumination pattern at several illumination wavelengths,
- detecting pressure signals from the target tissue biomarker with a detector device, wherein the pressure signals being produced in the target tissue in response to said illumination,
  and
- reconstructing a quantitative tomographic image of a distribution of the target tissue biomarker in the target tissue, wherein the pressure signals are analyzed using
  a light fluence in the target tissue for decomposing light absorption from the light fluence using blind source separation, wherein the light fluence is directly extracted from the detected pressure signals and/or from opto-acoustic images,
  at least one spectral professing scheme for differentiation of the target tissue biomarker from a background absorption in the target tissue, and
  an inversion scheme providing the quantitative tomographic image.

[0021] The Imaging device, which is adapted for multi-spectral opto-acoustic tomography (MSOT) imaging a target tissue including a target tissue biomarker according to the present invention, comprising:

- an illumination device adapted for illuminating the target tissue with at least one pulsed illumination pattern at several illumination wavelengths that are absorbed by the target tissue biomarker,
- a detector device adapted for detecting pressure signals being produced from the target tissue biomarker in the target tissue in response to said illumination, and
- a reconstruction device adapted for reconstructing a quantitative tomographic image of a distribution of the target tissue biomarker in the target tissue, whereas the reconstruction device includes
  a processor adapted for using a light fluence in the target tissue for decomposing light absorption from the light fluence using blind source separation, wherein the light fluence is directly extracted from the detected pressure signals and/or from opto-acoustic images,
  a processor adapted for implementing a spectral processing scheme for differentiation of the target tissue biomarker from a background absorption in the target tissue, and
  a processor adapted for implementing an inversion scheme providing the quantitative tomographic image.

[0022] Preferably, the reconstruction device is adapted for applying inverse methods and spectral processing in order to build the image of a vessel, in particular blood vessel, like a coronary or a carotid artery, wherein the image represents a spatial distribution of the biomarker at a wall of the vessel.

[0023] Furthermore, the invention provides the multi-spectral illumination biomarker reporter imaging device that can be built with a small form factor to detect tissue biomarkers. Advantageously, this device can be applied to imaging molecular markers in biological samples and in clinical applications. Particular advantageous applications comprise resolving fluorescent proteins and/or extrinsically-administered chromogenic or fluorescent dyes in clinical inflammatory and cardiovascular applications and in other living biological samples.

[0024] The invention is based on the following considerations of the inventors. To detect a biomarker in the target tissue with optical methods, light is delivered locally at the area of the biomarker (or biomarker reporter). However, as light propagates in tissue, intrinsic tissue absorption and overall light propagation characteristics alter the propagation pattern, by creating a heterogeneous deposition of energy in the various tissue elements which is also wavelength-dependent. Thus it becomes challenging to isolate the contribution of the biomarker on the detected signal.

[0025] As outlined in the above background section, multi-spectral methods, including opto-acoustic methods, have been utilized in functional measurements to resolve tissue attenuation in selected wavelengths, and derive the concentrations of oxy- and deoxy-hemoglobin, cytochrome oxidase and possibly other tissue chromophores and externally administered dyes. However the conventional implementations assume simple photon propagation patterns. A common conventional assumption is that plane wave illumination will result in a plane-wise uniform photon distribution in tissue,

which is a very crude assumption that has so far resulted in only superficial blood vessel images.

[0026] Contrary to the conventional techniques, the inventors have developed a method to perform opto-acoustic imaging of tissue biomarker reporter, offering high-fidelity, true three-dimensional and quantitative imaging not only of superficial but also of deeper seated contrast.

[0027] The correction for light distribution can be applied to the reconstructed images of biomarker distribution. Alternatively, the correction for light distribution is directly applied to the detected raw opto-acoustic signals. In this case, the final quantified optical absorption image will be reconstructed (by e.g. back-projection) using already normalized raw opto-acoustic recordings.

[0028] Imaging molecular marker distribution in real tissues by means of opto-acoustics may further present an additional challenge. First, *in-vivo* optical absorption contrast can reach up to two orders of magnitude at some wavelengths. In particular, some areas with high blood content are very absorptive, making the marker hard to distinguish from the highly absorbing background. Images obtained from real tissues will usually represent an added contribution of absorption not only by molecular markers of interest but also by numerous tissue chromophores, like melanin, red blood cells etc. that may also considerably change their optical absorption with the wavelength, especially in the visible. Some of these chromophores may have a significant cross-talk with the extinction / absorption spectra of the biomarker of interest, which might further complicate its detection over background.

[0029] Therefore, another important feature of the invention is the application of a multi-wavelength spectral matching procedure, incorporating an a-priori known or measured spectra of the marker as well as the mostly important intrinsic tissue constituents. This is crucial for reaching the ability of quantification of molecular marker accumulation in highly heterogeneous tissues. Advantageously, the spectral matching procedure can be applied during various phases of the image formation, e. g. during the image reconstruction from the opto-acoustic data by back-projection.

[0030] Multi-wavelength excitation is considered particularly advantageous for molecular imaging applications since it does not require "baseline" measurements, i.e. measurements before the administration of the molecular marker. Therefore molecular marker with long accumulation or activation times, or the modulation of intrinsic tissue molecular markers, such as fluorescent proteins can be accurately detected with high sensitivity. Conversely, since illumination at multiple wavelengths is provided, the method is even applicable in imaging dynamic phenomena, such as hemo-dynamics or the circulation of non-specific dyes of varying concentration over small period of times (such as ICG), whereas preferably correction steps are applied based on prior knowledge on kinetics.

[0031] The invention enables molecular imaging with powerful potential applications due to its superior spatial resolution in the opto-acoustic mode, the use of non-ionizing radiation and the increased availability of molecular markers that can impact detection sensitivity, such as numerous targeted or activatable fluorochromes, fluorescence proteins or chromophoric substances.

[0032] As compared to most pure chromophores, having relatively broadband optical absorption characteristics, many fluorochromes, e. g. Alexa or Cy-based dyes, ICG, fluorescent proteins (GFP, RFP), exhibit sharp resonances in the vicinity of their peak excitation spectra, making them convenient candidates for highly sensitive multi-wavelength imaging. Also, some fluorochromes, especially in the near-infrared, possess relatively high molar extinction coefficients in excess of 10^5 $M^{-1}cm^{-1}$ in conjunction with low quantum yield (acting in favor of opto-acoustic signal generation). Thus, even though more specific pure chromogenic molecular markers may be developed, imaging of readily available fluorochromes can be achieved at physiologically useful concentrations even in the presence of highly absorbing tissue chromophores. Acquisition at an even larger number of wavelengths could lead to independently resolving multiple absorbers, markers and fluorochromes at the expense of longer acquisition times.

[0033] Preferably, the pressure signals are detected with an acoustic detector device. Alternatively, the pressure signals can be obtained with optical measurements sensing variations of the target tissue surface. Operating with optical detection, the inventive method can be utilized in free-space mode and complete projection mode for complete-body small animal imaging (G. Zacharakis et al., PNAS 102 (51): pp. 18252-18257, 2005) or mesoscopic imaging C. Vinegoni, C. Pitsouli, D. Razansky, et al., NATURE METHODS 5(1), 2008) with varying resolution depending on the dimensions of the object imaged.

[0034] Implementations in tomographic reflection or transillumination can be further utilized for clinical imaging in detecting through several centimeters of breast tissue in e.g. transillumination mode or at a depth of 4 cm to 5 cm in reflectance mode, for example in detecting cardiovascular or neurological disease. Operating with acoustic detection this method can be applied with increased (ultrasound like) resolution in similar applications and geometrical implantations, typically however through matching media for acoustic detection, for example matching fluids or gels.

[0035] According to a preferred embodiment of the invention, the illumination pattern includes at least two spectrally distinct wavelength ranges in a time-shared fashion. Preferably, the illuminating step comprises illuminating the target tissue with at least two pulse-shaped illumination patterns, which are subsequently directed onto the target tissue. Particularly preferred, the illumination patterns are provided with a time interval below 1 s, preferably below 1 ms, down to 10 us depending on size of the imaged object and its distance from the point where pressure measurement are recorded. The minimal possible interval has to be selected such that the pressure signals originating from all the points

in the imaged area have to be measured before launching the next illumination pulse. In this way, distortions of the pressure signals collected with the distinct wavelength ranges can be avoided.

[0036] According to a further preferred embodiment of the invention, the at least two spectrally distinct wavelength ranges of the illumination pattern include at least two wavelengths with different absorptions of the target biomarker, resp.. The distinct wavelength ranges cover at least two spectral absorption areas, in which the target tissue biomarker has different absorption values. Preferably, the biomarker molecules have a variation in the absorbing spectrum within a range below 100 nm, particularly preferred below 70 nm, e.g. in the range of 20 nm to 50 nm.

[0037] According to the invention, the detected pressure signals and/or opto-acoustic images produced at any reconstruction stage can be used. In this advantageous case, no assumptions on the illumination field are needed, so that this method can operate in any illumination set-up, from operating a handheld scanner with multiple illumination areas, to intravascular imaging. This is one of the particularly preferred features of this invention. While most conventional systems follow guidelines that are directed towards utilizing matching fluids and certain optical arrangements that allow for homogenous illumination of tissue, this embodiment is independent of the particulars of the geometrical setup of the source and the detector. In addition, the use of multi-spectral imaging approach allows to resolve important tissue biomarkers in a functional and molecular imaging sense over nonspecific absorption background.

[0038] With other words, in the preferred embodiment, instead of indirect photon propagation modeling, the photon fluence in tissue can be directly extracted from the opto-acoustic data. As outlined with further details below, the opto-acoustic signals represent a product between the local light fluence and the local absorption coefficient. In most practical cases, it can be assumed that the fluence exhibits much slower spatial dependence as compared to more rapid absorption coefficient variations. This fact can be utilized in order to effectively decompose these two contributions using blind source separation methods, e.g. by fitting the combined opto-acoustic response $\psi^k(\lambda)=U^k(\lambda)\mu^k(\lambda)$ into sparse representation dictionary that contains two or more bases with distinct spatial characteristics. The particular advantage of this methodology is its independence from the particular experimental geometry and measurement conditions.

[0039] The inversion step of the inventive method is provided for reconstructing the e. g. three-dimensional distribution of the biomarker from a set of measured pressure signals. The specific inversion scheme will differ in each case depending on particular geometrical and physical characteristics and spatial distribution of the detection elements used. Typically, the inversion can be done by backprojecting the raw or spectrally processed signals recorded by each point detector into the virtual imaged volume and summarizing over all the detector positions (projections).

[0040] As a further advantage of the invention, the spectral processing scheme can be conducted during various phases of the image reconstruction. In particular, according to preferred embodiments of the invention, the spectral processing scheme includes an integration into the inversion scheme, a processing step on the collected pressure signal data, and/or a processing step on the reconstructed image data.

[0041] Due to the improved processing of the pressure signal data the invention offers new options of designing the imaging device, which is adapted for implementing the inventive imaging method. According to a first advantageous variant of the invention, both the illumination device and the detector device, in particular illumination light output elements and sensor elements thereof, can be integrated into an integral component (so called: measuring head unit). Using the measuring head unit provides essential advantages in terms of conducting the imaging and detecting steps. Positioning the illumination and detector devices is essentially facilitated as the measuring head unit simply can be positioned in contact with a target tissue component to be investigated. In particular, the measuring head unit can be positioned on an inner surface of the target tissue, e.g. in a hollow organ or a vessel, like a blood vessel, or on an outer surface of the target tissue, e.g. on the outer skin.

[0042] Accordingly, with a particular advantageous variant of the invention, at least one of the illumination device and the detector device of the imaging device is included in an endoscopic, laparoscopic or interstitial device.

[0043] As a particular advantage, the measuring head unit can be provided as a hand-held device for non-invasive or endoscopic and intravascular applications. Furthermore, the measuring head unit, according to the invention, can be used without a matching fluid between the measuring head unit and the target tissue. Advantageously, the contact of the measuring head unit with the target tissue is sufficient for introducing the illumination pattern and for collecting the pressure signals.

[0044] Advantageously, the measuring head unit can be designed in dependence on particular requirements of application. According to a preferred embodiment of the invention, the measuring head unit comprises an array of illumination elements and sensor elements. The array of illumination and sensor elements comprises an arrangement of the illumination and sensor elements with distances relative to each other on a contact surface of the measuring head unit, which depending on the application of the invention is a plane contact surface or a curved contact surface.

[0045] The array of illumination and sensor elements provides the illumination pattern (geometric pattern of illumination light to be introduced into the target tissue) and a geometric pattern of sensor elements collecting the pressure signals for tomographic image reconstruction. With a particular preferred embodiment of the invention, the array of illumination and sensor elements comprises at least one line-shaped arrangement of the illumination elements and at least one line-shaped arrangement of the sensor elements, and/or a matrix-shaped arrangement of the illumination and sensor elements

with an alternating distribution thereof.

[0046] According to a second variant of the imaging device, the illumination device and the detector device, in particular, the illumination elements and sensor elements thereof, can be provided as separate components. In this case, advantages in terms of adapting the geometry and position of the illumination and detector devices relative to the target tissue can be obtained. As a first example, both the illumination and detector devices are commonly arranged on an outer surface or an inner surface of the target tissue as noted above. Preferably, one of the illumination and detector devices is arranged in the target tissue, in particular, in contact with an inner surface thereof, while the other of the illumination and detector devices is arranged outside the target tissue, in particular in contact with the outer surface thereof. If the illumination device is arranged in the target tissue, e.g. in a vessel or in a subcutaneous condition directly in the tissue, the illumination of the target tissue can be improved, while with the detector device arranged on the outer surface of the target tissue, the collection of the pressure signals can be facilitated.

[0047] In the opposite case, the illumination device can be arranged on the outer surface of the target tissue, so that the positioning of the illumination elements relative to the tissue to be investigated can be improved. In this case, the detector device, e.g. as a part of an endoscopic device can be arranged in the target tissue, like e.g. in a hollow organ or a vessel of the target tissue or if necessary even in a subcutaneous condition.

[0048] Another advantage of the array of illumination elements is obtained if the illumination elements are configured for providing illumination light with different projection directions relative to the target tissue. Preferably, the illumination elements are arranged such that at least two different diffusive projection directions are obtained. Illuminating the target tissue with at least two different projection directions has the particular advantage of providing a complex illumination light field which facilitates the inversion of the collected pressure signals to the reconstructed target tissue image.

[0049] According to the invention, the detection of tissue biomarkers can be accomplished by resolving intrinsic tissue chromophores and fluorochromes or utilize biomarker reporters i.e. at least one endogenous reporter such as a fluorescent protein or an extrinsically administered probe with specificity to certain tissue biomarkers. Reporters that absorb light such as fluorochromes and fluorescent dyes or fluorescent conjugates, chromophoric agents and substrates or nanoparticle agents based on noble (gold, silver etc) or other metals are preferred. Advantageously, existing molecular markers can be resolved with the inventive method, including fluorescent probes, absorbing targeted or encapsulated nanoparticles and fluorescent proteins. Accordingly, with a further preferred embodiment of the invention, the target tissue includes a light-absorbing reporter to target the biomarker. This allows applications in basic biological imaging as well as in pre-clinical imaging and clinical applications.

[0050] As preferred examples, the light-absorbing reporter includes at least one of fluorescent or chromophoric molecules, e. g. AlexaFluor, fluorescent proteins, e. g. GFP, noble-metal-containing particles, e. g. gold nanoparticles, superparamagnetic particles, e. g. iron-oxide nanoparticles (SPIO), carbon particles, and activatable substrates, e. g. X-gal.

[0051] Accordingly, the inventive method operates with a plurality of substances that absorb light. Preferably, imaging performance is increased by selecting predetermined biomarker reporters with a characteristic pattern in their absorption spectrum, for example a steep absorption change. The term "steep change in the absorption spectrum" refers to an absorption property according to which at least 80% of the peak extinction (or absorption) of the reporter is lost within spectral window of less than 100 nm, particularly preferred less than 50 nm, like e.g. 20 nm (as it is the case with the fluorescent molecule AlexaFluor750) in the window 750 nm to 770 nm.

[0052] Of particular general interest is imaging near-infrared fluorescent markers since their extinction / absorption spectrum exhibits a steep drop in the spectral window above 630 nm compared to the smooth absorption variation of the spectra of common tissue chromophores in this region. In this way, intrinsic tissue contrast can be readily suppressed with a multi-wavelength approach, yielding highly sensitive cancerve imaging of fluorochrome distribution in tissue obtained by spectral matching of opto-acoustic images acquired at several different adjacent wavelengths. In addition, multi-spectral imaging can be employed to resolve multiple absorbers/fluorochromes in tissues and, as mentioned above, the overall method can be further improved by more accurately considering the relative background absorption attenuation of tissue at each of the wavelengths used.

[0053] Preferably, the invention is used for imaging tissue of small animals, tissue of mesoscopic size i.e. tissue having a typical dimension in the range of 100 μm to 5 cm in particular from 0.5 mm to 1 cm, or tissue or a tissue component of a human body (or an animal body having a size comparable with a human body). Preferably, the imaging allows to obtain information on the basis of which subsequently a diagnosis can be prepared. The inventive imaging of target tissue biomarkers in particular provides information for diagnosing a cancer disease, a cardiovascular disease, in particular including arteriosclerotic plaque, an inflammatory disease. Alternatively, the imaging allows to obtain an information on a disease state and/or the development of a disease treatment.

[0054] A particular preferred implementation is described herein that can image fluorescent proteins in biological specimen such as insects, worms, fish and mice, rabbits, pigs, noninvasively. In another embodiment, a particular implementation is described to detect atherosclerotic biomarkers in cardiovascular disease. However different approaches in cancer, immunology, neurodegenerative disease etc can be foreseen.

[0055] The quantitative tomographic image is provided as the result of the inventive method. Additionally, the image

can be at least one of being displayed by a display device, stored in a computer storage device, recorded with a recording device, like e.g. a printer or other image output device, and provided as input data for an image processing method.

Brief description of the drawings

[0056] Further details and advantages of the invention are described in the following with reference to the attached drawings, which show in:

Figure 1: a schematic representation of embodiments of target tissue biomarker imaging according to the invention;

Figures 2 to 4 schematic illustrations of a measuring head unit of an imaging device according to the invention;

Figure 5: an illustration of an array of illumination and sensor elements of an imaging device according to the invention;

Figures 6 to 8: schematic illustrations of alternative embodiments of the inventive imaging method and device; and

Figure 9: an experimental set-up for imaging small animals in a laboratory experiment.

Description of the preferred embodiments

[0057] With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taker with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice. As used herein, an element or step recited in the singular and proceeded with the word "a" or "an" should be understood as not excluding plural elements or steps, unless such exclusion is explicitly recited. In the description of the figures, like numbers refer to like parts. The drawings are generally not to scale. For clarity, non-essential elements.were omitted from some of the drawings. Some optional elements may be drawn in dashed lines.

1. Features of preferred embodiments

[0058] The essential components of the imaging method and imaging device of the invention are illustrated in Figure 1. The imaging device 100 comprises the illumination device 10, the detector device 20 and the reconstruction device 30. The illumination device 10 is arranged for introducing illumination light with a predetermined illumination pattern into the target tissue 1 including a distribution of biomarker 2 to be imaged.

[0059] The illumination device 10 can be embodied by various light sources as outlined below. The particular light source used is selected in dependence on the requirements of the application of the invention. Typically, the illumination device 10 comprises a light source, like a laser source or a light-emitting diode (LD), and a light guiding device, like an optical fibre transmitting the illumination light from the light source to an output or a contact surface of the illumination device 10. Furthermore, the illumination device 10 is preferably adapted for emitting at least one pulsed illumination pattern at several illumination wavelengths in the far red or near-infrared wavelength range, i.e. preferably with wavelengths above 630 nm.

[0060] The detector device 20 is adapted for sensing pressure signals from the target tissue 1, which are produced by the biomarker 2 in the target tissue 1 in response to the illumination. Typically, the detector device 20 is an acoustic detector device including at least one movable detector element and/or a plurality (array) of detector elements. The latter is known e.g. from ultrasonic imaging techniques. Alternatively, the pressure signals can be collected with an optical detector device immersed in a matching liquid or noncontactly by sensing surface variations of the target tissue with optical means, e.g. by an optical interferometric set-up.

[0061] The reconstruction device 30 generally is adapted for reconstructing a quantitative tomographic image of the biomarker 2 in the target tissue 1. The reconstruction device 30 includes at least one processor 31, which is adapted for using a light fluence in the target tissue for decomposing light absorption from the light fluence using blind source separation, wherein the light fluence is directly extracted from the detected pressure signals and/or opto-acoustic images, implementing the spectral processing scheme and implementing the inversion scheme for providing the tomographic image. Additionally, a processor 32 adapted for raw data processing can be provided. Processors 31 and 32 can be

implemented in a common circuitry. Alternatively, the above functions of the processor 31 can be fulfilled by a plurality of separate processor elements included in the reconstruction device 30. Each processor can be implemented with a microprocessor programmed for fulfilling the particular function thereof.

[0062] The reconstruction device 30 is connected with an output device 33, which is adapted for providing the reconstructed tomographic image for further processing or application. In particular, the output device 33 includes at least one of a display device, like e.g. a display of a computer, a storage device, like e.g. a storage medium in a computer, and a recording device, like e.g. a printer.

[0063] The inventive imaging method is conducted with the imaging device 100 of Figure 1 as outlined in the following. Illumination light is beamed upon the imaged region of interest in tissue 1 using the illumination device 10. In the preferred embodiment, a pulsed illumination at multiple wavelengths is emitted at one or more positions, or angles, into the tissue 1 in the visible and/or near-infrared spectral range. This ability to utilize light forming multiple projections (positions or angles) facilitates the provision of the imaging device as a handheld scanner, or intravascular scanner (see below). Preferably, the duration of individual pulses lie in the nanosecond range (i.e. below 100 ns, particularly preferred below 10 ns) with an interval of at least 10 to 100 μs.

[0064] A broadband acoustic radiation is induced in tissue 1 following the instantaneous temperature elevation caused by absorption of the above pulses in tissue 1. The magnitude of the induced acoustic waves is proportional to the local light fluence, optical absorption coefficient and thermoelastic properties of the object.

[0065] The pressure signals (acoustic waves, in particular sound) generated in response to the illumination is subsequently detected by the detector device 20. The induced response is collected by translating acoustic detector elements around the tissue 1 or, alternatively, by placing an array of stationary detector elements in the vicinity of the tissue 1.

[0066] The optical absorption can be then reconstructed by backprojecting the detected pressure signals into the virtual imaged volume or by various Radon transformations.

[0067] Preprocessing of raw data with the processor 32 may include basic filtering and denoising. The image formation processor 31 applies the inversion scheme appropriate for the particular illumination and detection configuration. It also applies the spectral processing step responsible for differentiation of biomarker from the background absorption in tissue 1 and photon propagation modeling step intended for biomarker image quantification.

[0068] The specific inversion scheme will differ in each case depending on particular geometrical and physical characteristics and spatial distribution of the detection elements used. For example, in case a phased-array of acoustic detector elements is used, the images can be formed in the real-time by incorporating into the inversion process simple ultrasound beam forming algorithms.

[0069] The basic result of the inversion can be presented in a form of image/s 3 representing local optical absorption coefficient of tissue 1.

2. Theoretical considerations

[0070] In practice, the detected opto-acoustic response does not directly provide the local absorption coefficient $\mu(\lambda)$ but the reconstructed image of absorbed energy density $\psi^k(\lambda)$ rather represents a combination of the absorption coefficient $\mu(\lambda)$ and optical fluence $U^k(\lambda)$ in the sample, i.e. $\psi^k(\lambda)=U^k(\lambda)\mu^k(\lambda)$. Due to strong optical attenuation and heterogeneity of biological tissues, the fluence cannot usually be assumed constant throughout the region of interest. Yet, only the absorption coefficient itself can provide the relevant quantitative information on biomarker distribution. Therefore, the ability to quantify the actual distribution of the marker within the sample heavily relies on the initial accuracy of reconstruction of the optical absorption map at each wavelength that is to be deconvolved from the light fluence distribution.

Opto-acoustic inversion

[0071] A broadband acoustic radiation is induced in tissue following the instantaneous temperature elevation caused by absorption of short pulses of light energy in matter. The magnitude of the induced acoustic waves is proportional to the local energy density, optical absorption coefficient, and thermoelastic properties of the object. Their spectrum, in turn, is mainly dependent upon the spatial frequency of energy deposition variations and duration of the emitted pulses. For pulse durations in the ns range, a biologically relevant opto-acoustic spectrum will be of ultrawideband nature with useful information contained between several tens of kHz and several tens of MHz, depending on size and spatial distribution of optical absorption variations within the imaged object.

[0072] Preserving the correct shape of the detected response is important for the correct quantification of the resulting images. Since it may be difficult to effectively implement such a broadband detection, a preferred way to restore the initial tissue response is to deconvolve the recorded signal from the frequency response of the detector. Alternatively, ultrawideband detection approaches may be used, such as optical interferometric approaches based on detection of surface movements or mechanical oscillations in optically resonant elements, e.g. Fabry-Perot films, ring resonators, or etalons.

[0073] The inversion is provided for reconstructing the e. g. three-dimensional distribution of the biomarker from the collected ultrasonic pressures $p(\vec{r},t)$ by backprojecting the raw or spectrally processed signals. The specific inversion scheme will differ in each case depending on particular geometrical and physical characteristics and spatial distribution of the detection elements used. For example, in case a phased-array of detector is used, the images can be formed in the real-time by using the simple ultrasound beam forming algorithms.

[0074] Generally, under conditions of heat confinement, i.e. when the light energy pulse is short enough so that the thermal diffusion is insignificant during the pulse, the spatiotemporal dependence between opto-acoustically induced pressure $p(\vec{r},t)$, absorbed energy density $\psi(\vec{r},t)$ (in J/m^3) and local temperature elevation $T(\vec{r},t)$ can be expressed as

$$\nabla^2 p(\vec{r},t) - \frac{1}{v_s^2}\frac{\partial^2 p(\vec{r},t)}{\partial t^2} = -\rho_m \beta \frac{\partial^2 T(\vec{r},t)}{\partial t^2} = -\frac{\beta}{C}\frac{\partial \psi(\vec{r},t)}{\partial t} \qquad (1)$$

where v_s, ρ_m, β, and C are the corresponding speed of sound, mass density, isobaric volume expansion, and specific heat of the medium, all are in general spatially and frequency dependent.

[0075] In practice, the thermal confinement conditions are fulfilled for excitation pulse durations less then 1 μs. When for instance a point-shaped detector element of small diameter (e.g. below 1 mm) is placed in the position $\vec{r}'$, at the first approximation it will sense an integrated pressure wave, which is the solution of (1), namely,

$$p(\vec{r}',t) = -\frac{\beta}{4\pi C}\int_V \frac{\partial \psi(\vec{r},t')}{\partial t'}\frac{d^3\vec{r}}{\left|\vec{r}-\vec{r}'\right|}\Bigg|_{t'=tv_s} \qquad (2)$$

[0076] The basic result of the inversion step can be presented in a form of image/s representing local deposition of tissue biomarker.

Spectral processing

[0077] The current invention provides an efficient method for imaging of molecular marker of interest by suppressing intrinsic tissue contrast with the multi-wavelength approach. This yields highly sensitive imaging of molecular marker distribution in tissue obtained by spectral matching of images acquired at several different wavelengths. While the simplest qualitative version of this operation can be achieved by image subtraction at two wavelengths, three- and overall multi-wavelength imaging will further suppress the background signals. This processing can occur in several stages, an efficient one being the simultaneous inversion of spectral data so that all information is accurately accounted for.

[0078] One preferred embodiment, which simplifies computation however will utilize the following general quantification formula for the reconstructed amount (concentration) of the molecular marker of interest C^k on a per pixel basis:

$$C^k = \min_{c^k} \sum_{\lambda=\lambda_1}^{\lambda_N} \left[\psi^k(\lambda) - c^k \varepsilon(\lambda)\right]^2 \qquad (4)$$

where C^k is the reconstructed amount (concentration) of the molecular marker of interest on a per pixel/voxel basis, N is the total number of illuminating wavelengths, $\psi^k(\lambda)$ is the reconstructed absorption in pixel/voxel k, c^k and $\varepsilon(\lambda)$ are the concentration and wavelength-dependent molar absorptivity of the marker, respectively. We note that the wavelength-dependent absorption coefficient $\mu(\lambda)$ in each pixel/voxel will be written in a conventional form as

$$\mu(\lambda) = \sum_{m=1}^{M} c_m^k \varepsilon_m(\lambda), \qquad (5)$$

where *M* is the total number of wavelength-dependent markers and tissue chromophores considered in the reconstruction procedure. The procedure in Eq. (4) will then include minimization over a set of concentrations $c_m^k \quad (m=1, \ldots, M)$.

[0079] Alternatively, it can be assumed that every pixel *k* in the opto-acoustic image may represent a combined contribution of the molecular and other background tissue chromophores. For every imaged wavelength λ, this can be written in the form of linear equation:

$$\mu_a^k(\lambda) = \alpha_{MM}(\lambda) c_{MM}^k + \alpha_1(\lambda) c_1^k + \alpha_2(\lambda) c_2^k + \ldots,$$

where $\mu_a^k(\lambda)$ is the reconstructed wavelength-dependent absorption in pixel *k*, $\alpha_{MM}(\lambda)$ and $\alpha_1(\lambda),\alpha_2(\lambda),\ldots$ are the molar extinction spectra of the molecular marker and the background chromophores, and c_{MM}^k and $c_1^k, c_2^k, \ldots$ are the corresponding concentrations. Using the measured absorption values and the known spectra for the seven wavelength, the concentration c_{MM}^k of the molecular marker/s and the background chromophores can be subsequently reconstructed from the above linear equations on a per-pixel basis using linear regression method.

[0080] The preferred methodology for achieving molecular marker differentiation resides in including spectral information into the inversion mode using a single-step or a two step method.

[0081] The single-step method comprises inverting a tomographic equation simultaneously for the different wavelengths employed, therefore simultaneously accounting for 1) the photon attenuation as a function of depth (distance from the source), 2) the detection process and 3) the wavelength dependence of the measurements.

[0082] The dual step method pre-processes the raw data using a spectral matching or decomposition algorithm and then utilizes one processed measurement as the input to an inversion code that accounts only for 1) the photon attenuation as a function of depth (distance from the source) and 2) the detection process. An alternative two-step method can be implemented by reconstructed images at different wavelengths and then processing the resulting images on a pixel by pixel basis.

3. Further applications

[0083] There is a wealth of applications for the invented method. While not limited only to the biomedical field, the application of the technique to medical and biological imaging is an important direction.

3.1 Biological imaging

[0084] Figure 2 schematically illustrates an embodiment whereas the invention is used for imaging a part of a human proband 4 (e. g. patient), e. g. the target tissue 1 comprising an organ 5. The imaging device 100 comprises the illumination device 10, the detector device 20 and the reconstruction device 30, which are integrated into a common casing 34 and a measuring head 40 being connected with the illumination and detector devices 10, 20 via optical fibres and electrical cables.

[0085] The measuring head 40 can include separate components of illumination and sensor elements as illustrated below in Figure 3. Alternatively, the measuring head comprises an integral measuring head unit including the illumination elements and sensor elements in a common casing as outlined with further details below (Figures 4, 5).

[0086] In a preferred embodiment an agent is injected intravenously or locally to the proband 4, and targets areas or processes of interest. The measuring head unit 40 is brought in contact with the tissue so that illumination light is coupled into it and pressure signals can be sensed. The collected pressure data are processed and presented in the form of two- or three-dimensional image on a monitor.

[0087] An application example includes the administration of fluorescence emitting agents that are preferentially uptaken by macrophages. Image of their absorption yields areas of increased inflammation as in the case of image atherosclerotic plaque, in the carotids or other vessels. Similarly targeted absorbing particles can show information on targeted molecules such as peptides, receptors etc..

[0088] Figure 3 schematically illustrates the adjustment of the imaging device 100 relative to the target tissue 1 to be investigated. The illumination device comprises at least two illumination elements 11, 12, which are arranged with a

distance relative to each other, e.g. 15 mm. The distance of the illumination elements 11, 12 from the outer surface 6 (e.g. skin) of the target tissue 1 comprises e.g. 20 mm. Alternatively, the illumination elements 11, 12 can be arranged in contact with the outer surface 6. The illumination elements 11, 12 comprise e.g. LED's with a predetermined emission characteristic defining the projection direction towards the target tissue 1. Alternatively, the illumination elements 11, 12 comprise the output ends of optical fibres being connected with a laser source of the imaging device 100, e.g. in the casing 34.

[0089] The detector device 20 comprises an array of detector elements 21 being embedded in a surface (contact surface) of the detector device 20. The contact surface is adapted to be brought into contact to the outer surface 6 of the target tissue 1. The detector device 20 comprises e.g. a sound sensor as it is known from conventional ultrasound imaging devices.

[0090] Alternative embodiments, wherein the illumination and sensor elements 11, 12, 21 are integrated within a common measuring head unit 40 are illustrated in Figures 4 and 5. The measuring head unit 40 comprises a casing body 41, into which the illumination elements 11, 12 and the sensor elements 21, 22 are embedded. The illumination and sensor elements 11, 12, 21, 22 are integrated into the contact surface 42 of the measuring head unit 40. Elements 11, 12, 21, 22 are respectively connected via optical fibres 13, 14 and electrical wires 23, 24 with the associated parts of the illumination and detector devices 10, 20 integrated in the casing 34 (see e.g. Figure 2).

[0091] Figures 5A, 5B and 5C illustrate embodiments of the invention being characterized by different distributions of the illumination and sensor elements 11, 12, 21, 22 in the contact surface 42 of the measuring head unit 40. According to Figure 5A, line-shaped arrangements are provided with two outer rows of illumination elements 11, 12 (e.g. LED's or output ends of optical fibres) and a central row of sensor elements 21 (acoustical sound sensors). Figure 5B illustrates the opposite geometry with a central row of illumination elements 11 and outer rows of sensor elements 21, 22. Figure 5C shows a matrix arrangement of the elements 11, 12, 21, 22.

[0092] The illumination elements 11, 12 are configured for illuminating the target tissue with at least one pulsed illumination pattern at several illumination wavelengths. As an example, for providing two distinct wavelength ranges, a first group of illumination elements 11 (e.g. indicated with "a") is adapted for emitting illumination light with wavelengths in the range of 610 nm to 650 nm, while a second group (indicated with "b") is adapted for emitting wavelengths in the range of 670 nm to 730 nm. For emitting a larger number of wavelength ranges, a third or more groups are provided.

[0093] It is emphasized that the number of illumination and detector elements shown in Figure 5 is selected for illustrative proposes only. In practice, the number of elements can be selected in dependence on the illumination and sound detection requirements.

[0094] Figures 6 to 8 illustrate further embodiments of the invention, wherein illumination and detector elements are used that are separated from each other. As an example, imaging a target tissue 1 including a blood vessel 7 is illustrated.

[0095] According to Figure 6, the illumination device 10 comprises a light source 15 and an optical fibre 16, that is introduced into the blood vessel 7 to the position of the target tissue 1 to be imaged. The detector device 20 comprises an array of detector elements, which is adapted to be brought into contact with the outer surface 6 of the target tissue 1, e.g. skin of a human body. In operation, illumination light patterns with distinct wavelength ranges are emitted via the optical fibre 16 onto the inner surface of the blood vessel 1. Pressure signals created by absorbing biomarkers within tissue 1 are sensed with the detector device 20.

[0096] For example, if Cy5.5 dye is used for bio-marker targeting with peak absorption at 670 nm, the multi-spectral illumination device might include diode-laser-based illumination device emitting light at 7 distinct wavelengths, namely, 610, 630, 650, 670, 690, 710, and 730 nm, that cover areas of both high and low absorption of the dye to ease on the subsequent multi-spectral processing and suppression of background absorption signals.

[0097] According to Figure 7, both the optical fibre 16 of the illumination device 10 and the sensor element 25 of the detector device 20 are arranged in the blood vessel in the target tissue 1. Both components can be integrated in an endoscopic device (not shown).

[0098] According to Figure 8, the illumination elements 11, 12 of the illumination device 10 are arranged outside the target tissue, while the detector element 25 of the detector device 20 is provided in the vessel within the target tissue 1. Figure 9 illustrates a preferred application of the inventive technique in biomedical imaging of mesoscopic-size objects and small animals, like mice or other rodents, flies, fishes, worms, animal embryos. A container device 50 is provided, which comprises a tank 51 and holding elements 52, 54 which are adapted for positioning components of the imaging device 100. The tank 51 contains a matching fluid 53, e.g. water or oil. The object to be investigated (living mouse 8) is positioned on the lower part 54 of the rod or plate shaped holding element.

[0099] The illumination device 10 and the detector device 20 are partially integrated in a casing 34 (see above, Figure 2), that is are arranged outside the container device 50. The illumination device 10 comprises a pulsed laser source whose light is directed to the mouse 8 from two opposite directions 17,18 by e.g. using optical mirrors or fibers. The detector device 20 comprises an array 26 of acoustic detector elements. The detector device 20 is arranged in the neighbourhood of the holding element 52 with the mouse 8. Advantageously, there are no particular restrictions with regard to the position of the detector device 20. The preferred location however will be as close as possible to the object

to obtain measurements with high signal-to-noise ratios. For implementing the above image reconstruction, it is only necessary to have an information on the location of the array of detector elements relative to the object (mouse 8).

[0100] The embodiment schematically illustrated in Figure 9 is not restricted to the investigation of small animals. Alternatively, other biological objects can be imaged, e.g. human beings or larger animals or parts thereof. As an example, tank 51 can be adapted for accommodating a part of a human patient instead of the mouse 8.

3.2 Clinical imaging

[0101] Areas of preferred clinical applications include imaging of cardiovascular disease, cancer, inflammation and neurodegenerative disease, to name a few examples. Imaging of natural states such as growth and aging are also contemplated. As a particular advantage, the inventive near-field imaging can be conducted without using a matching fluid between the near-field source device and the object to be investigated, thus essentially facilitating the clinical applications.

[0102] Another application example includes imaging of the effect of treatment, via drugs, radiation or chemotherapy, by similarly administrating absorbing particles in the body and monitoring their relative update or targeting over time.

[0103] In other embodiments, the same detection can be achieved by portable devices, or endoscopic devices inserted into body cavities or through invasive procedures by operatively inserting the device into the tissue.

Claims

1. Method of multi-spectral opto-acoustic tomography (MSOT) imaging of a target tissue including a target tissue biomarker, comprising the steps of:

   - illuminating the target tissue with an illumination device emitting at least one pulsed illumination pattern at several illumination wavelengths,
   - detecting pressure signals from the target tissue biomarker with a detector device, wherein the pressure signals being produced in the target tissue in response to said illumination,
   and
   - reconstructing a quantitative tomographic image of a distribution of the target tissues biomarker in the target tissue, wherein the pressure signals are analyzed using
   a light fluence in the target tissue for decomposing light absorption from the light fluence using bling source separation, wherein the light fluence is directly extracted from the detected pressure signals and/or from opto-acoustic images,
   at least one spectral processing scheme for differentiation of the target tissue biomarker from a background absorption in the target tissue, and
   an inversion scheme providing the quantitative tomographic image.

2. The imaging method according to claim 1, wherein

   - the illumination pattern includes at least two spectrally distinct wavelength ranges in a time-shared fashion.

3. The imaging method according to one of the foregoing claims, wherein the spectral processing scheme includes at least one of the following:

   - it is integrated in the inversion scheme,
   - a processing step on the collected data, and
   - a processing step on the reconstructed data.

4. Imaging method according to one of the foregoing claims, wherein one or more of the following applies

   - the illumination device and the detector device are integrated in a common measuring head unit and the illuminating and detecting steps include positioning the measuring head unit in contact with a target tissue component or matching fluid,
   - the illumination device is arranged in the target tissue and the detector device is arranged in contact with an outer surface of the target tissue or matching fluid,
   - the detector device is arranged in the target tissue and the illumination device is arranged outside or in contact with an outer surface of the target tissue,

- the illumination device and the detector device are arranged in close proximity or in contact with an outer surface of a target tissue, or
- the detection device measures opto-acoustically induced pressure signals in a non-contact manner through e.g. optical detecting of surface movements.

5. Imaging method according to one of the foregoing claims, wherein

- the illumination device and the acoustic detector device having a position inside a blood vessel using an intravascular catheter, or
- the measuring head unit of the illumination and detector devices is a hand-held device.

6. The imaging method according to one of the foregoing claims, wherein

- the target tissue includes a light-absorbing reporter to target the biomarker.

7. The imaging method of claim 6, wherein the light-absorbing reporter includes at least one of:

- fluorescent or chromophoric molecules,
- fluorescent proteins,
- noble-metal-containing particles,
- super-paramagnetic particles,
- carbon particles, and
- activatable substrates.

8. The imaging method of claim 6 or 7, wherein

- the light-absorbing reporter includes steep change in its absorption spectrum.

9. The imaging method of claim 8 wherein

- the illumination wavelengths include at least two wave-lengths that are differentially absorbed by the target bio-marker.

10. Imaging method according to one of the foregoing claims, wherein the target tissue biomarker targets at least one of:

- a cancer disease,
- a cardiovascular disease, in particular including atherosclerotic plaque,
- inflammatory disease,
- an aspect of disease for diagnostic purposes,
- an aspect of disease state, and
- an aspect of disease treatment.

11. Imaging method according to one of the foregoing claims, wherein the target tissue includes at least one of:

- tissue of a small animal,
- tissue of mesoscopic size, i.e the sub-millimeter to centimeter range,
- tissue of at least one human organ.

12. Imaging device, which is adapted for multi-spectral opto-acoustic tomography (MSOT) imaging a target tissue including a target tissue biomarker, comprising:

- an illumination device adapted for illuminating the target tissue with at least one pulsed illumination pattern at several illumination wavelengths that are absorbed by the target tissue biomarker,
- a detector device adapted for detecting pressure signals being produced from the target tissue biomarker in the target tissue in response to said illumination, and
- a reconstruction device adapted for reconstructing a quantitative tomographic image of a distribution of the target tissue biomarker in the target tissue, whereas the reconstruction device includes
a processor adapted for using a light fluence in the target tissue for decomposing light absorption from the light

fluence using blind source separation, wherein the light fluence is directly extracted from the detected pressure signals and/or from opto-acoustic images,
a processor adapted for implementing a spectral processing scheme for differentiation of the target tissue biomarker from a background absorption in the target tissue, and
a processor adapted for implementing an inversion scheme providing the quantitative tomographic image.

13. Imaging device according to claim 12, wherein

- the illumination device and the detector device are integrated in a common measuring head unit.

14. Imaging device according to claim 13, wherein

- the measuring head unit comprises an array of illumination elements and sensor elements.

15. Imaging device according to claim 14, wherein the array includes at least one of:

- line-shaped arrangements of the illumination elements and the sensor elements, and
- matrix-shaped arrangements with an alternating distribution of the illumination elements and the sensor elements.

16. Imaging device according to one of the claims 12 to 15, wherein

- the illumination device is adapted for illuminating the target tissue among at least two different diffusive projection directions.

17. Imaging device according to one of the claims 12 to 16, wherein the illumination device and the acoustic detector device are configured for at least one of

- being arranged in a blood vessel, the illumination device in particular including an optical fiber or a light waveguide, and
- for providing a contact with an outer surface of the target tissue.

18. Imaging device according to one of the claims 12 to 17, wherein

- at least one of the illumination device and the detector device is included in an endoscopic, laparoscopic or interstitial device.

19. Imaging device according to one of the claims 12 to 18, wherein the reconstruction device is adapted for applying inverse methods and spectral processing in order to build the image of a blood vessel, in particular a coronary or a carotid artery, wherein the image represents a spatial distribution of the bio-marker in the target tissue.

Patentansprüche

1. Verfahren zur Darstellung eines Zielgewebes mit einem Zielgewebebiomarker mittels multispektraler opto-akustischer Tomographie (MSOT), das folgende Schritte umfasst:

- Beleuchtung des Zielgewebes mit einer Beleuchtungseinrichtung, die zumindest ein gepulstes Beleuchtungsmuster bei mehreren Beleuchtungswellenlängen aussendet,
- Detektieren von Drucksignalen des Zielgewebebiomarkers mit einer Detektoreinrichtung, wobei die Drucksignale im Zielgewebe als Reaktion auf die Beleuchtung erzeugt werden,
und
- Rekonstruktion eines quantitativen Tomographiebildes einer Verteilung des Zielgewebebiomarkers in dem Zielgewebe, wobei die Drucksignale analysiert werden unter Verwendung

einer Lichtfluenz im Zielgewebe zum Abspalten der Lichtabsorption von der Lichtfluenz unter Verwendung von blinder Quellentrennung, wobei die Lichtfluenz direkt aus den detektierten Drucksignalen und/oder aus optoakustischen Bildern extrahiert wird,

zumindest eines spektralen Verarbeitungsschemas zur Differenzierung des Zielgewebebiomarkers von einer Hintergrundabsorption in dem Zielgewebe, und
eines Inversionsschemas, welches das quantitative Tomographiebild bereitstellt.

2. Bildgebungsverfahren nach Anspruch 1, wobei

- das Beleuchtungsmuster zumindest zwei spektral unterschiedliche Wellenlängenbereiche auf zeitlich verzahnte Weise aufweist.

3. Bildgebungsverfahren nach einem der vorhergehenden Ansprüche, wobei das spektrale Verarbeitungsschema zumindest eines der Folgenden umfasst:

- es ist in das Inversionsschema integriert,
- einen Verarbeitungsschritt der gesammelten Daten, und
- einen Verarbeitungsschritt der rekonstruierten Daten.

4. Bildgebungsverfahren nach einem der vorhergehenden Ansprüche,
wobei eine oder mehrere der folgenden Aussagen gelten

- die Beleuchtungseinrichtung und die Detektoreinrichtung sind in einer gemeinsamen Messkopfeinheit integriert und die Beleuchtungs- und Detektionsschritte beinhalten die Positionierung der Messkopfeinheit in Kontakt mit einer Zielgewebekomponente oder Anpassungsflüssigkeit,
- die Beleuchtungseinrichtung ist in dem Zielgewebe angeordnet und die Detektoreinrichtung ist in Kontakt mit einer Außenseite des Zielgewebes oder der Anpassungsflüssigkeit angeordnet,
- die Detektoreinrichtung ist in dem Zielgewebe angeordnet und die Beleuchtungseinrichtung ist außerhalb oder in Kontakt mit einer Außenseite des Zielgewebes angeordnet,
- die Beleuchtungseinrichtung und die Detektoreinrichtung sind in unmittelbarer Nähe einer oder in Kontakt mit einer Außenseite eines Zielgewebes angeordnet, oder
- die Detektoreinrichtung misst optoakustisch angeregte Drucksignale auf berührungslose Weise, z.B. durch optische Detektion von Oberflächenbewegungen.

5. Bildgebungsverfahren nach einem der vorhergehenden Ansprüche, wobei

- die Beleuchtungseinrichtung und die akustische Detektoreinrichtung eine Position in einem Blutgefäß unter Verwendung eines intravaskulären Katheters aufweisen, oder
- die Messköpfeinheit der Beleuchtungs- und Detektoreinrichtungen ein Handgerät ist.

6. Bildgebungsverfahren nach einem der vorhergehenden Ansprüche, wobei

- das Zielgewebe einen lichtabsorbierenden Reporter zum Anzielen des Biomarkers aufweist.

7. Bildgebungsverfahren nach Anspruch 6, wobei der lichtabsorbierende Reporter zumindest eines der Folgenden aufweist:

- fluoreszierende oder chromophore Moleküle,
- fluoreszierende Proteine,
- Edelmetall enthaltende Teilchen,
- superparamagnetische Teilchen,
- Kohlenstoffteilchen, und
- aktivierbare Substrate.

8. Bildgebungsverfahren nach Anspruch 6 oder 7, wobei

- der lichtabsorbierende Reporter eine steile Veränderung seines Absorptionsspektrums aufweist.

9. Bildgebungsverfahren nach Anspruch 8, wobei

- die Beleuchtungswellenlängen zumindest zwei Wellenlängen aufweisen, die von dem Zielgewebebiomarker

unterschiedlich absorbiert werden.

10. Bildgebungsverfahren nach einem der vorhergehenden Ansprüche, wobei der Zielgewebebiomarker zumindest auf eines der Folgenden abzielt:

- eine Krebserkrankung,
- eine Herz-Kreislauf-Erkrankung, insbesondere einschließlich atherosklerotischem Plaque,
- eine entzündliche Erkrankung,
- ein Aspekt einer Krankheit für diagnostische Zwecke,
- ein Aspekt eines Krankheitszustands, und
- ein Aspekt einer Krankheitsbehandlung.

11. Bildgebungsverfahren nach einem der vorhergehenden Ansprüche, wobei das Zielgewebe zumindest eines der Folgenden einschließt:

- Gewebe eines kleinen Tieres,
- Gewebe mesoskopischer Größe, d.h. im Submillimeter- bis Zentimeterbereich,
- Gewebe von zumindest einem menschlichen Organ.

12. Bildgebungsvorrichtung zur Darstellung eines Zielgewebes mit einem Zielgewebebiomarker mittels multispektraler optoakustischer Tomographie (MSOT), umfassend:

- eine Beleuchtungseinrichtung zur Beleuchtung des Zielgewebes mit zumindest einem gepulsten Beleuchtungsmuster bei mehreren Beleuchtungswellenlängen, die von dem Zielgewebebiomarker absorbiert werden,
- eine Detektoreinrichtung zum Detektieren von Drucksignalen, die von dem Zielgewebebiomarker in dem Zielgewebe als Reaktion auf die Beleuchtung erzeugt werden, und
- eine Rekonstruktionseinrichtung zur Rekonstruktion eines quantitativen Tomographiebildes einer Verteilung des Zielgewebebiomarkers in dem Zielgewebe, wobei die Rekonstruktionseinrichtung Folgendes aufweist:

  einen Prozessor zur Verwendung einer Lichtfluenz im Zielgewebe zum Abspalten der Lichtabsorption von der Lichtfluenz unter Verwendung von blinder Quellentrennung, wobei die Lichtfluenz direkt aus den detektierten Drucksignalen und/oder aus optoakustischen Bildern extrahiert wird,
  einen Prozessor zur Umsetzung eines spektralen Verarbeitungsschemas zur Differenzierung des Zielgewebebiomarkers von einer Hintergrundabsorption in dem Zielgewebe, und
  einen Prozessor zur Umsetzung eines Inversionsschemas, welches das quantitative Tomographiebild bereitstellt.

13. Bildgebungseinrichtung nach Anspruch 12, wobei

- die Beleuchtungseinrichtung und die Detektoreinrichtung in einer gemeinsamen Messkopfeinheit integriert sind.

14. Bildgebungseinrichtung nach Anspruch 13, wobei

- die Messkopfeinheit eine Reihe von Beleuchtungselementen und Sensorelementen aufweist.

15. Bildgebungseinrichtung nach Anspruch 14, wobei die Reihe zumindest eines der Folgenden beinhaltet:

- linienförmige Anordnungen der Beleuchtungselemente und der Sensorelemente, und
- matrixförmige Anordnungen mit einer abwechselnden Verteilung der Beleuchtungselemente und der Sensorelemente.

16. Bildgebungseinrichtung nach einem der Ansprüche 12 bis 15, wobei

- die Beleuchtungseinrichtung zur Beleuchtung des Zielgewebes entlang zumindest zwei unterschiedlichen diffusiven Projektionsrichtungen ausgelegt ist.

17. Bildgebungseinrichtung nach einem der Ansprüche 12 bis 16, wobei die Beleuchtungseinrichtung und die akustische

Detektoreinrichtung für zumindest eines der Folgenden konfiguriert sind:

- Anordnung in einem Blutgefäß, wobei die Beleuchtungseinrichtung insbesondere eine Glasfaser oder einen Lichtwellenleiter aufweist, und
- zur Bereitstellung eines Kontakts mit einer Außenseite des Zielgewebes.

18. Bildgebungseinrichtung nach einem der Ansprüche 12 bis 17, wobei

- die Beleuchtungseinrichtung und/oder die Detektoreinrichtung in einer endoskopischen, laparoskopischen oder interstitiellen Einrichtung enthalten ist bzw. sind.

19. Bildgebungseinrichtung nach einem der Ansprüche 12 bis 18, wobei die Rekonstruktionseinrichtung zur Anwendung von Inversionsverfahren und spektraler Verarbeitung zum Aufbauen des Bildes eines Blutgefäßes, insbesondere einer Koronararterie oder Karotis, ausgelegt ist, wobei das Bild eine räumliche Verteilung des Biomarkers in dem Zielgewebe darstellt.

Revendications

1. Procédé d'imagerie par tomographie acousto-optique multi-spectrale (MSOT) d'un tissu cible comprenant un biomarqueur de tissu cible, comprenant les étapes:

- d'irradiation du tissu cible par un dispositif d'irradiation émettant au moins un motif d'irradiation pulsé à plusieurs longueurs d'onde d'irradiation,
- de détection des signaux de pression provenant du biomarqueur de tissu cible par un dispositif de détection, dans lequel les signaux de pression sont produits dans le tissu cible en réponse à ladite irradiation, et
- de reconstruction d'une image tomographique quantitative d'une distribution du biomarqueur de tissu cible dans le tissu cible, dans lequel les signaux de pression sont analysés en utilisant

la fluence de la lumière dans le tissu cible pour décomposer l'absorption de lumière de la fluence de la lumière en utilisant une séparation aveugle de source, dans lequel la fluence de la lumière est directement extraite des signaux de pression détectés et/ou des images acousto-optiques,
au moins une méthode de traitement spectral pour différentier le biomarqueur de tissu cible d'une absorption d'arrière-plan dans le tissu cible, et
une méthode d'inversion fournissant l'image tomographique quantitative.

2. Procédé d'imagerie selon la revendication 1, dans lequel

- le motif d'irradiation comprend au moins deux plages de longueur d'onde spectralement distinctes d'une manière partagée dans le temps.

3. Procédé d'imagerie selon l'une des revendications précédentes, dans lequel la méthode de traitement spectral comprend au moins l'un des éléments suivants :

- elle est intégrée dans la méthode d'inversion,
- une étape de traitement des données collectées, et
- une étape de traitement des données reconstruites.

4. Procédé d'imagerie selon l'une des revendications précédentes, dans lequel un ou plusieurs des cas suivants s'appliquent

- le dispositif d'irradiation et le dispositif de détection sont intégrés dans une unité de tête de mesure commune et les étapes d'irradiation et de détection comprennent le positionnement de l'unité de tête de mesure en contact avec un composant de tissu cible ou un fluide correspondant,
- le dispositif d'irradiation est agencé dans le tissu cible et le dispositif de détection est agencé en contact avec une surface extérieure du tissu cible ou un fluide correspondant,
- le dispositif de détection est agencé dans le tissu cible et le dispositif d'irradiation est agencé à l'extérieur d'une surface extérieure du tissu cible ou en contact avec celle-ci,

- le dispositif d'irradiation et le dispositif de détection sont agencés à proximité d'une surface extérieure d'un tissu cible ou en contact avec celle-ci, ou
- le dispositif de détection mesure les signaux de pression induits de manière acousto-optique d'une manière sans contact, par exemple, par la détection optique de mouvements superficiels.

5. Procédé d'imagerie selon l'une des revendications précédentes, dans lequel

- le dispositif d'irradiation et le dispositif de détection acoustique sont positionnés à l'intérieur d'un vaisseau sanguin en utilisant un cathéter intravasculaire, ou
- l'unité de tête de mesure des dispositifs d'irradiation et de détection est un dispositif portable.

6. Procédé d'imagerie selon l'une des revendications précédentes, dans lequel

- le tissu cible comprend un rapporteur absorbant la lumière pour cibler le biomarqueur.

7. Procédé d'imagerie selon la revendication 6, dans lequel le rapporteur absorbant la lumière comprend au moins l'un :

- de molécules fluorescentes ou chromophores,
- de protéines fluorescentes,
- de particules contenant un métal noble,
- de particules super paramagnétiques,
- de particules de carbone, et
- de substrats activables.

8. Procédé d'imagerie selon la revendication 6 ou 7, dans lequel

- le rapporteur absorbant la lumière présente une forte variation dans son spectre d'absorption.

9. Procédé d'imagerie selon la revendication 8, dans lequel

- les longueurs d'onde d'irradiation comprennent au moins deux longueurs d'onde qui sont absorbées de manière différentielle par le biomarqueur cible.

10. Procédé d'imagerie selon l'une des revendications précédentes, dans lequel le biomarqueur de tissu cible cible au moins l'un :

- d'une maladie cancéreuse,
- d'une maladie cardiovasculaire, comprenant en particulier une plaque d'athérome,
- d'une maladie inflammatoire,
- d'un aspect de maladie à des fins de diagnostic,
- d'un aspect d'état de maladie, et
- d'un aspect de traitement de maladie.

11. Procédé d'imagerie selon l'une des revendications précédentes, dans lequel le tissu cible comprend au moins l'un :

- d'un tissu d'un petit animal,
- d'un tissu d'une taille mésoscopique, c'est-à-dire dans la plage du sous-millimètre au centimètre,
- d'un tissu d'au moins un organe humain.

12. Dispositif d'imagerie, qui est conçu pour l'imagerie par tomographie acousto-optique multi-spectrale (MSOT) d'un tissu cible comprenant un biomarqueur de tissu cible, comprenant:

- un dispositif d'irradiation conçu pour irradier le tissu cible avec au moins un motif d'irradiation pulsé à plusieurs longueurs d'onde d'irradiation qui sont absorbées par le biomarqueur de tissu cible,
- un dispositif de détection conçu pour détecter les signaux de pression produits par le biomarqueur de tissu cible dans le tissu cible en réponse à ladite irradiation, et
- un dispositif de reconstruction conçu pour reconstruire une image tomographique quantitative d'une distribution du biomarqueur de tissu cible dans le tissu cible, alors que le dispositif de reconstruction comprend:

un processeur conçu pour utiliser une fluence de la lumière dans le tissu cible pour décomposer l'absorption de lumière de la fluence de la lumière en utilisant une séparation aveugle de source, dans lequel la fluence de la lumière est extraite directement des signaux de pression détectés et/ou des images acousto-optiques, un processeur conçu pour mettre en oeuvre une méthode de traitement spectral pour différentier le biomarqueur de tissu cible d'une absorption d'arrière-plan dans le tissu cible, et
un processeur conçu pour mettre en oeuvre une méthode d'inversion fournissant l'image tomographique quantitative.

13. Dispositif d'imagerie selon la revendication 12, dans lequel

- le dispositif d'irradiation et le dispositif de détection sont intégrés dans une unité de tête de mesure commune.

14. Dispositif d'imagerie selon la revendication 13, dans lequel

- l'unité de tête de mesure comprend un réseau d'éléments d'irradiation et d'éléments de détection.

15. Dispositif d'imagerie selon la revendication 14, dans lequel le réseau comprend au moins l'un :

- d'agencements linéaires des éléments d'irradiation et des éléments de détection, et
- d'agencements matriciels avec une répartition alternée des éléments d'irradiation et des éléments de détection.

16. Dispositif d'imagerie selon l'une des revendications 12 à 15, dans lequel

- le dispositif d'irradiation est conçu pour irradier le tissu cible le long d'au moins deux directions de projection de diffusion différentes.

17. Dispositif d'imagerie selon l'une des revendications 12 à 16, dans lequel le dispositif d'irradiation et le dispositif de détection acoustique sont configurés pour au moins l'un :

- d'un agencement dans un vaisseau sanguin, le dispositif d'irradiation comprenant en particulier une fibre optique ou un guide d'ondes de lumière, et
- de l'établissement d'un contact avec une surface extérieure du tissu cible.

18. Dispositif d'imagerie selon l'une des revendications 12 à 17, dans lequel

- au moins l'un du dispositif d'irradiation et du dispositif de détection est inclus dans un dispositif endoscopique, laparoscopique ou interstitiel.

19. Dispositif d'imagerie selon l'une des revendications 12 à 18, dans lequel le dispositif de reconstruction est conçu pour appliquer des procédés inverses et un traitement spectral afin de construire l'image d'un vaisseau sanguin, en particulier d'une artère coronaire ou carotide, dans lequel l'image représente une répartition spatiale du biomarqueur dans le tissu cible.

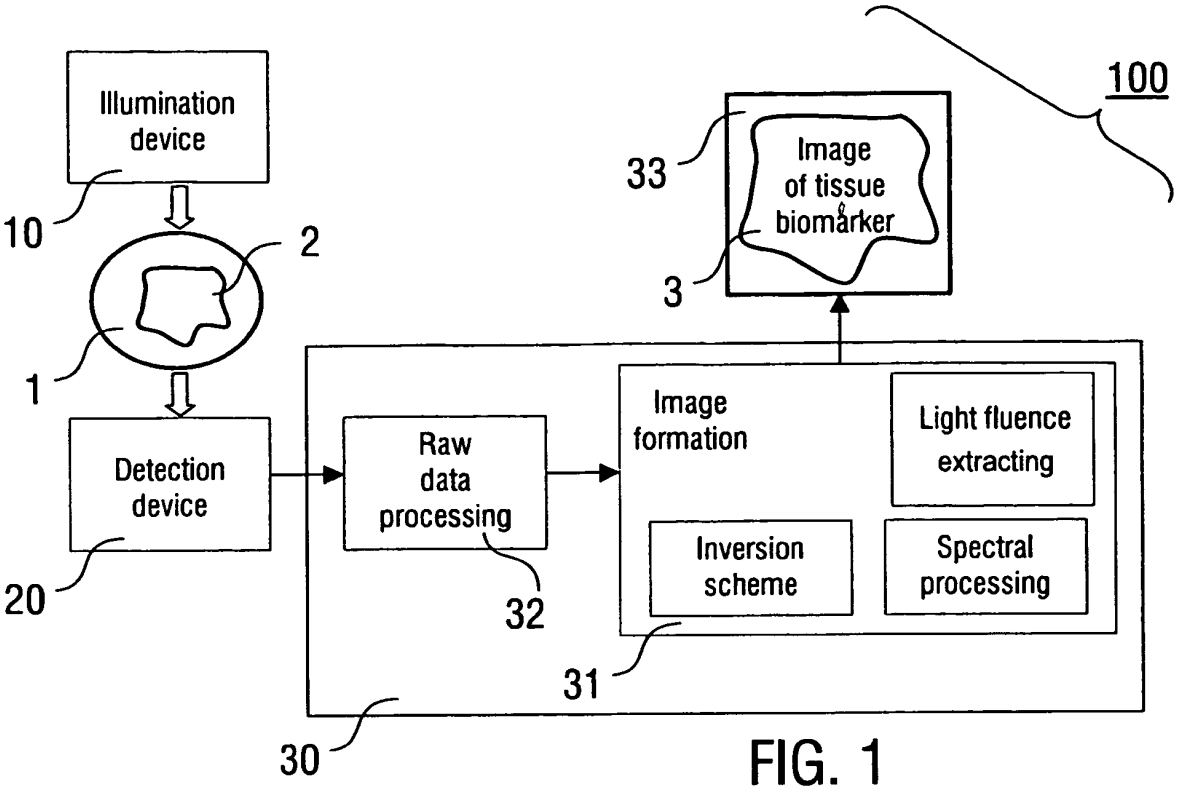
Illumination device
10
2
1
Detection device
20
Raw data processing
32
30
Image formation
Light fluence extracting
Inversion scheme
Spectral processing
31
33
Image of tissue biomarker
3
100

FIG. 1

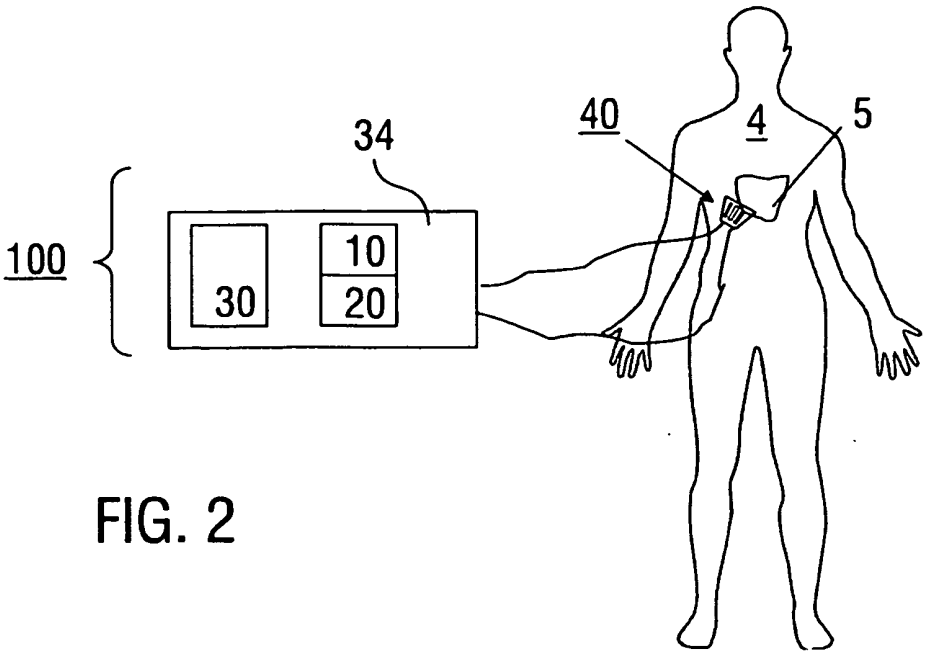

FIG. 2

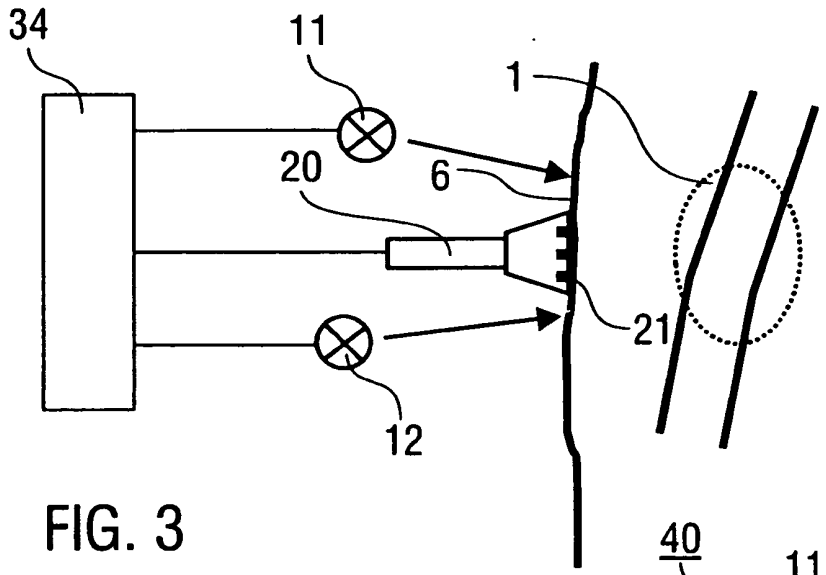

FIG. 3

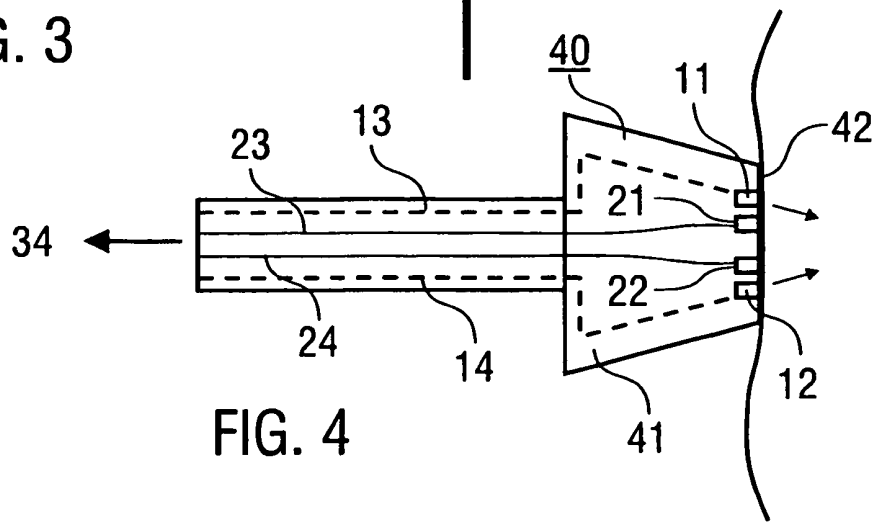

FIG. 4

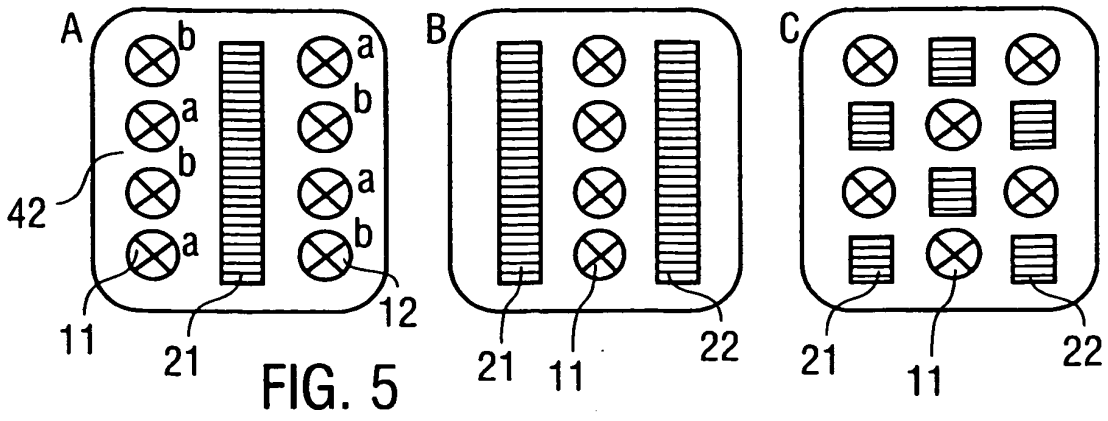

FIG. 5

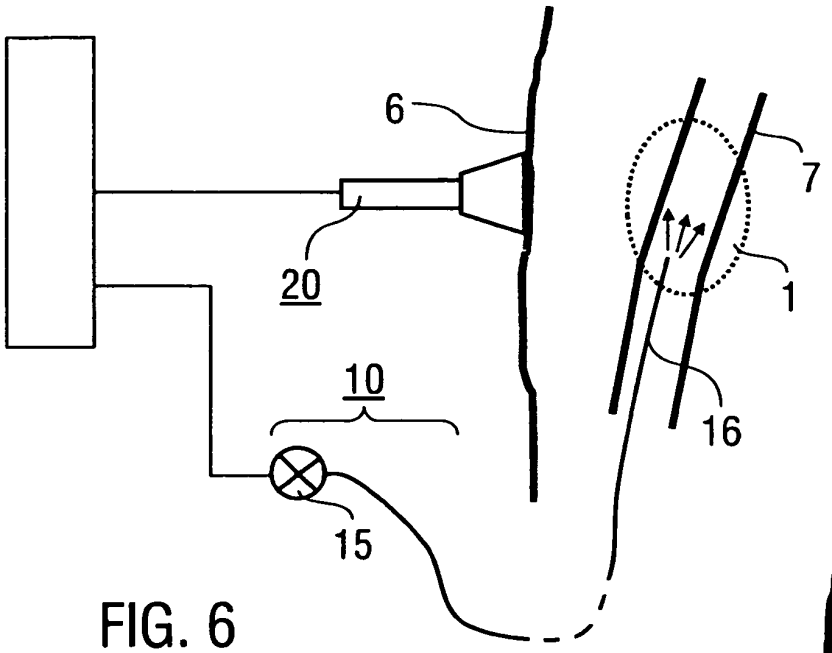

FIG. 6

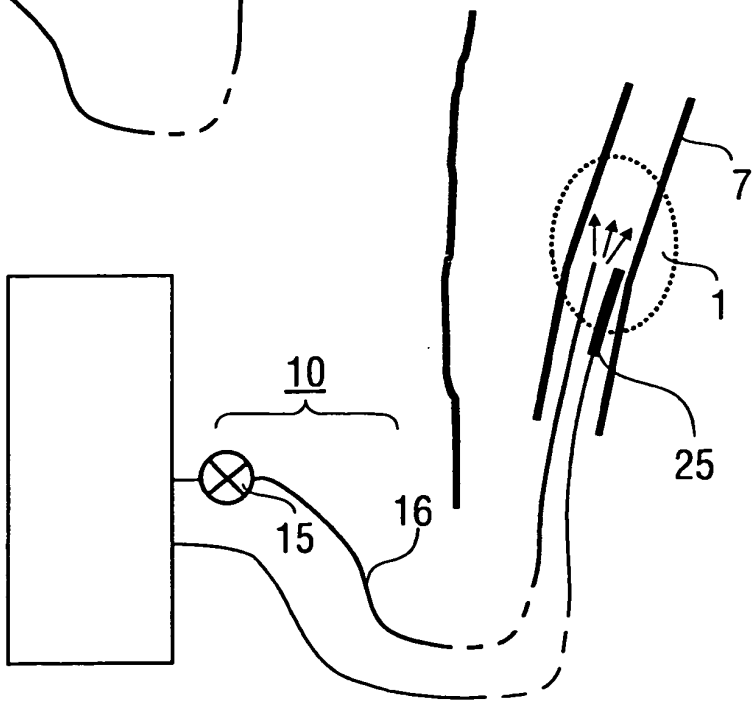

FIG. 7

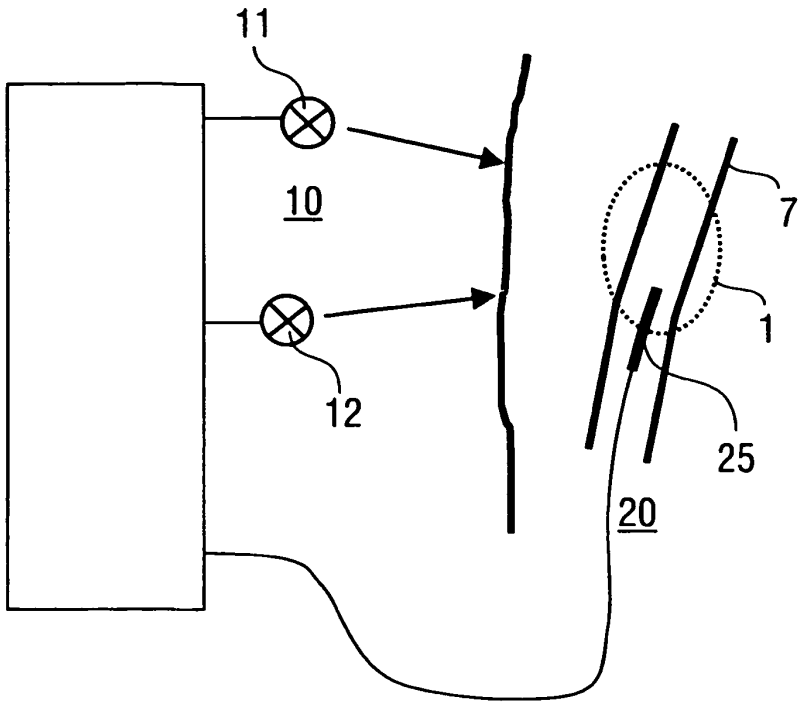

FIG. 8

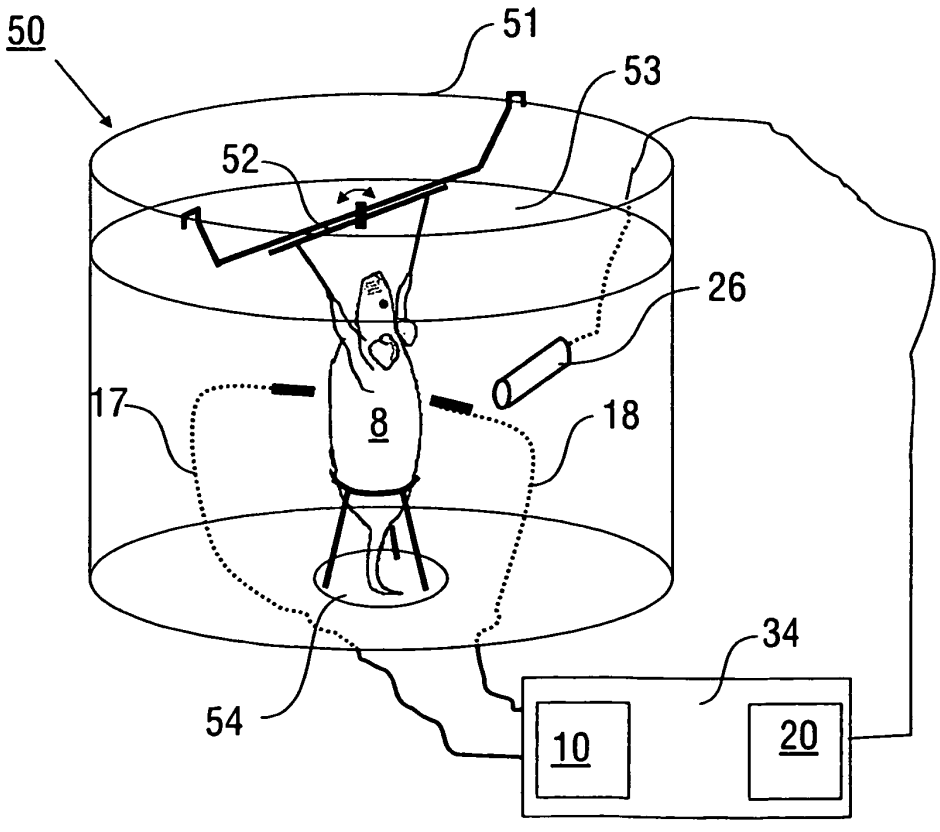

FIG. 9

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	组织生物标志物的定量多光谱光声层析成像（MSOT）		
公开(公告)号	EP2344019B1	公开(公告)日	2013-11-27
申请号	EP2008785095	申请日	2008-07-25
申请(专利权)人(译)	亥姆霍兹慕尼黑中心的德国研究中心的健康和环境（GMBH）		
当前申请(专利权)人(译)	亥姆霍兹慕尼黑中心的德国研究中心的健康和环境（GMBH）		
[标]发明人	RAZANSKY DANIEL NTZIACHRISTOS VASILIS		
发明人	RAZANSKY, DANIEL NTZIACHRISTOS, VASILIS		
IPC分类号	A61B5/00		
CPC分类号	A61B5/0073 A61B5/0095		
其他公开文献	EP2344019A1		
外部链接	Espacenet		

摘要(译)

包括靶组织生物标记的靶组织的多光谱光声层析成像（MSOT）成像的方法包括用照射装置照射靶组织的步骤，所述照射装置在若干照射波长处发射至少一个脉冲照射图案，检测压力信号来自具有检测器装置的靶组织生物标志物，其中响应于所述照射在靶组织中产生压力信号，并且重建靶组织中靶组织生物标志物的分布的定量断层图像，其中压力信号使用光子传播模型分析，其取决于目标组织中的照射光通量和照射波长，至少一种光谱处理方案，以及提供断层图像的反转方案。此外，描述了一种用于多光谱光声层析成像的成像装置。