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Nonlinear Microscopy with Shaped Laser Pulses - Shedding New Light on Tissue[1]

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The advent of ultrafast pulsed lasers substantially advanced studies of nonlinear optical effects by providing high peak intensities at low average power. When applied to microscopy in highly scattering tissue, the localized nature of the nonlinear interaction leads to high spatial resolution, optical sectioning, and larger possible imaging depth than linear methods. However, nonlinear contrast (other than fluorescence) is generally difficult to measure because it is overwhelmed by the large background of detected illumination light. This background can be suppressed by using femtosecond pulse shaping to encode nonlinear interactions in background-free regions of the frequency spectrum. We will discuss two techniques aimed at measuring nonlinear absorptive and nonlinear dispersive contrast, respectively. Nonlinear absorption offers a dramatically expanded range of molecular contrast, because not all markers that absorb photons fluoresce. We will describe a technique that utilizes shaped pulse trains of multiple colors, where an amplitude modulation of the pump beam is transferred onto the probe beam of a different wavelength, thereby generating a new frequency in the probe beam. Using this technique we have been able to detect non-fluorescent metabolic markers in tissue (e.g. the imaging of different types of melanin in pigmented lesions and the mapping of oxygenation in blood vessels). We also have developed a technique that is able to measure nonlinear phase contrast (e.g. self-phase modulation) in tissue with very moderate laser power. The key concept of this technique is the fact that nonlinear processes can create new frequency components within the pulse spectrum. We can efficiently detect these spectral changes by appropriately pre-shaping the spectrum such that the changes show against a small background. Using these pulse shaping techniques we have been able to detect nonlinear optical signatures of neuronal activity in live neurons.

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