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Session 3

Lectures:

Elastic light scattering spectroscopy for the detection of early cancer and pre-cancer

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Optical spectroscopy mediated by fiber-optic probes can be used to perform noninvasive, or minimally-invasive, real-time assessment of tissue pathology *in-situ*. The most common approaches have been based on UV-induced fluorescence spectroscopy and Raman spectroscopy, which are assumed to be responsive to biochemical changes in cells. On the other hand, the method of elastic-scattering spectroscopy (ESS) is sensitive to the sub-cellular architectural changes, such as nuclear grade and nuclear to cytoplasm ratio, mitochondrial size and density, etc., which correlate with features used by pathologists when performing histological assessment. The ESS method senses those morphology changes in a semi-quantitative manner, without actually imaging the microscopic structure. Clinical demonstrations of ESS have been conducted in a variety of organ sites, and promising results have been obtained. Larger-scale clinical studies are now starting.

Fluorescence Lifetime based Functional Optical as a tool for Early Detection of Cancer

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Fluorescent lifetime imaging is a relatively novel approach used for molecular, cellular and tissue imaging. Lifetime is an intrinsic parameter of the fluorescent molecule, and may hold additional information (with respect to traditional intensity measurement), regarding the environmental conditions. Lifetime is intrinsic parameter thus independent of concentration or laser's excitation intensity but could sense body condition like: PH, temperature, oxygen concentration and other bio-energetic changes. These are known to differ in early stages of tumor development from the normal surroundings, hence by using fluorescent dyes which are sensitive to these conditions i.e. change dye's lifetime, there exist the basis for functional mapping.

Furthermore, a major concern while dealing with cancer imaging is the possibility to localize the malignant region in 3D from 2D information (image). For this approach a complete scanning system for mapping time-resolved fluorescent signals was designed and built.

Four 2D images were extracted in every scanning operation. The images describe four parameters that are affected by light propagation pattern: first photon, first moment, max intensity and lifetime. These parameters are discovered as hold in store information of the 3D localization of the marked area.

In order to find out theoretically these interesting parameters, a new Monte Carlo forward model was developed simulating this scanning procedure, scanning of sample with a buried marked area (fluorophore). The results showed identical, reasonable behavior of the listed parameters in the experimental and theoretical models. The significance of this forward model is the fact that is a good base, to develop an algorithm for the inverse problem solution which will make this method (given sufficiently sensitive fluorescent dyes) as a potentially powerful tool for early, minimally invasive, bedside diagnosis of tumors deep under tissue surface.

NON-COHERENT PHOTONICS IN LIEU OF LASERS FOR HIGH-EFFICACY PHOTOTHERMAL SURGERY

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Abstract: We have demonstrated *non-coherent* photonic fiber-optic surgical devices for interstitial photothermal procedures, that are at least as effective as corresponding laser fiber-optic systems, at potentially two orders of magnitude lower cost. The immense power density within the plasma discharge region of ultra-bright Xenon short-arc discharge lamps was reconstituted remotely in an optical fiber by aplanatic optics that perform near the thermodynamic limit for flux transfer. We first demonstrated the feasibility of supplanting laser fiber-optic surgical systems with far less expensive non-coherent photonics with highly concentrated solar radiation. However the ephemeral nature of sunlight clearly restricted its applicability. Our experimental trials on live animals – for both solar surgery and lamp surgery – are reviewed, including elucidation of the phenomenon of delayed tissue death.

Selective Elimination of Fungal Infections Within and Below Surfaces Using a Femtosecond Laser

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Abstract

A new method based on near-infrared femtosecond lasers is described for the elimination of near-surface and surface fungal infections. Such infections are difficult and often impossible to treat using a variety of protocols including drugs that in any event have significant side effects. Our method employs a near-infrared ultrafast ($\sim 60 \times 10^{-15}$ sec) laser to affect non-linear optical processes within a relatively small focal volume at, within and under tissue surfaces. It is found that these non-linear processes, which are most probably associated with dielectric breakdown, have an extremely low threshold for the fungal infection, considerably lower than for hard tissue, such as nails, that are investigated in this work. Thus, by scanning in three dimensions such a laser spot the fungi can be removed without collateral damage or heating to the surrounding tissue. The effect on the tissue of such a near-infrared laser is monitored by both using biological cultures and by physical characterization using electron microscopy. Such studies show that both the macro and micro structure of human nails is maintained by the microablation process and that the biological efficacy of the fungal infection is dramatically reduced or in fact eliminated. The technique has significant potential for the removal of fungal infections in a variety of tissues since such infections often are found to incubate under tissue surfaces and the near-infrared lasers employed in this method affect these infections at extremely low thresholds and have significant penetration depths in such translucent media.

Shedding light on life:

Optical Monitoring of Tissue Viability in Biology and Medicine.

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Abstract

Optical monitoring of various tissue physiological and biochemical parameters in real-time , represents a significant new approach and a tool for better animal studies and clinical diagnosis. The multiparametric monitoring system, that was developed and applied in experimental and clinical situations, is the first medical device that enables the real time monitoring of 4 parameters representing the vitality of the tissue. Tissue vitality, which is correlated to the oxygen balance in the tissue, is defined conceptually as the ratio between O₂ supply and O₂ demand.

The device enables the monitoring of microcirculatory blood flow (O₂ supply), microcirculatory blood oxygenation (HbO₂) , mitochondrial NADH redox state (O₂ balance), and tissue reflectance, which correlates to blood volume. In this presentation the theoretical basis for the monitoring of the 4 parameters and the technological aspects of the device will be described. The comparison between the device and the existing single parameter monitoring instruments shows a statistically significant correlation as evaluated *in vitro* as well as in various *in vivo* animal models. The clinical applications of the new device include two situations where the knowledge of tissue vitality can improve clinical practice. The major application is the monitoring of Vital (brain, heart) or less-vital organs of the body (i.e. the skin, G-I tract, urethra) in emergency situations, such as in the operating rooms and intensive care units. Also, the monitoring of specific (vital) organs, such as the brain or the heart, during surgical procedure is of practical importance.

Prospects for diagnosis of pre-malignancy in intestinal anastomosis using infrared micro-spectroscopy

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The developments in FTIR spectroscopy for cells and tissues supported by recent advances of computational methods of analysis has opened up enormous possibilities for rapid diagnosis of diseases/cancer in an objective manner. Colon cancer is one of the most prevalent and aggressive cancers and there has been considerable interest in developing safe optical based probes for its diagnosis. The five-year survival rate for colon cancer treated at a very early stage is 90% but this falls to 9% when the detection is made at a premalignant stage, making an urgent need to develop novel diagnostic methods to detect colonic premalignancy. In this respect approaches have been made to understand colonic carcinogenesis in terms of chemical (spectral) changes using FTIR spectroscopy and advanced computational methods [1]. A good correlation was observed between the spectral character of the tissues with the grades of malignancy or premalignancy (polyp) using this technique. This advance has been further supported by elucidation of the biochemical changes as spectral changes in the FTIR spectra during normal and abnormal crypt proliferation[2]. These developments have opened up possibilities of reexamination of tissue biopsies in a more stringent manner to identify abnormality in resection margins that have been diagnosed as normal based on conventional histopathology [2]. The current work evaluates this concept on resection margins with an aim to add a new dimension to colonic premalignancy detection and grading. The results are encouraging when viewed in the light of patient history and gastrointestinal surgeon's/oncologist's predictions based on clinical evaluations. Further improvement and research in these areas and a synergistic effort among computer workers, pathologists, gastroenterologists and physicists would perhaps pave way for *in vivo/ex vivo* detection and evaluation of colonic malignancies using IR spectroscopy. Work in the past few years has focused not only in elucidating these chemical changes but also studying the patient history in tandem with histopathological diagnosis and FTIR spectroscopy of tissues.

The presentation will highlight these advances along with future potentials and challenges faced in adapting FTIR spectroscopy as an advanced tool in biomedicine.

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ENHANCED DETECTION OF TUMORS WITH A NOVEL TARGETED FLUORESCENCE AGENT

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Objectives: Early, accurate detection of small human tumors, before they become systemic, is essential for successful treatment. Fluorescence-based imaging enables safe, sensitive detection of malignancies. Delivery of specific, tumor-targeted fluorophores provides manifold increased sensitivity of endoscopic imaging.

Methods: We employed novel, custom-made somatostatin analogs, based on backbone-cyclic peptides, and conjugated them with fluorescent agents. Various conjugates differing in core peptide, length of alkyl linker, and fluorescence moiety (rhodamine and fluorescein) were tested *in vitro*, and the more promising conjugates were tested *in vivo* using implanted xenografts of H69 human Small Cell Lung Cancer (SCLC) and H29 human colon carcinoma in nude mice. State-of-the-art technologies included qualitative, high-resolution multispectral imaging, corroborated by quantitative fiber optic spectrofluorimetry. In addition, we performed 3-D confocal microscopy imaging of tumors, taken from mice 24 hours after injection of the targeted fluorescent agents, to study intratumoral and intracellular uptake.

Results: The lead compound, a peptide (a cyclic analog of somatostatin) linked to fluorescein, showed **exceptional** tumor/normal tissue (T/NT) ratios: lung (8.9 ± 2.8); skin (9.6 ± 3.1); liver (48.2 ± 5.2); kidney (27.2 ± 3.4); pancreas (28.5 ± 3.2) and spleen (89.4 ± 6.4). These values should be compared with uptake of standard, non-targeted diagnostic agents displaying T/NT ratios of 2 or 3.

Conclusions: Ratios, ranging from 9 to 90, enable high-quality fluorescence imaging of malignancies, against a background of normal tissue, and provide potential for enhanced endoscopic detection of early stage tumors. Our results demonstrate, for the first time, that human malignancies can be specifically targeted with high selectivity by a fluorescent bioconjugate of somatostatin analog, providing unmatched T/NT ratios.

Non-Invasive Sensing of Glucose and Hemoglobin

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There is a global growing need in non-invasive devices for the measurement of body analytes levels such as hemoglobin and glucose. This applies to hospital, clinical and home settings, where continuous monitoring is especially beneficial.

OrSense has developed a technology and a device (NBM-100) based on Red-Near Infrared Occlusion Spectroscopy to meet the needs of non-invasive, continuous measurements. The device utilizes an opto-pneumatic probe located on the finger that generates a multi-channel optical signal with strong dynamics, while occluding the blood flow. The large dynamic range of the signal enables the detection of a transmission signal through the finger. This is beneficial due to the sensitive nature of the long path-lengths of the photons, which have much larger interaction with the analytes of interest, e.g., glucose. In addition, a transmission signal, in contrast to reflection, avoids local and surface effects and better represents the average features of the bulk, which is physiologically more stable. The strong dynamics enables time-dependent analysis of the signal, which filters unnecessary factors that appear in the more conventional DC analysis.

Physically, the optical signal is influenced by absorption changes resulting mainly from hemoglobin and scattering changes induced mainly by glucose. The signal is processed using advanced algorithms to extract analyte concentrations. We use analytical models, in-vitro and Monte-Carlo simulations and in-vivo analysis to facilitate accurate analyte extraction.

Clinical trials of glucose monitoring show useful correspondence of the NBM-100 results with standard references. The results are obtained both in prospective and in profiling modes. The clinical utility of the NBM-100 has also been demonstrated for anemia screening, in which hemoglobin values were measured by the NBM-100 and then compared to standard invasive measurements.