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Mid-infrared Lasers for Medical Applications: introduction to the feature issue

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Abstract: This feature issue contains a series of papers that report the most recent advances in the field of mid-infrared light sources used for medical applications, including tissue imaging, reconstruction, excision, and ablation. Many biomolecular compounds have strong resonances in the mid-infrared region and medicine is ideally suited to exploit this. The precision, sterility, and versatility of light in mid-infrared is opening more opportunities and this feature issue captures some of the most exciting.

The mid-infrared (mid-IR) spectral region, which spans 3-30 μm, is a rich area for medical research and instrumentation. This is because many important biomolecules, such as proteins, lipids, and amides, contains strong characteristic vibrational transitions and the region contains two atmospheric transmission windows of 3-5 μm and 8-13 μm that are useful for free space communication. Due to the unique specificity of a biological molecule's spectrum in the mid-IR, lasers in this wavelength regime have a unique advantage over ultraviolet (UV) and visible or near-IR lasers. Common mid-IR emitters for biomedical applications include CO_2 lasers, free electron lasers (FELs), optical parametric oscillators (OPOs), fiber lasers and semiconductor laser diodes. This Feature Issue comprises a collection of invited and contributing papers from world-leading groups reporting the recent developments using innovative mid-IR lasers and the associated systems for biomedical applications.

The issue includes an invited review by Dr. Nathaniel Fried of University of North Carolina at Charlotte [1] on the use of mid-IR laser technologies, including an Erbium:YAG (Er:YAG) laser (λ = 2940 nm), a Thulium:YAG laser (λ = 2010 nm), and a thulium fiber laser (TFL) (λ = 1908 and 1940 nm) as an alternative to the holmium:YAG laser (λ = 2120 nm) for lithotripsy (the medical procedure to remove urinary stones) is presented. The flashlamp pumped, solid state, infrared Holmium:YAG laser is currently the clinical gold standard for lithotripsy during ureteroscopy, due in part to its cost effective treatment of all stone compositions. However, this mature technology has several fundamental technical limitations. Several mid-IR lasers have been tested as potential alternatives to the Holmium laser for lithotripsy, including Thulium:YAG, Er:YAG, and TFLs. The review discusses the benefits and limitations of these alternative lasers relative to the Holmium:YAG laser. The review concludes while initial clinical studies have been conducted, more extensive clinical studies with direct comparison to the Holmium laser are still lacking and will be required to validate the performance of the alternative laser technologies.

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Basov *et al.* [2] present a system that combines a previously reported laser soldering system that operates at 1.9 μm wavelength, with a robotic system and demonstrate its feasibility on the incision-closure of ex-vivo mice skins. In this demonstration, tearing forces of ~2.5N, 73% of the tearing force of a mouse skin without an incision were measured. This robot-assisted laser soldering technique has the potential to make laser tissue soldering more reproducible and transform surgical tissue bonding. This article was also selected as the OSA Spotlight technology.

Fried *et al.* [3] present the use of diode-pumped solid state (DPSS) Er:YAG that operates at 2.94 μm, in dental applications. Relative ablation rates of composite and enamel were determined and composite was removed from tooth surfaces using a DPSS Er:YAG laser. Composite was removed very rapidly with ablation rates approaching 50-μm per pulse. The DPSS Er:YAG laser appears to be better suited for the removal of composite than conventional flash-lamp pumped Er:YAG lasers since composite is ablated at higher rates than dental enamel and the high pulse repetition rates enable greater selectivity while maintaining high removal rates.

Hanninen *et al.* [4] present a third-order sum-frequency generation (TSFG) microscopy system to study the vibrational resonances in biological samples. The microscopy systems contain an optical parametric oscillator (OPO) that allows signal generation in the 1350–2000 nm wavelength range. TSFG microscopy is a new technique that enables the generation of images with contrast based on the IR-activity of molecular vibrations. The TSFG process relies on a third-order light-matter interaction and is sensitive to the $\chi^{(3)}$ properties of the sample. This nonlinear version of the IR microscope offers a lateral resolution of 0.5 μm and an axial resolution of about 10 μm, thus enabling intrinsic 3D imaging with vibrational sensitivity. The technique can be incorporated into a laser-scanning microscope that uses common visible photodetectors, offering straightforward visualization of biological samples in a manner similar to coherent Raman scattering microscopy.

Li *et al.* [5] present the theoretical analysis of the vibration and rotation of homocysteine molecules using density functional theory to confirm that the absorption peaks are in the terahertz spectrum range. Next the paper presents terahertz time-domain spectroscopy data to show the absorption peaks at 1.29 and 1.93 THz are measured for homocysteine, which agrees well with the theoretical calculation results. The absorbance increases linearly at the two peaks as a function of homocysteine concentration (mol/L). These results indicate the significance of using terahertz spectroscopy for the exact and quick diagnosis of homocysteine-related diseases in clinical medicine.

Tseng *et al.* [6] presents a cancer diagnostic system based on a quantum cascade lasers (QCL) for illumination and an upconversion system for efficient, high-speed detection using a silicon (Si) detector. Absorbance spectra and images of regions of ductal carcinoma in situ (DCIS) from the breast were acquired using both upconversion and Fourier-transform infrared (FTIR) systems. Only few discrete wavelengths are required to identify the microcalcifications in breast cancer tissue for the phosphate and carbonate bands at 1020 cm^{-1} and 875 cm^{-1}. The upconverted spectrum showed a good agreement with FTIR spectrum. Generally, upconversion detection gives a superior SNR at low signal levels (high absorbance's due to the very low dark noise in the Si detector). This is relevant to the highly absorbing breast calcifications and may allow for the use of thicker samples.

Yumoto *et al.* [7] present the development of a tunable (2.25 - 3.08 μm) Cr:CdSe laser with nanosecond pulse operation. The laser output energy peaked at 2.64 μm wavelength exceeding 4 mJ. Cr:CdSe is an inexpensive mid-IR laser material for biomaterial processing given its high fluence of around 2 J/cm^2.

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