

Optically Pinpointing Magnetic Nanoparticles within Biological Tissue

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An emerging imaging technology known as optical coherence tomography (OCT) provides microscopic in vivo imaging by using interferometry to detect light reflected from deep tissue structures. OCT imaging has been adopted by medical practitioners in many areas, including ophthalmology, cardiology and gastroenterology. Currently, there is an intense search for stains or contrast agents to use with OCT, because conventional markers such as fluorescent dyes emit incoherent light, for which there is no OCT interference signal.¹

Magnetic iron oxides, such as carbohydrate-coated magnetite (Fe_3O_4) nanoparticles, have recently been FDA-approved as human injectable contrast agents for MRI.² This class of particles is highly responsive to a magnetic field gradient, and at lower frequencies than those used in MRI (10 to 100 Hz), they can be mechanically modulated or “wiggled” within the tissue microenvironment. The magnetomotive “wiggling” exhibits a unique optical light scattering signature when probed using OCT. Our group developed a technique in which a modulated magnetic field is applied during OCT imaging, dubbed magnetomotive OCT (MMOCT).³ Using MMOCT, magnetic iron oxides are pinpointed within a standard OCT image, requiring only the addition of a small electromagnet to the imaging system.

The basic MMOCT technique involves querying the tissue both before and after application of the magnetic field gradient. By comparing the OCT data before and after, differences are attributed to a magnetic field-specific reaction, thus pinpointing the locations of the magnetic particles. This concept was first demonstrated in tissue scaffolds containing macrophage cells labeled with magnetic particles, allowing one to distinguish labeled and unlabeled cells within a thick (1.5 mm deep) sample.³ However, the

original MMOCT technique was plagued with motion artifacts during the study of larger living organisms, which are subject to respiration and cardiac-based motions.

The motion artifact problem was resolved in recent work,⁴ where the imaging sample is queried three times: twice with no magnetic field, and once with the magnetic field, analogous to pulse sequences used in MRI. Thus, non-specific background motion is estimated from the first two measurements, which is then subtracted from the magnetic particle-specific signal. This results in the ability to track magnetic nanoparticles within living animals such as the *Xenopus laevis* African frog tadpole. (See figure.) These tadpoles internalize nanoparticles through their suction feeders, which are subsequently observed inside their gastrointestinal tract.

The nature of particle magnetomotion experimentally agrees with a basic physical model.⁴ Each magnetic particle is displaced a distance that is proportional to the magnetic gradient force. This displacement also disturbs adjacent non-magnetic particles (such as cells and organelles), further enhancing the local MMOCT signal. Because of the high sensitivity of a typical OCT imaging system, nanometer-scale displacements of these particles can be detected.

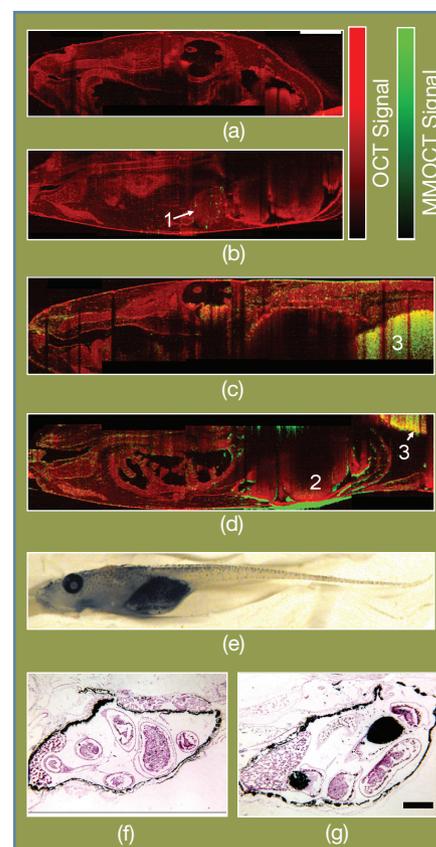
Another interesting consequence of this technique is that the magnetomotive displacement depends on the elasticity and binding of the nanoparticle within the tissue microenvironment. This has exciting potential applications for tissue elastography, and also measurement of particles binding to cell surface receptors. Ultimately, MMOCT provides a unique platform for studying nanoparticle movement in vivo, with better depth penetration than in conventional microscopy. ▲

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Combined OCT/MMOCT imaging in live African frog tadpoles (*Xenopus laevis*) without (a,b) or with (c,d) exposure to about 25 nm iron oxide nanoparticles. Red displays tissue structure and green displays magnetic nanoparticles (scale bar 500 μm). Region 1: The beating heart. Region 2: Intestine with surface features that are highly modulated by internal magnetic nanoparticles. Internalization of particles is verified by histology (g) compared to control (f); the scale bar is 200 μm . Region 3 is a mounting surface unintentionally embedded with excreted magnetic particles. (e) Photograph of tadpole.