Industrialization Potential of Optics in Biomedicine
i-POB by POB

7-8.X.2020 ONLINE

Abstract Book

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 666295.

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In vivo detection of residual tumour in breast-conserving surgery using OCT based elastography

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Breast-conserving surgery is the most common type of breast cancer surgery, accounting for more than two thirds of all breast surgeries. In this surgery, the goal of the surgeon is to remove the tumour and a rim of healthy tissue surrounding the tumour. A main challenge facing the surgeon is knowing if they have removed all tumour. A substantial issue is that they currently don't have tools available that enable them to accurately make this assessment. As a result, they are typically limited to using their sense of touch and eyesight to evaluate if all of the tumour has been excised. Not surprisingly given such crude assessment techniques, in 20-30% of cases, the pathologist finds tumour at the edge of the excised specimen. In these cases, the patient must return for an additional surgery, causing further physical and physiological distress to the patient and increasing costs for the healthcare system.

In our laboratory, we are developing an OCT-based elastography technique, quantitative microelastography, to address this issue. Quantitative micro-elastography provides micro-scale images of tissue elasticity by using OCT to measure deformation introduced to the tissue and then using a mechanical model of tissue to quantify elasticity at each pixel in the image. We have demonstrated on excised tissue in a study on 90 patients that this technique has a sensitivity of 93% and a specificity of 96% in detecting tumour at the edge of freshly excised specimens. We have translated this technology into a handheld probe to allow surgeons to identify residual tumour in the surgical cavity during surgery. So far, we have scanned 16 patients in vivo and have demonstrated that we can detect residual tumour using this probe.

In this talk, I will describe the development we have undertaken with this technology from concept to in vivo clinical studies and will describe how the technology is being commercialised by a start-up company, OncoRes Medical.

4D Megahertz-OCT: Technology and applications

Robert Huber
Institute of Biomedical Optics, University of Lubeck, Germany

The fastest OCT systems today can acquire more than several million depth scans, according to several billion voxels per second (MHz-OCT). It is now possible to acquire, process and display full OCT volumes at video rate or faster. This enables a series of entirely new applications. The talk will present the design of a special MHz-OCT system using a Fourier Domain Mode Locked laser with low latency live display of the volumetric data in a tracked virtual reality headset. The results of ex vivo testing of surgical procedures on an enucleated porcine eye will be presented. The outlook will discuss other future application fields of MHz-OCT.

Crosstalk-free volumetric in vivo imaging of a human retina and cornea with Fourier-domain full-field optical coherence tomography

Egidijus Auksorius
Institute of Physical Chemistry, Polish Academy of Sciences, Warsaw, Poland

Fourier-domain full-field optical coherence tomography (FD-FF-OCT) is currently the fastest volumetric imaging technique that is able to generate a single 3D data volume in less than 10 ms. FD-FF-OCT is based on a rapidly tunable laser source and a Fourier-domain signal detection in a wide-field configuration using a fast 2D camera. However, use of spatially coherent laser source results in crosstalk noise limiting the imaging depth in retina. It also makes corneal imaging challenging since the laser focuses down on the retina causing safety concerns. To address that we reduced the spatial coherence of the laser by using a fast phase modulator that effectively allowed to better visualise choroidal structure and delineate retinal layers. It also enabled corneal imaging with FD-FF-OCT due to the lifted safety concern. We thus were able to show that 3D volumes of retina and cornea could be acquired in a fraction of a second with significantly improved image contrast.

Label-free Optical Sensing of Cell State During Biomanufacturing

Alex J. Walsh, Katherine P. Mueller, Kayvan Samimi, Kelsey Tweed, Dan Pham, Emmanuel Contreras, Krishanu Saha, and **Melissa C. Skala**

Morgridge Institute for Research, University of Wisconsin – Madison, USA

Cell-based therapies have the potential to treat, or even cure, a myriad of diseases. However, these complex biological products display intrinsic variability within a tightly regulated industry. Process optimization and thorough product characterization prior to clinical development is critical. Typical quality assessments require labels to characterize functional subsets of cells, however standard analytics are laborious, time-consuming, susceptible to reagent quality variability, and may potentially alter cell function. To improve the fidelity of quality assessments, we have developed a label-free, nondestructive optical detection approach to quantify overall cell state, viability, and activation with single-cell resolution. The technology is based on the autofluorescence lifetime of the metabolic co-enzyme NAD(P)H. T cells isolated from human peripheral blood and activated in culture using tetrameric antibodies against the surface ligands CD2, CD3 and CD28 showed specific activation-state-dependent patterns of autofluorescence NAD(P)H lifetime. Logistic regression models and random forest models classified T cells according to activation state with 97–99% accuracy, and according to activation state (quiescent or activated) and subtype (CD3+CD8+ or CD3+CD4+) with 97% accuracy. The hardware, optics, and analytical algorithms are readily integrated into a variety of quantitative imaging technologies, such as flow and image cytometry, enabling non-destructive assessment for early stage cell manufacturing process optimization and streamlining product development as therapies transition to commercial scale manufacture.

Romancing the Startup: Starting the Entrepreneurial Journey on the Right Foot

Eric Buckland
Translational Imaging Innovations, USA

Startups are romantic, even mythical. There is perhaps nothing more exciting in a career than capturing a Unicorn with the better-mousetrap we invented during our Ph. D. programs. The problem is that Unicorns are rare, and better mousetraps seem to be everywhere. To succeed with sanity intact, we need to come down to earth and get real. Taking the right steps from the beginning maximizes our chance at building not just a better mousetrap, but a business worthy of growing into that elusive Unicorn. We will discuss the earliest stages of business formation, starting with our co-founders, and proceeding through our first phases of funding, development, and market validation. We will discuss essential topics such as founder agreements, intellectual property rights, and negotiating licenses from our institutions, establishing product-market fit, and early-stage financing. Our objective is to remove the mythology from the startup experience. We can retain the romance.

Developing and validating quantification for OCT Angiography

Mary Durbin
Zeiss Meditec, USA

Quantitative measurements of vessel density based on OCT Angiography have shown promise as markers of disease and may be affected even before clinically apparent retinopathy is present. At ZEISS, we developed, validated, and commercialized such metrics. This talk will discuss some of the work that went into the development and validation processes, with a focus on validation required to make clinical use of such metrics and validation required for regulatory aspects of commercialization. Quantitative metrics were developed for CIRRUS 5000 with AngioPlex (ZEISS, Dublin, CA) for three scan patterns: 3x3 mm and 6x6 mm scans centered on the fovea, and 4.5x4.5mm scans centered on the optic disc. For the macular scans, the superficial retinal layer angiography en face images were used, and for the optic disc scan the radial peripapillary layer was used. Images were processed with vesselness algorithms followed by thresholding to generate a binarized map to calculate perfusion density. The binarized map was skeletonized to generate vessel density. For the disc scans, the unthresholded data was also used to generate a flux metric. We used physical and digital phantoms to study the impact of various aspects of imaging on the accuracy of the measurements. We also compared the results of vessel segmentation algorithms to the results of manual graders. These methods helped establish the level of accuracy possible with these quantitative measurements. We also studied the repeatability and reproducibility of the measurements, which is critical for evaluating whether changes observed in the clinic correspond to pathological change or statistical variation. Finally, we and others have studied the correlation of these measurements to other clinical metrics related to disease, and found that these measurements are highly relevant to managing and monitoring disease.

Beauty and power of two-photon excitation

Grazyna Palczewska
Polgenix, USA

Two-photon excitation (TPE) imaging utilizing near infra-red (IR) light is ideally suited for visualizing the transformation and distribution of metabolic components deep in the eye. TPE imaging of the mouse eye enabled the discovery of lipid droplets. Advances in TPE imaging enabled simultaneous characterization of the products of vitamin A transformations in mouse models of retinal degeneration, and the evaluation of drug candidates designed to mitigate photoreceptor degeneration. The collection of fluorescence data over a large area involves long acquisition time and/or high laser light exposure to enable characterization of fluorescent granules within retinal cells, imposing risk of tissue damage. Improvements in TPE efficiency enable reducing average power needed for imaging and can be achieved by modulating temporal properties of the excitation light. In these conditions, imaging and fluorescence lifetime data can be obtained without alterations to eye tissue.

High-frame rate multi-meridian corneal imaging of air-puff induced deformation for improved detection of keratoconus

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Abstract: Corneal biomechanics plays a fundamental role in the genesis and progression of corneal pathologies, such as keratoconus. It also contributes to corneal remodeling after corneal surgery, and it affects the measurement accuracy of glaucoma biomarkers, such as the intraocular pressure (IOP). Air-puff induced corneal deformation imaging reveals information that potentially differentiates normal and pathological corneal response to a non-contact mechanical excitation. However, current commercial systems are limited to monitoring corneal deformation only on one corneal meridian, reducing their sensitivity to keratoconus, as the weakened region is often eccentric. Here, we present a novel air-puff induced corneal deformation imaging system, based on a high-frame rate swept source optical coherence tomographer. The system is capable of detecting deformation on planes distributed over the corneal surface. We designed two scan patterns covering a transverse field-of-view of up to 15 mm, at a pattern repetition rate of 1 kHz, afforded by a galvanometer scanning mirror system with extremely low coil impedance. We provide nearly unobstructed views of the corneal surface through a modified collinear piston-based air-puff unit. We set the air-puff duration and maximum pressure, by controlling the piston's speed through custom electronics. We validate the need for such an instrument via numerical simulation of both healthy and keratoconic corneal deformations with FEA models. We introduce and obtain metrics of deformation and asymmetry in *ex vivo* keratoconus-mimicking *ex vivo* porcine eye, where the treated inferior area was made deliberately softer than the untreated superior cornea. Firstly, we confirmed the strong influence of IOP on corneal deformation parameters. Secondly, we detected deformation asymmetries in air-puff deflected areas up to 0.50 mm^2 for the vertical meridian, otherwise missed on a single meridian. Moreover, we present first results of the system in a pilot clinical study on both healthy human eyes and a keratoconic eye *in vivo.* We believe that our novel multi-meridian corneal deformation imaging system will substantially aid in corneal biomechanics diagnostics and pathology screening.

High finesse tunable Fabry-Perot filters in Fourier-domain mode-locked lasers

Thomas Klein
Optores, Germany

We demonstrate that the coherence roll-off and dynamic range of OCT systems using Fourier-domain mode-locked (FDML) lasers can be significantly improved by a high-finesse fiber Fabry-Perot tunable filter (FFP-TF). The newly developed high-finesse FFP-TFs have a finesse of more than 3000, a more than fivefold improvement over previous designs. We show that this results in reduced instantaneous laser linewidth and reduced noise for a 1310 nm FDML laser with 1.6 MHz sweep rate. Since in practice, OCT image range is limited by data acquisition bandwidth, we demonstrate OCT imaging over many centimeters by reducing the sweep range of the laser. In contrast to previous work, standard resampling using a pre-acquired signal (as in SD-OCT) with no k-clocking is sufficient for both small and large sweep range, significantly reducing the system complexity. 3D-OCT imaging at 20 cm imaging range is demonstrated.

MEMS Scanning Micromirror Based Multimodal Optical Endoscopic Imaging

Huikai Xie
Beijing Institute of Technology, China

Over 7 million people die of cancer worldwide each year. The high mortality is mainly due to the lack of early cancer detection modalities especially for internal organs. CT, MRI and ultrasound imaging have issues of low resolution, low contrast, radioactive hazard, or high cost. Several optical imaging techniques provide high-resolution, cross-sectional information suitable for *in vivo* noninvasive early cancer diagnosis. However, a single optical imaging modality often struggles to achieve the desired imaging resolution, depth and contrast simultaneously. Integrating multiple optical imaging modalities seems a natural choice, but such multimodal imaging probes may become too large for endoscopy in applying to internal organs where most cancers are originated. Fortunately, microelectromechanical systems (MEMS) technology can be used for miniaturizing optical scanners, thus providing a tremendous opportunity for realizing multimodal endoscopic imaging inside human body. In this talk, a unique type of electrothermally-actuated MEMS scanning mirrors that can generate large-range, two-axis angular scanning at low driving voltage will be introduced. These electrothermal MEMS mirrors also have high fill factors and they have become the enabling devices for various endoscopic optical "biopsy" modalities, resulting in a paradigm shift of optical imaging of internal organs. In particular, MEMS based 3D endoscopic optical coherence tomography imaging, confocal imaging, photoacoustic microscopy, and multi-modality endomicroscopic imaging will be discussed in the talk and *in vivo* imaging experimental results will be presented

From pioneer publications to commercial expansion

Yves Emery, Etienne Cuche, Tristan Colomb, Benjamin Rappaz,
Lyncée Tec SA, Lausanne, Switzerland.

In 1999, in two seminal publications, E.Cuche et.al. have been the first to present simultaneous phase and intensity maps reconstruction from a single hologram captured in off-axis configuration. Both lensless and microscopic optical set ups, in reflection and transmission configuration, are demonstrated. Off-axis Digital Holography Microscopy (DHM®) growth was ignited. Nowadays, multiple research groups and a few companies are active in this field. It is the subject of several conferences and of numerous publications.

Lyncée Tec SA has been founded by these pioneer researchers in 2003 and has continuously developed off-axis DHM®, in close collaboration with many academic partners and end-users. Applications have been demonstrated in many different fields. In material sciences, 4D in-situ metrological measurements are performed with interferometric resolution at ultra-high speed. In life sciences, the interpretation of Quantitative Phase Imaging (QPI) in term of underlying biological processes is now accepted by the biological community. The cornerstone commercial applications of this technology will be presented during this talk.

Single exposure holographic tomography

Arkadiusz Kus
Faculty of Mechatronics, Warsaw University of technology, Poland

Holographic tomography (HT) is currently becoming an established, label-free, quantitative measurement technique, which uses the refractive index (RI) as the contrasting agent for cell and tissue analysis. However, the three-dimensional RI imaging is performed at the cost of measurement time by sequentially acquiring the projections of the measured object. Here, a simple, single-exposure HT system, which allows to record a full set of projections in a single hologram at high speed is demonstrated. The projections are generated by a microlens array and the system works with a robust tomographic reconstruction algorithm to provide satisfactory quality of the 3D RI distribution. The result is demonstrated with reconstructions of calibration objects and biological samples.

Research at the edge of translation

Rainer Leitgeb
Medical University of Vienna, Austria

OCT has been a highly successful medical imaging modality that was quickly translated to the medical market. Research in this field is therefore often of immediate clinical and resulting commercial interest; especially, if this research happens in a multidisciplinary environment, with clinical experts evaluating and motivating those developments. A big hurdle in this process is the regulatory burden in Europe with the more rigorous national authorities and the new Medical Device Regulation. Translation of potentially useful technology however needs in addition either to liaise with a strong market player in the field, or motivated individuals ready to start their own companies. This presentation gives insight into our daily experience at the Medical University of Vienna in this tension field between physics or engineering, clinical and commercial interests.

Successful commercialization of a novel optical technology by a small start-up.

Fergal Shevlin
Dyoptyka, Ireland

An overview of the choices available on the journey from idea to industrialization; some of the unexpected challenges and rewards; and the rationale behind some specific decisions made and actions taken by our company.

Sensorless adaptive optics and angiography in spatiotemporal optical coherence (STOC) retinal imaging

Dawid Borycki
Institute of Physical Chemistry, Polish Academy of Sciences, Warsaw, Poland

We apply spatiotemporal optical coherence (STOC) manipulation with digital aberration correction to achieve aberration-free, crosstalk-free, high-speed, high-resolution Fourier-domain full-field optical coherence tomography (FD-FF-OCT). We demonstrate that our datasets can also be used for angiography and Laser Doppler holography. We show the results of in vivo human retinal imaging.

Industrial Advances Enabling OCT Adoption in Primary Care: From Commercial Optimization to Artificial Intelligence

Nishant Mohan
Photonicare Raleigh-Durham, Il, USA

Optical coherence tomography (OCT) is the most successful medical optical imaging technology of the modern times. The technique has intrigued researchers from a variety of domains since its invention in the 1990s, and was a commercial success in ophthalmology as early as the first decade of the 21st century.

The adoption of OCT in ophthalmology specialty is a great example of successful industrialization of an optical imaging technique. Similar commercial success has so far eluded this technology in other domains despite considerable scientific advances.

Primary and frontline care markets offer a massive opportunity for most imaging and diagnostic technologies. However, they come with their own set of commercial and technical challenges. PhotoniCare Inc has launched an OCT-based device, *TOMi* Scope, for assisting ear infection diagnosis, one of the leading causes of primary care visits.

Adaption of such a technique in the primary care setting requires both the enhancement in the ease of use as well as ease of interpretation of the data. The latest technological advances in machine learning and artificial intelligence are ideally suited at converting images into information, and are set to play a crucial role in assisting both with usability and interpretation.

In this presentation, we will discuss commercial factors behind successfully bringing OCT-based technique to the primary care market, using the example of TOMi Scope. In addition, we will consider practical issues in implementation of modern machine learning and artificial intelligence techniques in healthcare.

This project has received funding from
the European Union's Horizon 2020 research
and innovation programme under
grant agreement No 666295.