MA5.2 (Invited)
4:30 pm – 5:00 pm

Contrast Enhancement Methods for Optical Coherence Tomography

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Abstract*-Contrast in optical coherence tomography (OCT) images is often limited, particularly when pathological tissue is morphologically or optically similar to normal tissue. We present novel contrast enhancing methods designed to selectively identify tissues of interest.

I. Introduction

Contrast-enhancing techniques are used in virtually every medical or biological imaging modality including gadolinium-based agents for MRI, iodinated agents in CT, protein microbubbles for ultrasound, fluorescent probes in fluorescent, confocal, and multi-photon microscopy, and tissue staining for light microscopy of histopathology. Despite the application of optical coherence tomography (OCT) to a wide range of medical and surgical specialties in the last decade, little emphasis has been placed on enhancing the contrast in OCT images to selectively identify cells or tissues of interest. In recent years, groups have begun to investigate the use of hyperosmotic agents [1], exogenous contrast agents such as air-filled microbubbles [2] and engineered microspheres [3], molecular-sensitive pump-probe techniques [4], and adaptations of near-infrared fluorescent dyes utilizing their absorption rather than their fluorescent properties [5]. Endogenous molecular-specific contrast enhancement has been possible using spectroscopic OCT methods [6] as well as nonlinear optical methods to identify molecular bonds [7] and ultrastructural order in biological structures [8]. We expect that contrast enhancing methods utilizing exogenous agents and endogenous molecules will enhance the diagnostic capabilities and clinical utility of OCT. In this paper, we present an overview of our results in each of these areas.

II. Exogenous Contrast Agents

A. Liposomes and microspheres as in vivo scattering agents

Protein-shelled microspheres encapsulating vegetable oil and incorporating gold, melanin, or carbon nanoparticles in their shells have been investigated as scattering contrast agents for OCT (Fig. 1) [3]. Synthesized using high-intensity ultrasound, these agents are biocompatible and cleared by the hepatic and renal systems. Liposomes, consisting of a lipid bi-layer encapsulating water or aqueous gold colloid, Gd_2O_3, or hematite, have also been investigated as potential *in vivo* contrast agents for OCT. The liposomes are synthesized from DSPC (1,2-distearoyl-*sn*-glycero-3-phosphocholine) by extrusion. Liposomes 1μm in diameter were easily detected with OCT in tissue phantoms, and preliminary studies in an *in vivo* rat breast tumor model indicate that a solution of liposomes is detectible within the vasculature following a tail vein injection.

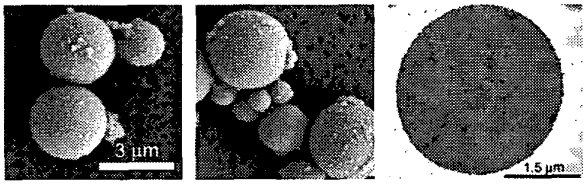

Fig. 1. SEMs and TEM of protein microspheres with embedded scattering nanoparticles to enhance local scattering in OCT images.

B. Magneto-motive detection of ferromagnetic agents

A novel means of detecting exogenous contrast agents is to utilize a magneto-mechanical effect and track magnetic field-induced movement of highly susceptible magnetic particles (Fig. 2). A solenoid is modulated so that alternating axial scan lines of the OCT image correspond to the magnetic field being on or off. Changes in the scattering between pairs of lines which would otherwise be identical are differenced to look for magnetic-specific motion. One advantage is that this technique may, in principal, be less dependent on the relative scattering of the contrast agent itself, if the agent can induce morphological changes to the surrounding scattering tissue, and provide enhanced sensitivity of detection by exclusion of the stationary background structures.

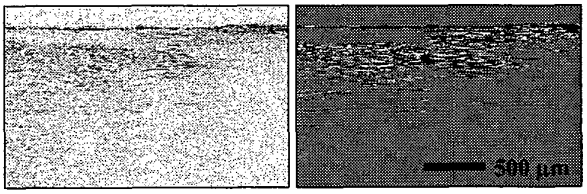

Fig. 2. Magneto-motive contrast enhancement using magnetic particles. Structural (left) and magnetically-modulated (right) OCT images of tissue.

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C. *Near-infrared dyes*

The development of near-infrared (NIR) contrast agents has been fueled by applications in confocal and multi-photon microscopy. However, the use of spectroscopic OCT (SOCT) techniques enables the spatially-resolved detection of absorption changes within the bandwidth of the OCT source. NIR dyes selected for spectral absorption characteristics within the OCT source spectrum can be detected in biological systems [5]. Dyes transported through plant vascular systems can be readily identified with SOCT and correlate strongly with fluorescence images.

D. *Plasmon-resonant nanorods*

Gold nanorods exhibiting surface-plasmon resonance have been developed with sharp narrow absorption bands above 800nm [9]. This is ideal for broadband Ti:Al_2O_3 laser-based OCT systems. The wavelength-dependent attenuation has been observed using SOCT in tissue phantoms by measuring the spectrum of embedded scatterers and observing the shift to shorter wavelengths due to the absorption by nanorods within the optical pathlength.

III. Endogenous Contrast Agents

A. *Spectroscopic optical coherence tomography*

Spectroscopic OCT [6] is a technique by which the wavelength-dependence of the backscattered light is measured and used to reconstruct an image. SOCT can be used to detect endogenous molecules or specific pathological tissues that have wavelength-dependent absorption or scattering. The advantage to this technique is that, in principal, the molecules can be distinguished from background features within the image by measuring localized changes in the scattered spectrum. The use of SOCT to detect highly absorbing exogenous agents or endogenous molecules enables many new potential contrast enhancing mechanisms for OCT.

B. *Nonlinear interferometric vibrational imaging*

Our group has recently developed a molecular imaging technique called Nonlinear Interferometric Vibrational Imaging (NIVI) [7,8] that utilizes Coherent Anti-Stokes Raman Scattering (CARS) spectroscopy principles for molecular sensitivity and contrast enhancement. The coherent nature of the CARS signal is exploited in a nonlinear interferometric set-up similar to OCT. Incident pump and Stokes beams are split into two arms of an interferometer. A reference molecular species is placed in the reference arm and a sample with unknown molecular composition is placed in the sample arm. A CARS beam is generated in the reference arm, but interference (and hence detection and spatial localization) is only produced if the same molecular species is present in the sample. Early NIVI results have produced molecular-sensitive imaging of benzene, acetone, water, and glasses, and novel interferometric-gated imaging has enabled background suppression of non-specific four-wave-mixing processes from the molecule-specific resonant signal (Fig. 3).

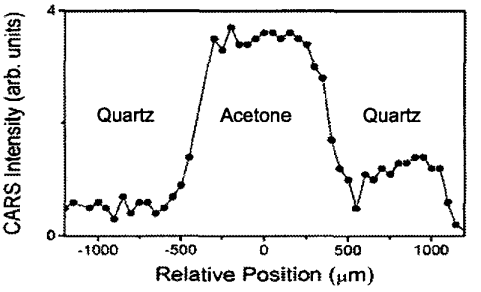

Fig. 3. NIVI A-scan line across an acetone-filled cuvette.

C. *Second harmonic generation contrast enhancement*

Using a similar but simplified optical set-up as in NIVI, the nonlinear second harmonic generation (SHG) has been used to provide enhanced OCT contrast in structures or regions that exhibit highly ordered molecules or ultrastructures [8]. In place of the reference molecular species in the reference arm of the NIVI interferometer, a BBO crystal is used to generate a reference SHG signal which is subsequently interfered with SHG generated in the sample.

IV. Conclusions

Novel methods for contrast enhancement have been investigated and are being developed for OCT. Future studies will further delineate the advantages and limitations of each of these methods. Molecular OCT imaging of endogenous molecules is emerging and functionalizing the surfaces of exogenous agents will enable targeting to cells and tissues with molecular specificity. Together, these contrast-enhancing methods are likely to improve the diagnostic ability and clinical utility of OCT.

References

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