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(54) **MAGNETOMOTIVE OPTICAL COHERENCE TOMOGRAPHY**

(75) Inventors: **Amy L. Oldenburg**, Urbana, IL (US);
Stephen A. Boppart, Champaign, IL
(US); **Vasilica Crecea**, Urbana, IL (US);
Xing Liang, Urbana, IL (US)

(73) Assignee: **The Board of Trustees of the
University of Illinois**, Urbana, IL (US)

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Primary Examiner—Tarifur Chowdhury
Assistant Examiner—Jonathon D. Cook
(74) *Attorney, Agent, or Firm*—Evan Law Group LLC

(57) **ABSTRACT**

A spectral-domain magnetomotive optical coherence tomography apparatus, includes (a) a spectral-domain optical coherence tomography device, and (b) a magnet. The magnet is coupled with the optical coherence tomography device so that changes in the magnetic field are coordinated with collection of data by the optical coherence tomography device. This device may be used to examine a sample by spectral-domain magnetomotive optical coherence tomography, which includes examining the sample with a spectral-domain optical coherence tomography device, to collect optical coherence tomography data. The sample contains magnetic particles, and the magnetic particles are subjected to a changing magnetic field during the examining.

30 Claims, 9 Drawing Sheets
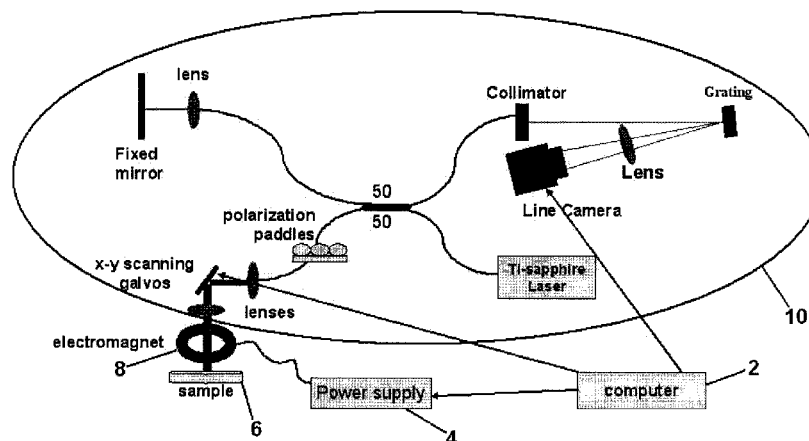
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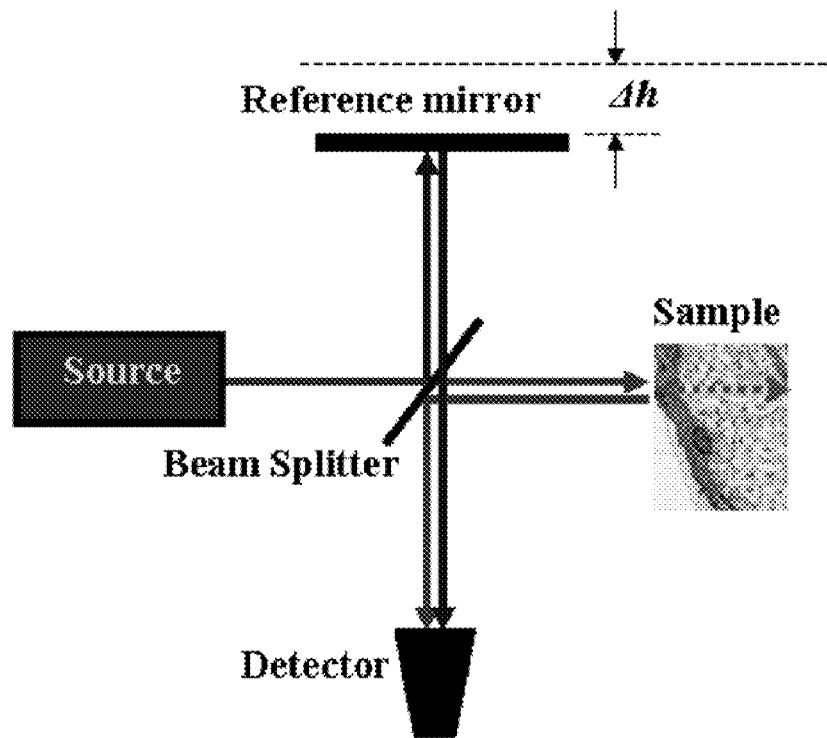
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Fig. 1

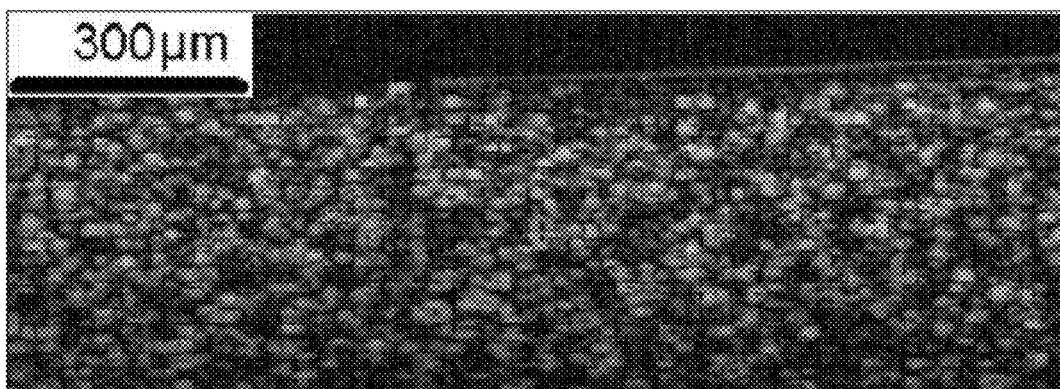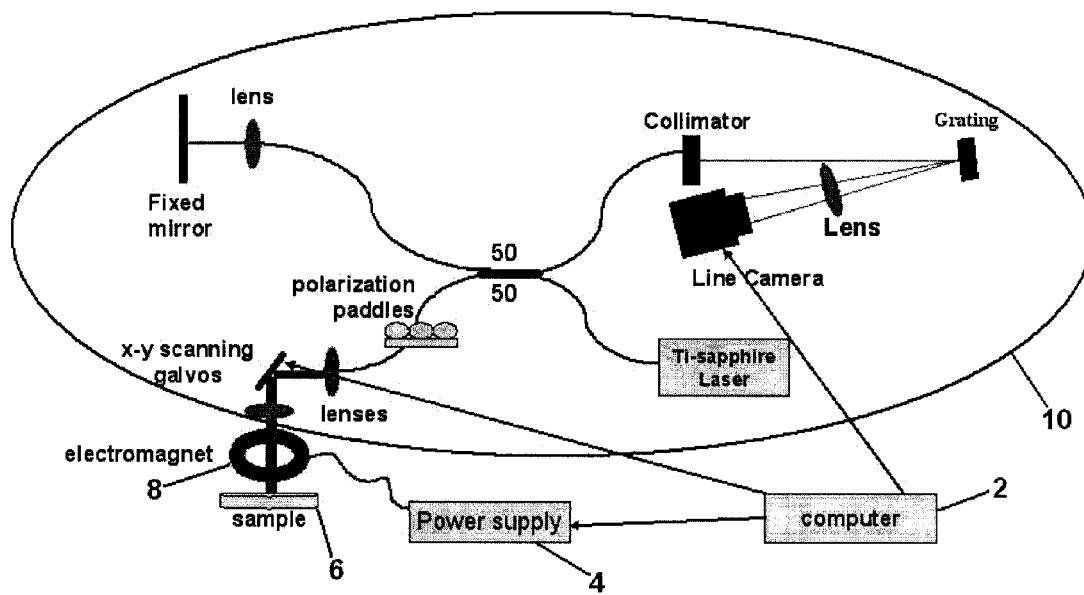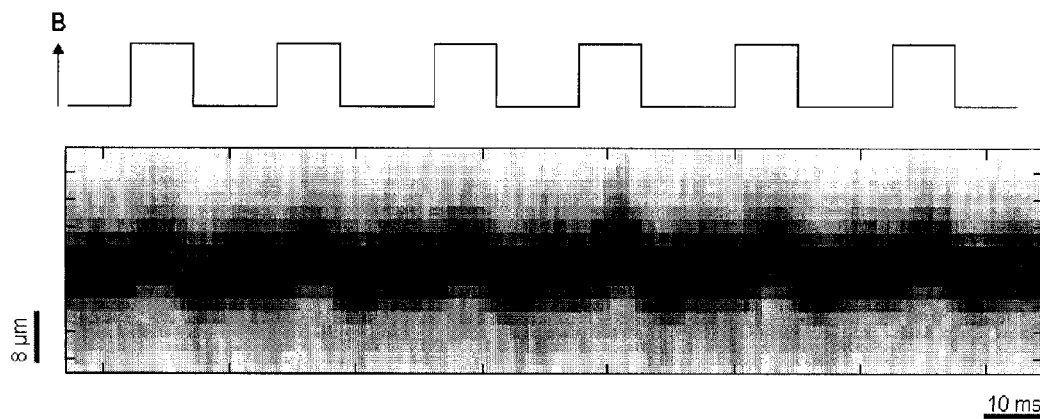**(Michelson-type Interferometer)**

Fig. 2

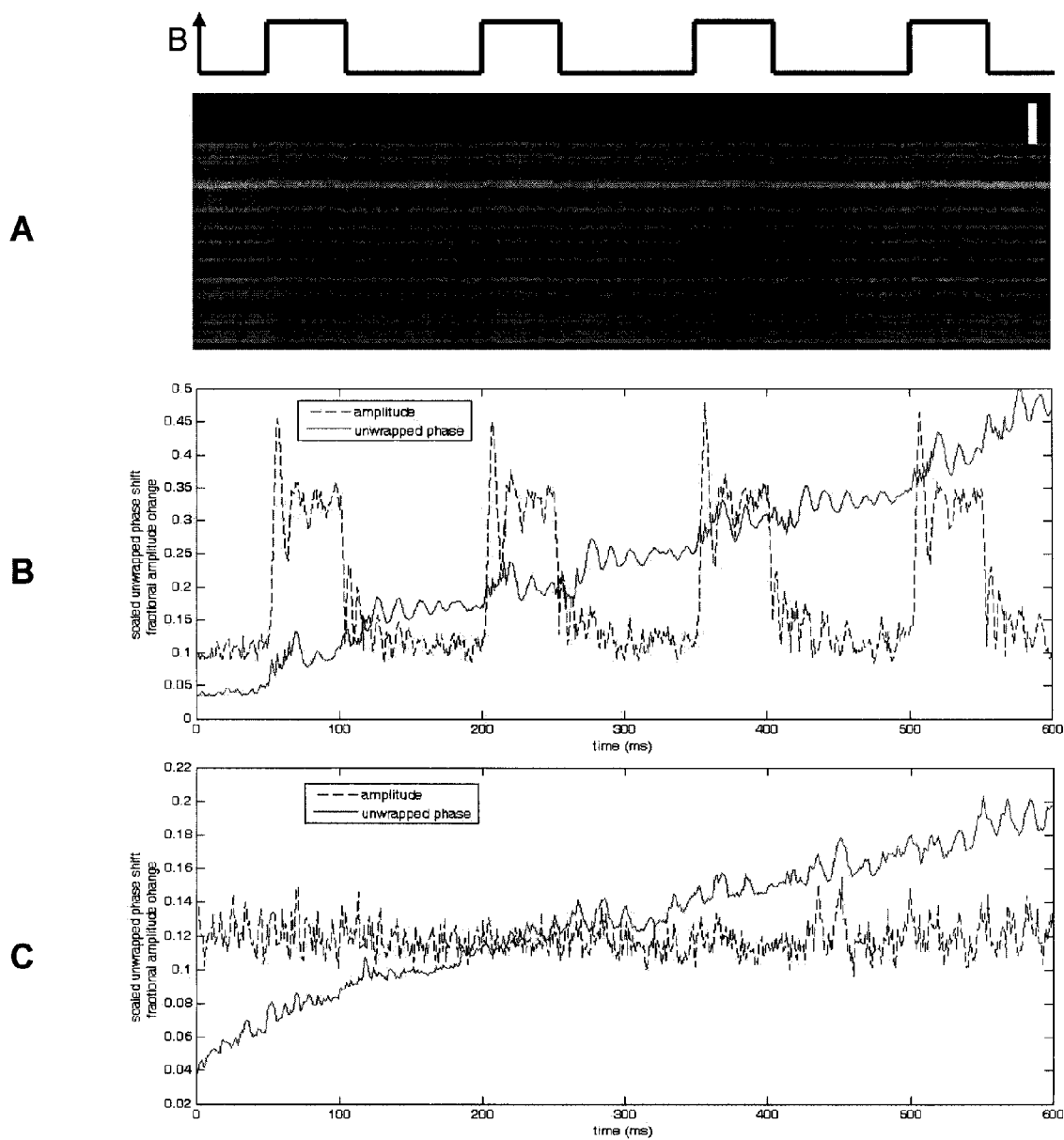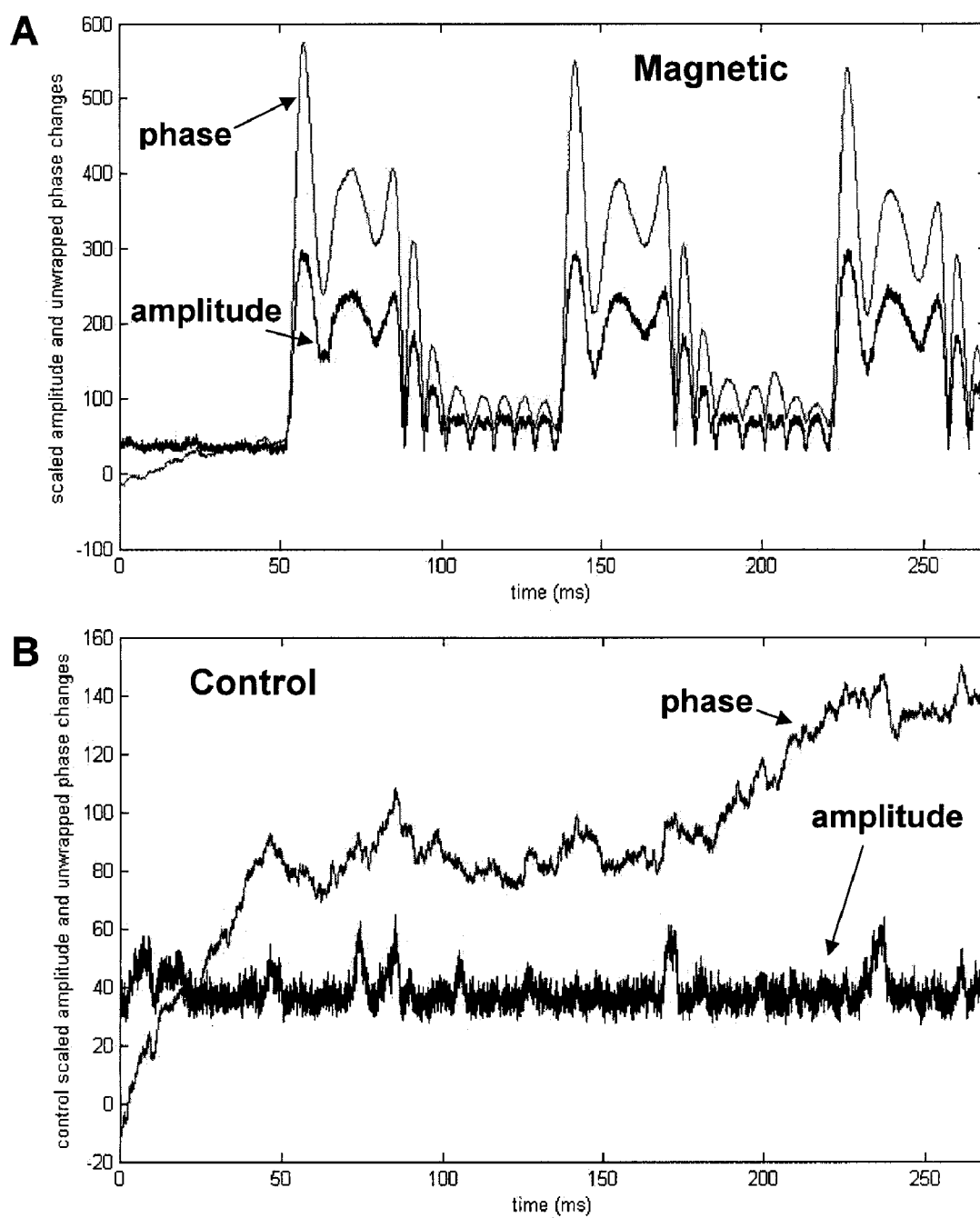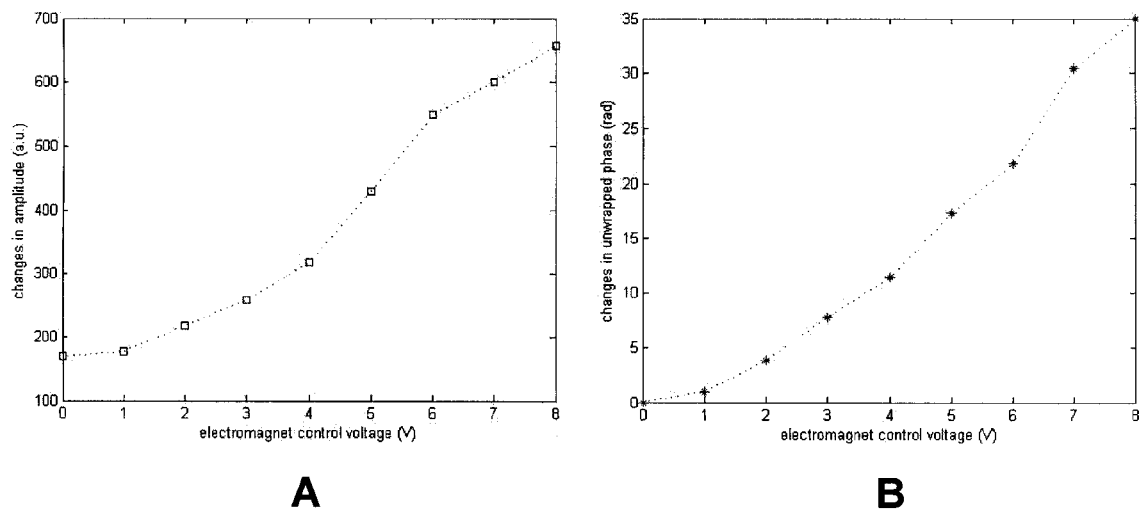**(Amplitude OCT Image)**

Fig. 3

Fig. 4
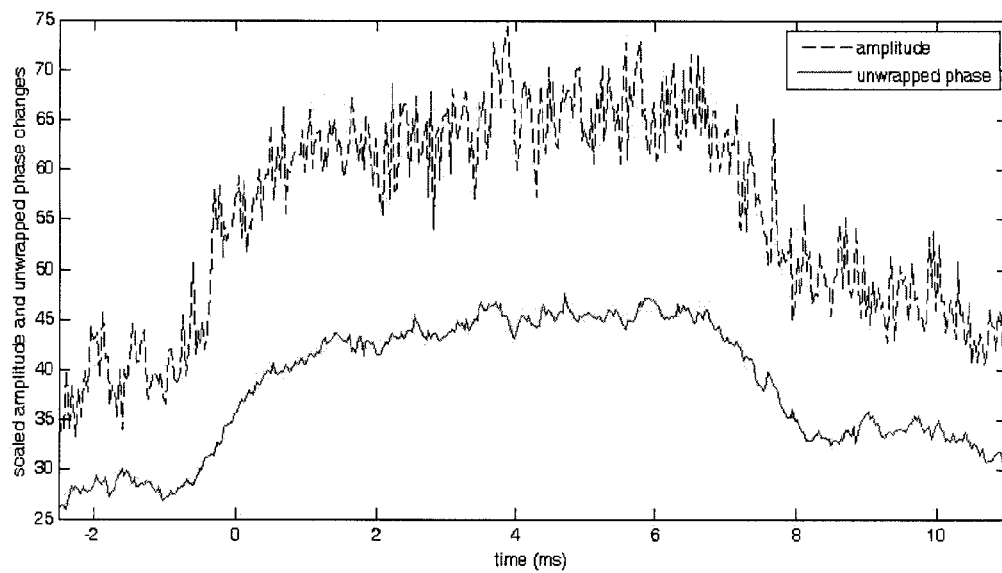
Fig. 5

Fig. 6

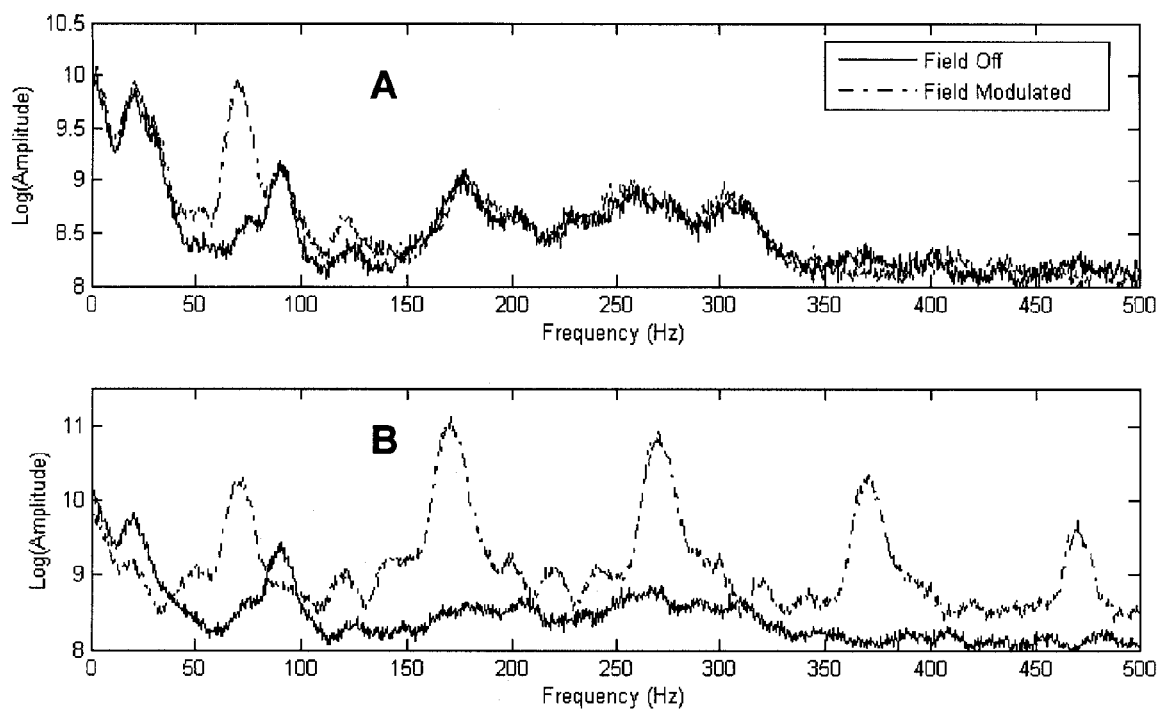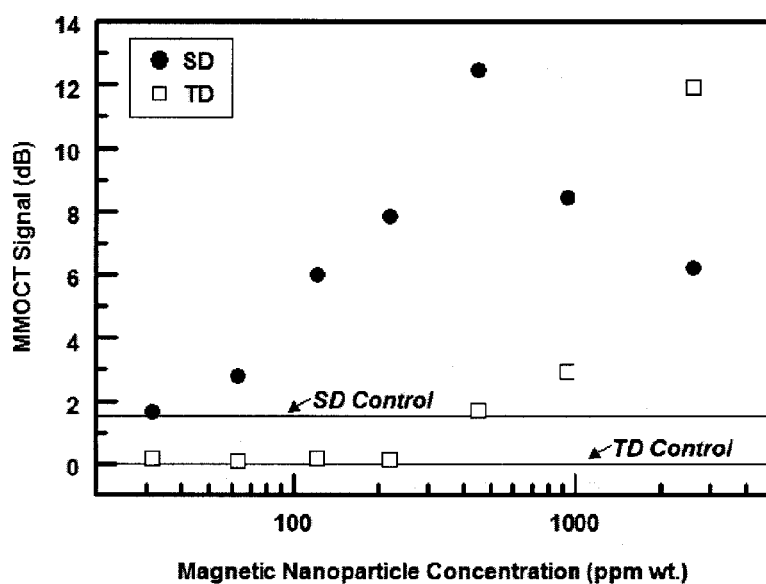A   B
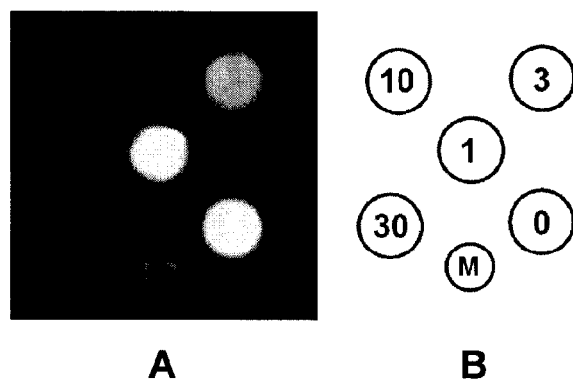
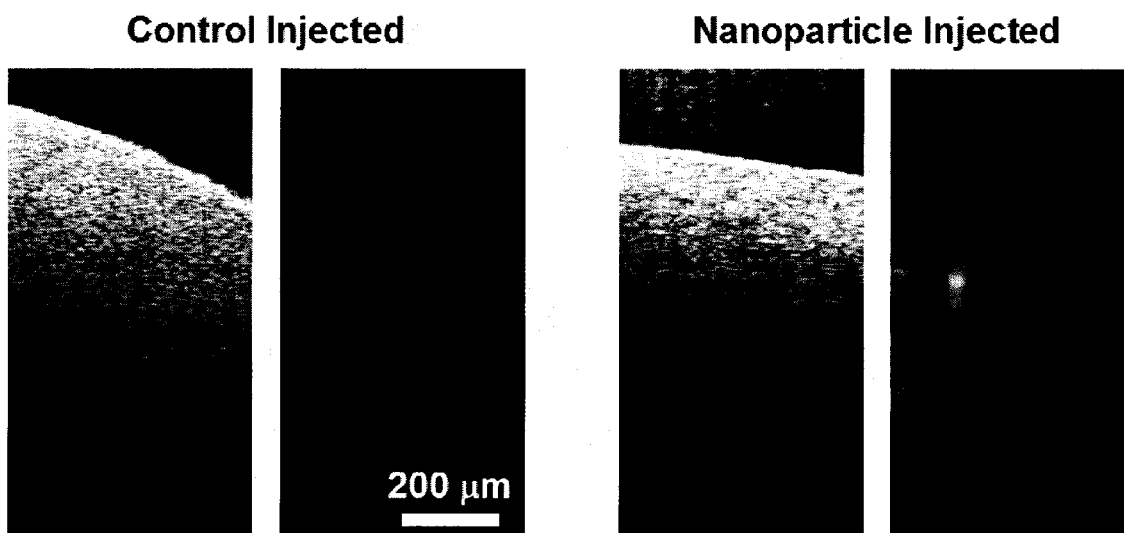Fig. 7

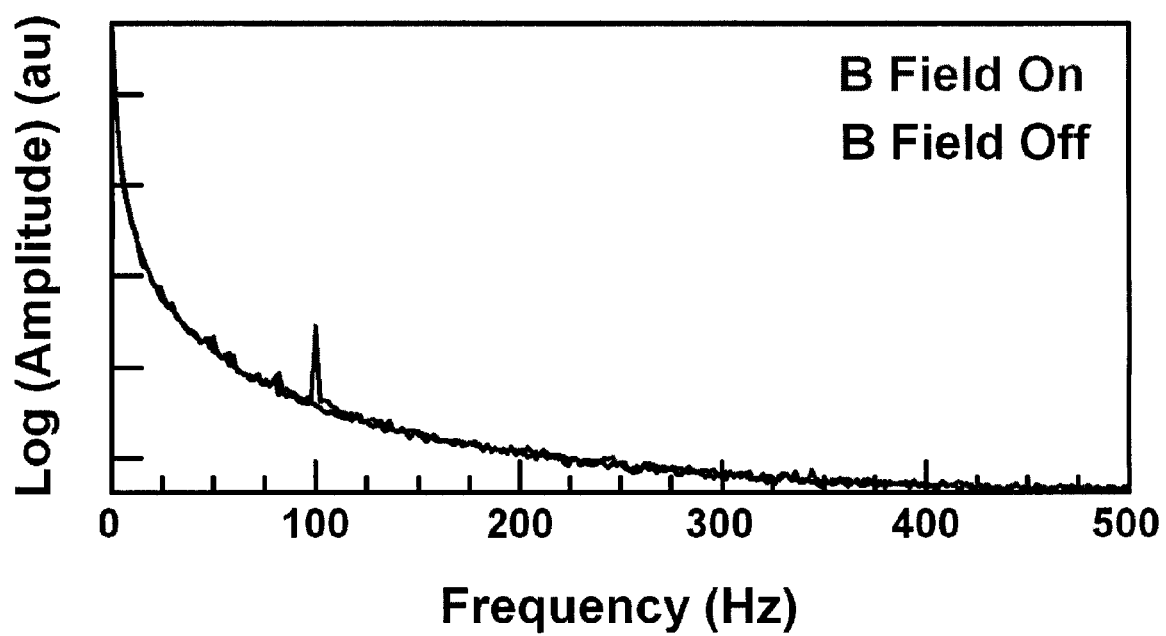

Fig. 8

Fig. 9

Fig. 10

Fig. 11

Fig. 12

Fig. 13

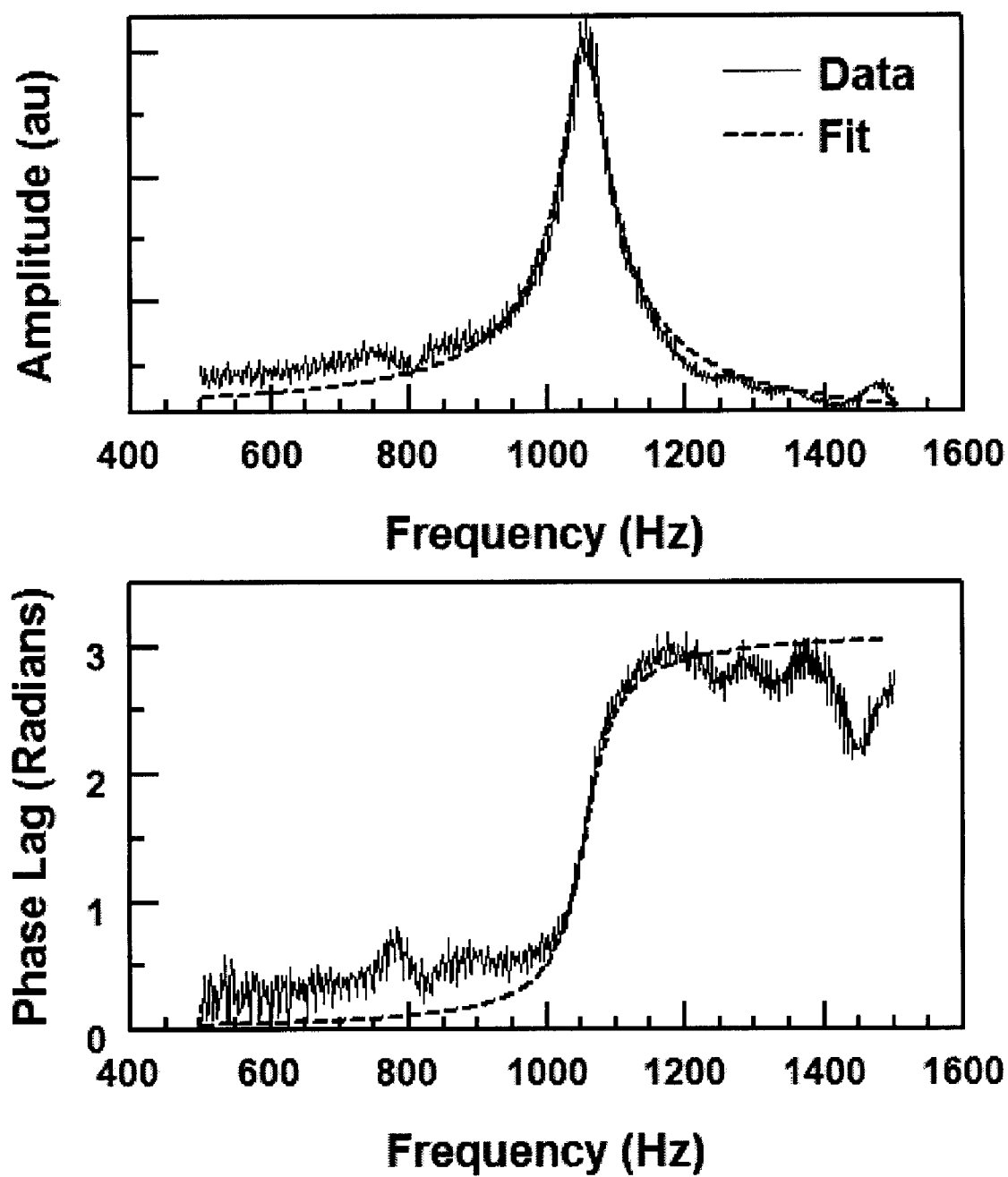Fig. 14

MAGNETOMOTIVE OPTICAL COHERENCE TOMOGRAPHY

CROSS REFERENCE To RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 61/022,276 filed 18 Jan. 2008.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

BACKGROUND

Optical coherence tomography (OCT) is a novel biomedical imaging technique that can render 2D and 3D structural and functional information in real time.[1,2] OCT is based on the theory of low-coherence interferometry. Biological samples absorb very little and scatter some of the near infrared light (NIR) that they are probed with.[2] OCT uses NIR to probe specimens as deep as a few millimeters, with micron resolution. OCT systems have been introduced recently in a clinical setting for use in ophthalmology.

In OCT the NIR probing light is equally split into a mirror arm that serves as a reference and a sample arm. The interference of the backscattered light fields in the two arms of the interferometer (E_r and E_s) is detected (as intensity I_d) and used to determine the structure of the scattering object in the sample arm. Image reconstruction is based on the theory of inverse scattering; by inverse Fourier-transforming the auto-correlation signal from the demodulated detected intensity at different times (time-domain OCT, or TD-OCT, FIG. 1) or wavelengths (spectral-domain OCT, or SD-OCT; also commonly referred to as Fourier domain OCT), one can retrieve the complex analytic signal that contains amplitude and phase information about the object. For interference to occur in TD-OCT the optical paths of the reference and the sample arms need to differ by no more than the coherence length I_c of the source. This also sets the limit on the axial resolution of the system, which is equal to I_c. For a Gaussian probing spectrum, I_c is inversely proportional to the bandwidth $\Delta\lambda$ of the source. Therefore, the use of a very broad bandwidth source for high axial resolution imaging is desired. The transverse resolution R_T is given by the diameter of the probing beam $2w_0$ and can be expressed in terms of the focal length f of the collimator, the center wavelength of the source λ_0, and the diameter of the focused beam D, as shown below (assuming a Gaussian probing beam).

$$I_d(t) = \frac{(I_r + I_s)}{2} + \text{Re} < E_r^*(t+\tau)E_s(t) >$$

$$I_c = \frac{2\ln 2}{\pi} \frac{\lambda_0^2}{\Delta\lambda} \approx 0.44 \frac{\lambda_0^2}{\Delta\lambda}$$

$$R_T = 2w_0 \approx 2.44 \frac{f\lambda_0}{D}$$

Superparamagnetic iron oxide (SPIO) particles have been used extensively as contrast agents for magnetic resonance imaging (MRI).[9] Magnetic particles with small core sizes

(<100 nm) are easily transported through the circulatory system and are able to extravasate, and are thus suitable for both in vivo and in vitro studies.[6,8] Depending on their composition and size, magnetic particles can be very responsive to external, non-invasive manipulation or detection due to their strong magnetic susceptibility. Moreover, they can be functionalized to target antigens and thus enhance contrast at the molecular and cellular level, aiding in pathogen localization and early diagnosis of disease. The use of these magnetic particles in OCT has several advantages: the ability to externally manipulate the particles, the low magnetic susceptibility inherent in human tissues, the availability of FDA approved biocompatible iron oxide particles for MRI contrast, and the potential for hyperthermic therapy with high frequency (>100 kHz) modulation.

Magnetomotive optical coherence tomography (MM-OCT) in a time-domain optical coherence tomography (TD-MMOCT) system has been used for detecting the displacements in different samples caused by the modulation of the magnetic field and it has been subsequently shown that the magnetomotive response in the system is predictable.[8] In this scheme, axial scans in a two-dimensional transversal sample plane are acquired with the magnetic field off and on, while allowing the particles and the sample sufficient time to complete motion and reach equilibrium between axial scans, for example at a line rate of 10 Hz. Thus, the images taken with the TD-MMOCT system represent a static description of the sample in the absence and in the presence of the magnetic field, and may be used as a background-rejecting method by estimating a background displacement signal when the magnetic field is off, compared to the magnetic-specific displacement when the magnetic field is off-on.[8]

This previous work demonstrated the ability to image magnetite (Fe_3O_4) micro-and nanoparticles after uptake by in vitro macrophages[4] and in vivo African frog tadpoles[8] by modulating an externally applied magnetic field and detecting the resultant magnetomotion specific to the particles. Other researchers have also used this principle to provide hemoglobin contrast in optical Doppler tomography,[31] and to detect iron uptake in tissues with differential phase OCT[32] and also in ultrasound.[9]

Phase measurements in common-path low-coherence light interferometry have been shown to render high sensitivity to sub-wavelength displacements or obstacles in the path of light.[10-12] Path length sensitivities as low as 25 m for spectral-domain optical coherence phase microscopy (SD-OCPM)[10] and 18 m (equivalent phase stability=0.4 mrad) for spectral-domain phase microscopy (SDPM)[11] have been reported. Phase-resolved methods[10-15] are often used in a dynamical regime, such as in measuring intralipid[16-18] or blood flow[19-23] velocities, nerve displacements,[24] or monitoring cell[10] and even cardiomyocyte[12] activity.

SUMMARY

In a first aspect, the present invention is a spectral-domain magnetomotive optical coherence tomography apparatus, comprising (a) a spectral-domain optical coherence tomography device, and (b) a magnet. The magnet is coupled with the optical coherence tomography device so that changes in the magnetic field are coordinated with collection of data by the optical coherence tomography device.

In a second aspect, the present invention is a method of examining a sample, comprising examining the sample with a spectral-domain optical coherence tomography device, to

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collect data. The sample comprises magnetic particles, and the magnetic particles are subjected to a changing magnetic field during the examining.

DEFINITIONS

The following definitions are included to provide a clear and consistent understanding of the specification and claims.

The signal-to-noise ratio (SNR) is defined as the integrated intensity at f_B compared to a control sample.

A "tissue phantom" or simply "phantom" is a synthetic control sample intended to mimic tissue when examined by OCT.

"Spectral-domain optical coherence tomography" or "SD-OCT" is any type of optical coherence tomography where a Fourier transform of the collected data is required to obtain temporal interference data or a temporal interferogram. SD-OCT is distinct from time-domain optical coherence tomography (TD-OCT) where a Fourier transform of the collected data is not required to obtain temporal interference data.

The term "substantially parallel" means parallel and up to 5° from parallel.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic of a Michelson-type interferometer set-up for time-domain OCT.

FIG. **2** is an amplitude OCT image of a tissue-like phantom showing presence of light scatterers throughout the volume.

FIG. **3** is a diagram of an experimental set-up for spectral-domain MMOCT.

FIG. **4** is a graph of amplitude (grey-scale pixelated) and group delay (line through center of graph) data obtained using SD-MMOCT in M-mode from the top surface of a tissue-like sample containing magnetic particles, while the magnetic field is turned on and off periodically (line over graph).

FIG. **5** shows M-mode SD-MMOCT data for a magnetic and a control sample with the magnetic field modulated at 6.67 Hz, camera line rate 1 kHz, and electromagnet control voltage of 7.5 V: (A) depth varying amplitude image (vertical scale bar=0.3 mm) for the magnetic sample; (B) a graph of fractional mean of absolute value amplitude variation and scaled mean unwrapped phase variation over all depths for the magnetic sample (according to Eqs. 1 and 2); and (C) a graph of fractional mean of absolute value amplitude variation and scaled mean unwrapped phase variation over all depths for the control sample.

FIG. **6** shows graphs of M-mode SD-MMOCT amplitude and phase data (according to Eqs. 1 and 2) with the magnetic field modulated at 11.6 Hz, camera line rate 29 kHz, and electromagnet control voltage of 7.5 V: (A) magnetic sample; and (B) control sample.

FIG. **7** shows graphs of maximum SD-MMOCT amplitude (A) and phase response (B) vs. electromagnet control voltage.

FIG. **8** shows a graph of M-mode SD-MMOCT amplitude and phase data (according to Eqs. 1 and 2) with the magnetic field modulated at 11.6 Hz, camera line rate 29 kHz, and electromagnet control voltage of 1 V.

FIG. **9** shows graphs of image-averaged transverse Fourier transforms of SD-MMOCT data for tissue phantoms with 120 ppm magnetic particles (A) and 930 ppm magnetic particles (B), with f_B=100 Hz and a downshift of −30 Hz due to the lens.

FIG. **10** is a comparison of concentration-dependent SNR (signal-to-noise ratio) for SD-and TD-MMOCT; horizontal lines indicate the SNRs of the control phantom.

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FIG. **11** is a spin-echo MRI image of agar phantoms (A) and a drawing showing the corresponding magnetic particle concentrations in the image in ppm (B); "M" is a marker.

FIG. **12** shows representative structural (A and C) and corresponding magnetomotive (B and D) SD-OCT images of the spleens of control and magnetic particle injected rats, post mortem, respectively.

FIG. **13** shows example spectra of ϕ from a 100 ppm phantom.

FIG. **14** shows the mechanical frequency spectra of (A) $A(\omega)$ and (B) $\phi(\omega)$, when a chirped modulated force is applied to the sample.

DETAILED DESCRIPTION

The present invention is based on the discovery of a method and apparatus for imaging a sample (such as biological tissue, in vivo and/or in vitro) which contains magnetic particles (more specifically, particles with a high magnetic susceptibility, such as magnetite and maghemite) that may be used to induce movement in the tissue at the location of the particle. This is referred to as magnetomotive imaging. The particles are referred to as a "contrast agents", although typically there is no imaging of the particles themselves; typically, the particles do not themselves scatter light. The imaging is carried out using OCT, preferably SD-OCT (which may be referred to as spectral-domain magnetomotive optical coherence tomography, SD-MMOCT). This technique may be used to image biological tissue, with microscopic resolution and millimeter scale or larger imaging volumes. The imaging of the particles is carried out by placing a magnet, preferably an electromagnet, near the sample surface to be scanned (biological or non-biological) and modulating the magnetic field, for example by modulating the current to the electromagnet, or by rotating or moving a permanent magnet, during imaging. The magnetic field gradient produced by the magnet pulls/pushes the magnetic particles toward/away from the magnet, and in doing so displaces them from their rest positions (for example, where they are bound to the surface of a diseased biological cell that has been targeted). These nano- or micro-scale displacements are modulated at the same frequency as the magnetic field, and are detected by the OCT system as a change in scattering by the environment immediately surrounding the particles.

Imaging light is preferably transversely scanned slowly, so that multiple modulations of the magnetic field are accomplished over the time it takes the imaging system to collect the data over one transverse resolution distance. A subsequent image in the same location is acquired with the magnetic field off, allowing for the contribution of background motions to be subtracted from the original image, and thus an image of the distribution of the particles is rendered. When using a SD-OCT system, the magnetomotive signal is dominated by a phase modulation in the OCT data, which is more sensitive than amplitude modulation.

The magnetic particles can be selected for biological or non-biological applications. For biological applications, the magnetic particles are preferably polymer-coated to make them biocompatible. The magnetic particles may be targeted using a variety of techniques: (1) the magnetic particles may be targeted for specific disease markers expressed by biological cells, by labeling the surfaces of the particles with antibodies, peptides, or other proteins that have specificity for the markers;[42] (2) the magnetic particles may be passively targeted using features of the disease, for example, the additional blood vasculature present in tumors; and/or (3) the magnetic particles may be manipulated into certain areas

(such as the body of a patient, or location within a sample) using an external magnetic field, (this method is known as magnetic drug targeting: for instance, collection of particles at the site of a mass for both imaging and treatment).[41]

Examples of these types of particles include SPIOs (Superparamagnetic Iron Oxides) and USPIOs (Ultrasmall Superparamagnetic Iron Oxide), which have been used as MRI contrast agents for several purposes, including prostate cancer detection by the specific uptake of SPIOs by healthy lymph nodes.[39] Examples of these commercially available magnetic particles include FERIDEX I.V.® (ferumoxides injectable solution, Bayer HealthCare Pharmaceuticals), RESOVIST® (SH U 555 A; Schering, Berlin, Germany), and COMBIDEX® (ferumoxides, USPIO, Advanced Magnetics).

Hyperthermic therapy may be used to killing cells, such as cancer cells, with the magnetic particles, once they have reached the desired site.[43] Furthermore, because these magnetic particles were developed originally for MRI, they may also be used for multimodal imaging: by injecting the magnetic particles in a patient or live animal, the particles can be traced over several hours or up to several days using both the MRI and OCT. This invention thus allows for the distribution of the particles to be imaged on the microscopic scale, which can be used concomitantly with MRI, and also with hyperthermic therapy.

In one specific application, a patient may be exposed to magnetic iron oxide particles targeting cancer, imaged with MRI to determine general regions of disease, then during surgical intervention the mesoscale imaging provided by this device would provide the surgeon with microscale images of the locations of the magnetic particles. Because OCT imaging in particular typically penetrates a few millimeters below the tissue surface, this would allow the surgeon to evaluate the surgical margins of, for example, a cancerous tumor.

This OCT system may also be used for elastography, to measure the stiffness of the tissue (elastic modulus) and/or the viscosity of the tissue. There are several ways to carry out elastography using OCT: (1) the magnetic field is rapidly switched on or off, and the resulting relaxation oscillations of the tissue are recorded; this decay signal contains the resonant frequency of the tissue (which is proportional to the square root of the elastic modulus) and the decay time of the tissue (which is proportional to the viscosity); and (2) the magnetic field is square-root sinusoidally modulated (to provide a sinusoidal force), and the frequency of modulation is chirped to cover a range of frequencies; the response of the tissue contains the frequency-dependent amplitude and phase of particle displacement (note: this is a different phase than the optical phase described above). These amplitude and phase changes versus frequency are mapped to the viscosity and elastic modulus of the tissue. Preferably, when carrying out the method of (1) or (2), an identical analysis is carried out on a homogeneous control sample having a known viscosity and/or known elastic modulus.

A changing magnetic field may be produced using an electromagnet, preferably cooled using a water-jacket attached to a chiller. Alternatively, one or more permanent magnets, which may be rotated or moved, may also be used to produce a changing magnetic field. In another aspect, the magnet could be an electromagnet within a catheter for insertion within the sample, such as a patient.

In order to study the dynamics of motion in tissue, we chose to take advantage of the capabilities of a SD-OCT system: fast acquisition rates, good phase stability for increased sensitivity of detection (the reference-arm mirror is fixed, unlike in TD-OCT systems), and not least, better signal

to noise ratios.[25-28] Using the faster axial line rates ($\geq$1 kHz) of SD-OCT, magnetomotion is dynamic,[33] and thus provides a new method which does not require excessive dwelling at each tissue location.

An aspect of the present invention includes an SD-MMOCT apparatus, illustrated in FIG. **3**. The apparatus includes a SD-OCT device, **10**. The specifics of the device used in the examples are described in that section, but any SD-OCT device may be used. The apparatus also includes an electromagnet, **8**, preferably arranged so that the dominant gradient of the magnetic field it produces in aligned with the axial scanning direction of the SD-OCT device; preferably, the electromagnet allows the light from the SD-OCT device to pass through it. The electromagnet is powered by a power supply, **4**, to which it is electrically connected, and optionally one or more computers, **2**, are connected to the SD-OCT device and the power supply, for controlling and directing them, and for storing and processing the data collected by the SD-OCT. Also illustrated in FIG. **3** is a sample, **6**, which is arranged for scanning by the SD-OCT device and near enough to the electromagnet to be subjected to the magnetic field produced.

The SD-OCT device includes a detector, such as a line camera. Preferably, the line rate of the detector is greater than $2f_B$; this is known as the Nyquist sampling criterion. In an aspect of the present invention, the SD-OCT will include a swept source, rather than the typical broadband source. In another aspect of the present invention, the SD-OCT is a common-path interferometer.

In TD-OCT the time-dependent signal measured, $S_{OCT}(T)$, is:

$$S_{OCT}(\tau) = \langle \mathrm{Re}(E^*_{sample}(t)E_{ref}(t-\tau)) \rangle$$

$$\tilde{S}_{OCT}(\tau) = Hilbert\{S_{OCT}(\tau)\}$$

$$= S_{env}(\tau)e^{i\phi(\tau)}$$

where E_{sample} and E_{ref} are the electric fields from the sample and reference arms, respectively, and τ is the delay time from the moving mirror. The complex analytic signal $\tilde{S}_{OCT}$ is obtained by the Hilbert transformation, and can be written in terms of a slowly-varying envelope S_{env} and fast-modulated phase ϕ (which are positive and real-valued numbers). Typically the OCT image is constructed from S_{env} alone.

In SD-OCT the frequency-dependent signal measured is:

$$S_{OCT}(\omega)=\langle E^*_{sample}(\omega)E_{ref}(\omega) \rangle$$

$$\tilde{S}_{OCT}(\tau)=Fourier\{S_{OCT}(\omega)\}$$

and the complex analytical time-domain signal $\tilde{S}_{OCT}$ is obtained by Fourier transformation of the data. This relationship is known as the Wiener-Khintchine theorem.

When embedded in tissue that is subsequently probed with an external magnetic field, magnetic particles that are far below saturation move along the axis on which the field B has a dominant gradient, as it follows from the force equation:

$$F_p = \frac{V_p(\chi_p - \chi_{bg})\nabla B^2}{2\mu_0},$$

where F_p is the magnetic force acting on a magnetic particle with volume V_p and magnetic susceptibility X_p, X_{bg} is the

magnetic susceptibility of the sample, and μ_0 is the space permeability.[4] When the magnetic field at the site being probed has a dominant vertical component along which it varies (parallel or substantially parallel to the probing beam as in the sample-magnetic field configuration of the sample arm of the system shown in FIG. **3**), it engages the magnetic particles in motion along this direction.

In a preferred aspect of the method of the present invention, the electromagnet current I(t) is continually modulated by an offset sinusoid at frequency f_B:

$$I(t) = I_{\max}\sqrt{\frac{\sin(2\pi f_B t) + 1}{2}}.$$

A square-root is used to achieve a resulting magnetic gradient force (proportional to the square of the magnetic field) that is a pure sinusoid with frequency f_B. When a sinusoidal force at frequency f_B is applied by the magnetic particles to a specific location (for example, at a depth position corresponding to τ_0) in the tissue, it will respond by undergoing a displacement

$$\Delta z(t) = A \sin(2\pi f_B t + \phi),$$

where A is the amplitude and ϕ the mechanical phase lag. The optical phase changes $\Delta\phi$ in the complex analytic signal are related to the displacements Δz in the sample by:

$$\Delta\varphi = \frac{4\pi}{\lambda_0}\Delta z.$$

We can then write the resulting time-varying OCT signal τ_0 as:

$$\tilde{S}_{OCT}(\tau_0, \Delta z) = S_{env}(\tau_0 + 2n\Delta z/c)\exp(i\phi(\tau_0) + i(4\pi n\Delta z/\lambda))$$

where n is the refractive index, c the speed of light in vacuo, and λ the center wavelength of light.

In the "slowly varying envelope approximation", which is often a valid assumption for OCT, we can assume that the phase term in the exponential carries the bulk of the signal if the displacements are small compared to the coherence length (the envelope width is essentially the coherence length):

$$\tilde{S}_{OCT}(\tau_0, \Delta z) \approx S_{env}(\tau_0)\exp(i\phi(\tau_0) + i(4\pi n\Delta z/\lambda)) \text{ for } \Delta z << l_c/n =$$

$$\tilde{S}_{OCT}(\tau_0, 0)\exp(i(4\pi n\Delta z/\lambda))$$

where I_c is the coherence length of the light.

To couple this with B-mode OCT scanning, the magnetic field is preferably modulated several cycles during the time taken to mechanically sweep the imaging light across one resolution length, which means that:

$$f_B > \frac{v_{scan}}{\Delta x},$$

where V_{scan} is the transverse scan velocity, and Δx is the transverse image resolution. In this way, the transverse Fourier transform of the spectral-domain interferogram yields a magnetomotive signal at a higher frequency than the struc-

tural OCT image data band. To produce an OCT image of tissue motion induced by the force of the magnetic field on the magnetic particles, the data $\tilde{S}_{OCT}$ is band pass filtered about f_B at each depth position τ_0 with a bandwidth of $v_{scan}/\Delta x$ and subsequently inverse Fourier transformed.

This works because for displacements small compared to the wavelength:

$$\exp(i(4\pi n\Delta z/\lambda)) \approx 1 + i(4\pi n\Delta z/\lambda) \text{ for } \Delta z << \lambda/n,$$

and thus $\tilde{S}_{OCT}$ is directly proportional to Δz. An advantage of this technique is that the magnetomotive signal is automatically weighted by the strength of the OCT signal (light scattering signal) at each point. This rejects large amounts of unwanted noise at pixels where there is low light intensity.

Example transverse Fourier spectra are shown in FIG. **9**. For each sample, a pair of images were acquired with and without magnetic field modulation at f_B=100 Hz, which is well above $v_{scan}/\Delta x$=12.5 Hz. In practice during transverse scanning across the imaging lens, a phase ramp is applied which downshifts the modulation signals by 30 Hz. However, this effect is predictable, and M-mode images exhibit no downshifting.

It was also found that for higher magnetic particle concentrations, harmonics of f_B appear. Under these conditions the displacement Δz is large and the approximation used above is not always valid. The signal, without any approximation, is:

$$\tilde{S}_{OCT}(\tau_0, 0)\exp(i(4\pi n\Delta z/\lambda)) = \tilde{S}_{OCT}(\tau_0, 0)\exp(i(4\pi n/\lambda)A\sin(2\pi f_B t + \phi)),$$

which is a Bessel function of the first kind exhibiting harmonics of f_B for sufficiently large displacements Δz. These harmonics of f_B reduce the strength of the signal at the fundamental frequency f_B.

Using this technique, the signal-to-noise ratio (SNR), defined as the integrated intensity at f_B compared to control, is greatly improved from the previous TD-MMOCT system using the 3-pulse method.[8] The concentration-dependent SNRs are shown in FIG. **10**. While TD-MMOCT affords a sensitivity to only 500 ppm magnetite particles, the SD-MMOCT system detected tissue phantoms with ~50 ppm particles. This is because the SD-MMOCT interferogram is phase-sensitive, whereas the previous TD-MMOCT data is demodulated to remove the phase contribution (because the moving delay arm decorrelates the phase between successive axial scans). The non-zero control value for the SD-MMOCT data is likely due to diamagnetic repulsion from the bulk phantom material which is made of silicone. Saturation of the SD-MMOCT SNR at higher magnetic particle concentrations occurs when the modulation signal shifts into the harmonics of f_B.

In an alternative aspect of the present invention, the "slowly varying envelope approximation" is not used, and the optical phase is directly processed by the full four-quadrant arctangent to pull out the phase term:

$$\phi(\tau_0, \Delta Z) = \text{unwrap}(\arctan(\tilde{S}_{OCT}(\tau_0, \Delta z))) = \phi(\tau_0) + 4\pi n\Delta z/\lambda.$$

A phase unwrapping technique[44] ("unwrap"; a one-dimension phase unwrapping technique) is preferably used in this aspect of the present invention. This no longer requires that Δz be small compared to the wavelength, unlike when the "slowly varying envelope approximation" is used. One can then bandpass filter ϕ around f_B at each depth position τ_0. The resulting signal is the MMOCT image. Thresholding based on the amplitude of $\tilde{S}_{OCT}$ at each pixel is preferably also be

performed, since this calculation does not have the advantage of the "slowly varying envelope approximation": the magnetomotive signal is not automatically weighted by the strength of the OCT signal at each point, and unwanted noise may be present at pixels where there is low light intensity. Example spectra of ϕ from a tissue phantom containing 100 ppm magnetic particles are shown in FIG. **13**.

In another aspect of the present invention, elastography imaging is carried out using SD-MMOCT, to determine the viscosity and elastic modulus of the sample or specific parts of the sample. A sinusoidally driven visco-elastic system can be modeled by the following equation of motion:

$$z''(t)=q_0\sin(\omega t)-\gamma z'(t)-\omega_0^2 z(t)$$

where z' and z" are the first and second derivatives of position z with respect to time t, q_0 is the force per unit mass, ω is the angular driving frequency (=2 πf_B), γ is a damping angular frequency that is proportional to the viscosity, and ω_0 is the natural angular frequency of the system, where the elastic modulus is proportional to ω_0^2. In the underdamped case ($\gamma < 2\omega_0$):

$$A = \frac{q_0}{\sqrt{\gamma^2\omega^2 + (\omega_0^2 - \omega^2)^2}}$$

$$\phi = \arctan\left(\frac{\gamma\omega}{\omega_0^2 - \omega^2}\right)$$

The amplitude thus exhibits a mechanical resonance at

$$\omega_{resonant} = \sqrt{\omega_0^2 - \frac{\gamma^2}{2}}$$

and the width of the resonance is proportional to γ.

By applying a chirped modulated force to the sample, $F(t)=I^2(t)$ (where I is the actual current applied to the electromagnet), the mechanical frequency spectra of $A(\omega)$ and $\phi(\omega)$ can now probed. If the system is similar to the under-damped model described above, it is then possible to determine γ and ω_0 (especially if a comparison is made with a sample of known viscosity and/or elastic modulus). This is done as follows: a chirped waveform from 0 to 2 kHz was applied to a sample consisting of 2% agarose gel embedded with magnetic particles, and imaged in M-mode. The optical phase was then directly processed by the full four-quadrant arctangent to pull out the phase term. Then the Fourier transform (FT) of the modulation force F(t) was divided from that of the unwrapped optical phase ϕ.

$$A(\omega) = \left|\frac{FT(\phi(t))}{FT(F(t))}\right|$$

$$\varphi(\omega) = \arctan\left(\frac{FT(\phi(t))}{FT(F(t))}\right)$$

$A(\omega)$ was averaged over the pixels of $\tilde{S}_{OCT}$ that were significantly above the noise floor. The "phasor sum" was used to average ϕ over the same region. This method was applied to a 2% agarose tissue phantom containing magnetic nanoparticles. A least-squares fitting method was used to extract the frequencies $\gamma/2\pi$ and $\omega_0/2\pi$ from $A(\omega)$ in the range from 500

to 1500 Hz, and the values obtained were 67 Hz and 1058 Hz, respectively. The spectra and fit curves are plotted in FIG. **14**.

This method allows one to measure the depth-dependent γ and ω_0 at a single transverse location in the sample (in M-mode). Transverse stepping can then be performed to construct a 2-or 3-D elastography image.

While the $\phi(\omega)$ was not used in the fitting in this example because it was noisy, it is a useful parameter for two reasons:

1. If it is close to zero, then the modulation response is in phase with the driver, and thus is below the resonance. If close to π, the driving frequency is above the resonance. Thus, no special fitting is needed and this simple test could be used to quickly find the general frequency range of the mechanical resonance before performing a frequency-swept scan.

2. ϕ can be used to differentiate between a sample that is paramagnetic or diamagnetic. A paramagnetic sample is pulled towards the magnet and thus will have an in-phase response ($\phi=0$) at low frequencies (such as the magnetic particles themselves). A diamagnetic sample (such as the water-filled agarose itself) is diamagnetic, and will be pushed away from the magnet, resulting in $\phi=\pi$. This can be used to better reject the diamagnetic response from the desired paramagnetic contrast from the magnetic particles, resulting in better imaging sensitivity.

EXAMPLES

Example 1

The SD-OCT system used in the examples includes two commercial lasers, a single-mode fiber interferometer, galvanometer mirrors for scanning the beam across the sample, a line scan CCD camera, commercial D-A and A-D converters, and computer software to control the scanning and data acquisition, and processing. In addition, for magnetic particle contrast, a water-jacketed solenoid coil which allows the laser light to pass through the central bore is positioned immediately above the sample (this electromagnet has been previously described[8]) and powered with a 1 kW power supply and controlled by the same computer, with software to synchronize the electromagnet modulation with the scanning and data acquisition.

This example demonstrates the feasibility of MMOCT in a spectral-domain OCT system (SD-MMOCT), and compares the sensitivities of amplitude and phase detection for improved imaging performance. The phase stability of the SD-OCT system was calculated as the standard deviation of the phase from a perfect reflector[10] (mirror) and was found to be 0.18 rad. In terms of physical displacement and given the bandwidth and the center wavelength of our source, this translates to approximately 11 nm displacement sensitivity. These values of sensitivity are larger than those reported for spectral-domain phase microscopy most likely because our SD-OCT system is a dual-path interferometer and thus the phase stability is vulnerable to jitter in the relative path lengths (such as those caused by temperature fluctuations and fiber bending or moving) and other noise sources that common-path systems can significantly reduce.[10-12] Compared to time-domain phase stability, however, this is an important improvement (for example, a time-domain OCT system with Fourier domain optical delay using a resonant scanning mirror exhibits a phase stability of ~1 rad at 100 Hz).

The optical and mechanical properties of the silicone-based tissue phantoms imaged in this study match closely those of biological tissue, for example human skin.[2] Titanium dioxide (TiO_2) microparticles with a diameter of about one

micron served as scatterers. Magnetite (Fe_3O_4) particles with a mean diameter between 20-30 nm were homogeneously dispersed in the sample medium for a magnetic sample (FIG. 2). A separate base stock was prepared for the control sample and no magnetic particles were added to it.

The samples were probed with 13 mW of optical power from a broadband titanium: sapphire laser (KMLabs, Inc.) centered at 800 nm and with a bandwidth of about 115 nm, providing an axial resolution of 3 μm. The magnetic field was applied by means of a computer-controlled electromagnet (FIG. 3) that was synchronized with the data acquisition and a lateral scanning mirror (the x galvanometer). The sample light was collimated through a 40 mm focal length achromatic lens and subsequently focused, providing 16 μm lateral resolution. The magnetic particle concentration of the sample used in this study of the magnetomotion was 2.5 mg/g, as the response of this sample to changes in magnetic field were evident in amplitude data and phase data.

In a first set of experiments, spectral domain data was acquired at a fixed position in the sample (M-mode imaging) in order to reveal the time evolution of the amplitude and phase over the depth of the sample, while the magnetic field was periodically turned on and off. Axial scans were acquired with a camera line rate of 1 kHz. The power dissipated on the electromagnet was 100 W, corresponding to a power supply control voltage of 7.5 V. The period of a cycle was about 25 ms, with a duty cycle of 32% (magnetic field modulated at 40 Hz). The results of this experiment indicate that the time scale of the sample response to magnetic field changes (either displacing when the field is turned on, or relaxing when the field is turned off), is comparable to, if not larger than, the duration of a cycle. It is difficult to assess if the agents and the sample have enough time to complete motion and reach equilibrium with the present magnetic field modulation period. Therefore, in order to better evaluate these time scales, measurements of magnetomotion with the magnetic field modulated at lower frequencies were done subsequently and are discussed below. Nonetheless, magnetomotion is evident in the data shown in FIG. 4. The fluctuations in the amplitude and in the group delay of the unwrapped phase match the magnetic field modulation, as expected. The stability of the phase allows for the unwrapping of the phase for the calculation of the group delay.[29]

Further, the magnetic field was modulated at 6.67 Hz, while the camera rate was kept at 1 kHz. The amplitude and unwrapped phase M-mode data are shown in FIG. 5. From the amplitude image alone (FIG. 5A) it might appear that at this frequency of the magnetic field the particles have enough time to reach an equilibrium position after both transitions. However, the averaged absolute value of the amplitude difference with respect to a background (zero-magnetic field) value for each row and the corresponding averaged unwrapped phase shift, defined as

$$a_{frac}(t) = \frac{< |a(z, t) - < a(z, t) >_{t\_beforeBon}| >_z}{< a(z, t) >_z},$$ (Eq. 1)

and

$$\phi_{frac}(t) = \frac{< |\phi(z, t) - < \phi(z, t) >_{t\_beforeBon}| >_z}{< \phi(z, t) >_z},$$ (Eq. 2)

and plotted in FIG. 5B, show that the scatterers appear to be exhibiting under-damped oscillations immediately after the changes in the magnetic field occur. This result constitutes the basis for dynamic studies of these oscillations. The phase

modulation and the amplitude modulation, synchronized with the magnetic field modulation, are in good agreement. The analyzed data indicates that the strongest achievable MMOCT signal can be captured within a few milliseconds of the onset of the magnetic field (in this case, the mean time between onset of magnetic field and maximum displacement is 7 ms), but this will be dependent on the regional micromechanical properties of the sample or tissue. The corresponding data for the non-magnetic phantom in the presence of the magnetic field modulation is shown in FIG. 5C. As expected, the power spectra of both amplitude and phase data for this control sample do not have peak components at 6.67 Hz, since the magnetic field should not trigger a response in a non-magnetic sample. A systematic phase drift over time is apparent in both the magnetic sample and the control data, while the amplitude has a steady profile throughout an entire scan. This indicates that phase measurements should utilize correction methods for measurements over longer times.[29]

In another experiment, the magnetic field strength was varied by changing the electromagnet power, and **8100** axial scans were acquired with a camera line rate of 29 kHz. This high frequency allows for higher sampling of the oscillations at the transitions between different states of the magnetic field. The magnetic field was modulated at 11.6 Hz in order to accommodate a set of three off-on transitions over the whole duration of a scan, which was 279.3 ms. The magnetic field strength is proportional to the power supply control voltage. The results of this experiment for a magnet control voltage of 7.5 V were in good agreement with those of FIG. 5, with the advantage of better temporal resolution, as evidenced in FIG. 6.

The changes in amplitude and phase as a function of electromagnet control voltage (which is linearly proportional to the magnetic field strength—for an 8V electromagnet control voltage the magnetic field strength is B=0.06 T and $\nabla B^2 \approx 1.3$ T^2/m) are plotted in FIG. 7. The maximum MMOCT amplitude/phase changes were calculated as the differences between the amplitude/phase values at the displacement peak immediately after the magnetic field is turned on and the mean values of amplitude/phase right before that. As expected, both amplitude and phase changes increase with the field, corresponding to an increase in the displacements in the sample.

Phase and amplitude changes for a low magnetic field corresponding to a control voltage of 1 V reveal the smallest displacement detected in this set of data. The corresponding amplitude and phase variations right before and after the magnetic field is turned on are plotted in FIG. 8. The amplitude data at this low value of the field becomes quite noisy, while the profile of the unwrapped phase is still smooth, suggesting more sensitive detection from phase analysis than from amplitude analysis. This may be close to the delineating zone between regimes in which phase versus amplitude measurements are preferred. The sensitivities for this data were calculated as the changes in amplitude and phase immediately after the field was turned on, relative to the idle state of the sample right before the field was turned on (averaging for before and after onset of field was done over ~1 ms), divided by the standard deviation of their value over the same period of non-magnetic activity. The phase signal-to-noise ratio was found to be 23.20 and the amplitude signal-to-noise ratio was 7.72, showing that in this regime phase analysis is preferable.

Example 2

Soft silicone-based tissue phantoms described previously[8] were impregnated with 4 mg/g TiO_2 microparticles to provide

a −30/cm scattering coefficient and were added with varying concentrations of magnetite (−25 nm) particles. The OCT imaging system included an 800 nm femtosecond laser (KM-Labs) pumping a single-mode fiber interferometer with 120 nm bandwidth and −8 mW at the sample. A 40 mm imaging lens provided 16 μm transverse resolution with axial resolution ~3 μm. The electromagnet provided −600 G at the sample as described previously.[8] For TD-MMOCT, a delay galvanometer was modulated at 10 Hz and dual-balanced detector (New Focus Nirvana) measured the interferogram. For SD-MMOCT, a line scan camera (Dalsa) measured the spectral interferogram with an exposure time of 250 μs and line rate of 1 kHz. The image dimensions were kept at 0.5 mm wide by 0.75 mm deep for comparison, and the imaging times were 50s for TD-MMOCT and 5s (2.5s each for control and modulated images) for SD-MMOCT. The data are shown in FIGS. 9 and 10.

Example 3

Agar phantoms (4%) were prepared with varying concentrations of magnetite particles (Ocean Nanotech, ~10 nm) and imaged using spin-echo MRI (4.7T Varian SISCO, Trep=4s, Techo=50 ms, 10 mm slice thickness). As shown in FIG. 11, the expected negative T_2 contrast increases with the magnetic particle concentration, and levels <10 ppm are detectible.

The same magnetic particles used in the MRI were tail-vein injected into a healthy rat (~0.5 mg/kg Fe in saline) which was euthanized after 2 hours circulation time. The major organs were harvested and compared to those from a second rat injected with a similar volume of saline only. Histology and Prussian blue staining was performed on harvested tissues, and only the spleen revealed a significant amount of magnetite particle uptake. Six sets of SD-MMOCT images (control and modulated) were then acquired from both the control and magnetic particle-laden spleens, at varying locations covering the length of the outside surface. For tissue imaging, the same SD-MMOCT parameters were used as in Example 2, except a larger depth (1 mm) was analyzed. The magnetic-specific SNR was computed for both groups, revealing an SNR of 0.095±0.29 dB for the control group. For the magnetic particle-laden spleen, four of the 6 images exhibited an SNR greater than 1 standard deviation above the control, with 0.62±0.42 dB for the group. As shown in FIG. 12, specific hot spots were observed in certain regions of the magnetic particle-laden spleen only.

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What is claimed is:

1. A spectral-domain magnetomotive optical coherence tomography apparatus, comprising:

(a) a spectral-domain optical coherence tomography device, and

(b) a magnet, coupled with the optical coherence tomography device so that changes in a magnetic field are coordinated with collection of data by the optical coherence tomography device;

wherein the magnetic field oscillates with a frequency,

$$f_B > \frac{v_{scan}}{\Delta x},$$

wherein V_{scan} is a transverse scan velocity of examining, and Δx is a transverse image resolution of the examining.

2. The spectral-domain magnetomotive optical coherence tomography apparatus of claim 1, wherein the magnet is arranged so that a dominant gradient of a magnetic field produced by the magnet is aligned substantially parallel with an axial scanning direction of the spectral-domain optical coherence tomography device.

3. The spectral-domain magnetomotive optical coherence tomography apparatus of claim 1, wherein the magnet is arranged so that light from the spectral-domain optical coherence tomography device passes through the magnet during operation of the apparatus.

4. The spectral-domain magnetomotive optical coherence tomography apparatus of claim 1, further comprising (c) a computer, connected with at least one member selected from the group consisting of a magnet and an optical coherence tomography device.

5. The spectral-domain magnetomotive optical coherence tomography apparatus of claim 1, wherein the magnet is an electromagnet.

6. The spectral-domain magnetomotive optical coherence tomography apparatus of claim 1, wherein the magnet is arranged so that a dominant gradient of a magnetic field produced by the electromagnet is aligned substantially parallel with an axial scanning direction of the spectral-domain optical coherence tomography device, and light from the spectral-domain optical coherence tomography device passes through the magnet during operation of the apparatus.

7. The spectral-domain magnetomotive optical coherence tomography apparatus of claim 1, wherein the spectral-domain optical coherence tomography device comprises a broadband source.

8. The spectral-domain magnetomotive optical coherence tomography apparatus of claim 1, wherein the spectral-domain optical coherence tomography device comprises a swept source.

9. A method of examining a sample, comprising:

examining the sample with a spectral-domain optical coherence tomography device, to collect data; and

subjecting the sample to a magnetic field which is oscillating with a frequency

$$f_B > \frac{v_{scan}}{\Delta x};$$

wherein the sample comprises magnetic particles, and

V_{scan} is a transverse scan velocity of the examining, and Δx is a transverse image resolution of the examining.

10. The method of claim **9**, wherein the magnetic field causes the magnetic particles to move in a direction substantially parallel to a probing beam of the spectral-domain optical coherence tomography device.

11. The method of claim **9**, wherein a resulting magnetic gradient force on the magnetic particles from the magnetic field is sinusoidal.

12. The method of claim **9**, wherein the magnetic field is chirped.

13. The method of claim **9**, wherein the magnetic field has a field modulation of 1 Hz to 10 kHz.

14. The method of claim **9**, wherein the examining is B-mode scanning.

15. The method of claim **9**, wherein the examining is M-mode scanning.

16. The method of claim **9**, wherein phase stability of the spectral-domain optical coherence tomography device during examining is less than 0.5 rad.

17. The method of claim **9**, wherein phase stability of the spectral-domain optical coherence tomography device during examining is 0.1-0.5 rad.

18. The method of claim **9**, wherein the sample comprises 3 to 1000 ppm of the magnetic particles.

19. The method of claim **9**, wherein the sample comprises 10 to 500 ppm of the magnetic particles.

20. The method of claim **9**, wherein the sample comprises 10 to 400 ppm of the magnetic particles.

21. The method of claim **9**, wherein the sample comprises 10 to 100 ppm of the magnetic particles.

22. The method of claim **9**, wherein the magnetic particles comprise superparamagnetic iron oxide and/or ultrasmall superparamagnetic iron oxide.

23. The method of claim **9**, wherein the magnetic particles further comprise antibodies.

24. The method of claim **9**, further comprising examining the sample with magnetic resonance imaging, to collect magnetic resonance imaging data.

25. The method of claim **9**, further comprising subjecting the sample to hyperthermic therapy.

26. The method of claim **9**, further comprising forming an image of the sample from the data.

27. The method of claim **9**, further comprising calculating an elastic modulus of the sample.

28. The method of claim **9**, further comprising calculating a viscosity of the sample.

29. The method of claim **13**, wherein the magnetic field has a field modulation of 1 Hz to 100 Hz.

30. The method of claim **26**, wherein the image is an optical coherence tomography image, an elastic modulus image or an image of the distribution of the magnetic particles.

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