Journal of Biomedical Optics

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Kirill V. Larin, Giuliano Scarcelli, Vladislav V. Yakovlev, “Optical elastography and tissue biomechanics,” *J. Biomed. Opt.* **24**(11), 110901 (2019), doi: 10.1117/1.JBO.24.11.110901.

Journal of Biomedical Optics 24(11), 110901 (November 2019)

REVIEW

Optical elastography and tissue biomechanics

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Abstract. Mechanical forces play an important role in the behavior and development of biological systems and disease at all spatial scales, from cells and their constituents to tissues and organs. Such forces have a profound influence on the health, structural integrity, and normal function of cells and organs. Accurate knowledge of cell and tissue biomechanical properties is essential to map the distribution of forces and mechanical cues in biological systems. Cell and tissue biomechanical properties are also known to be important on their own as indicators of health or disease states. Hence, optical elastography and biomechanics methods can aid in the understanding and clinical diagnosis of a wide variety of diseases. We provide a brief overview and highlight of the Optical Elastography and Tissue Biomechanics VI conference, which took place in San Francisco, February 2 and 3, 2019, as a part of Photonics West symposium. [DOI: 10.1117/1.JBO.24.11.110901]

Keywords: elastography; biomechanics; optical coherence elastography; cell biomechanics; ocular biomechanics; brillouin elastography.

Paper 190302VR received Sep. 8, 2019; accepted for publication Oct. 31, 2019; published online Nov. 22, 2019.

1 Introduction

This is the first attempt to provide a brief overview and highlight of the Optical Elastography and Tissue Biomechanics VI conference, which took place in San Francisco, February 2 and 3, 2019, as a part of Photonics West symposium.[1] This conference is devoted to developments and applications of biomedical optics, biophotonics, ultrasound (US), MRI, and optical microscopy in the assessment of the biomechanics of cells and tissues. Optical elastography is an emerging and fast-growing area of biomedical optics focused of characterization of cells and tissues based on their elastic and viscoelastic mechanical properties. In deploying the high-resolution and multimodal capabilities of optical imaging, optical elastography builds on and complements related methods for biomechanics, such as atomic force microscopy, traction force microscopy, and microrheology, and the fields of US and magnetic resonance elastography.

This conference provides a slice of the most recent advancements in biomedical optics, biophotonics, US elastography, MRI elastography, and biomechanical methods and technologies applied or related to estimation, monitoring, and functional assessment of the mechanical properties of normal and pathological biomaterials at all spatial scales, from cells and their constituents to tissues and organs.

This is the sixth edition of the conference, which was first organized in 2014 by Professor David Sampson (now at University of Surrey, United Kingdom) and Professor Kirill Larin (University of Houston) with 35 papers and has been steadily expanding over past few years (Fig. 1); this year it featured over 60 contributed presentations and posters including keynote and invited talks. Major topics of the conference include novel methods (NM) in elastography, optical coherence elastography (OCE)-based methods and techniques, Brillouin elastography (BE), as well as methods and techniques in cellular biomechanics (CB). Figure 2 summarizes the relative ratio of contributed papers in the various themes of the conference during the last three years of the conference. Interestingly, when most of the topics maintain an apparent equilibrium, the novel methods topic seems to increase over the years, which highlights how optical elastography is still an evolving field.

Below, readers can find an overview of these topics as well as highlights from keynote and poster sessions.

2 Novel Methods in Elastography

A special part of the conference was devoted to novel methods and was divided into two sessions that included three invited presentations (Dr. Rolland, Dr. Catheline, and Dr. So) and eight contributed talks.

Dr. Jannick P. Rolland from the University of Rochester, USA, gave a broad perspective on the field of the emerging field of optical elastography and its biomedical applications, especially in ophthalmology and dermatology.[2] She provided a sort of taxonomy for optical elastography, including classifications of tissue models (semi-infinite, single thin layer, and composite stacks), clinical tasks (classification or estimation), and excitation modes (transient, continuous, quasistatic, or molecular shift). She also discussed recent technological advances, specifically describing OCE using reverberant shear wave fields and discussed how current and future techniques may address clinical needs.

Dr. Stefan Catheline from the University of Lyon, France, presented the latest work of his group on elastography, specifically the application of time reversal or noise correlation techniques.[3] Borrowing concepts from the conceptually related field of seismology, his group takes advantage of shear waves naturally present in the human body due to muscles activities to construct shear elasticity map of soft tissues. Since no external sources of shear waves are used, the technique is named passive elastography. He provided examples where different readout modalities (US, MRI, or optic) are used to detect shear waves

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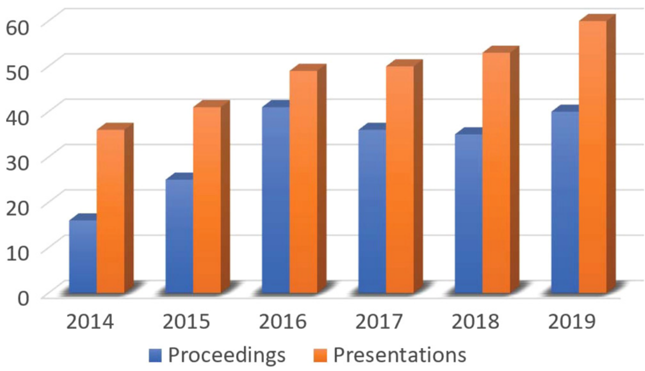

Fig. 1 Number of presentations given at the conference and the proceedings published at the end of the conference for every year since its first inauguration in 2014.

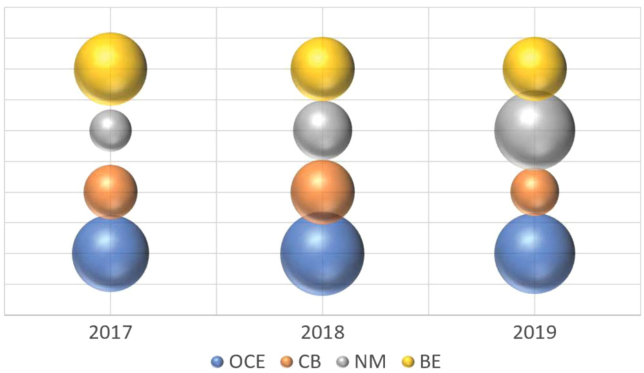

Fig. 2 Number of presentations given at different sessions OCE, CB, NM, and BE, during the last three years of the conference.

and reconstruct a speed tomography in a human liver, thyroid, brain, in a mouse eye, and a single cell.

Dr. Peter T. C. So, from Massachusetts Institute of Technology (MIT), USA, presented his recent result on applications of interferometric imaging for quantitative assessment of biomechanical properties of cells and tissues.[4] Interferometric measurements offer high-precision measurements[5] that can be combined with the wide-field illumination measurements[6] for precise, noninvasive measurements of cellular structures and their dynamics. In particular, biomechanical markers of sickle red blood cells can be analyzed on a fly in a cytometric setting.[7] Potential applications also include cancer cell nuclear mechanics as a possible marker for metastasis.

The University of Edinburgh group (United Kingdom) presented on using digital holographic microscopy as an optical readout modality combined with the well-controlled application of hydrostatic pressure to study cellular mechanical properties in real time and in a noncontact manner.[8] This enabled measuring cellular mechanical properties in a label-free and contactless mode, over time, and within extracellular matrix. In this study, the mechanical properties of pancreatic ductal adenocarcinoma were measured as a function of knocking out focal adhesion kinase, an established mechano-regulator.

Sean Kirkpatrick from Michigan Technological University, USA, presented on the noninvasive determination of retinal temperature through stimulated laser speckle imaging.[9] Monitoring of the human retina temperature is useful for several applications (metabolism, damage, and laser surgery feedback), but the location of the retina makes it difficult to perform traditional contact temperature measurements and standard thermal imaging. He used laser speckle imaging in combination with a stimulating laser scanning system altering the speckle pattern to monitor thermal deformations in the retina and infer retina ground temperature. Temperature measurements of optical phantoms and biological media were shown as well as validating data through thermocouple measurements of sample temperature.

The Oldenburg group from the University of North Carolina at Chapel Hill (USA) reported on depth-resolved rheometry using cross-correlation tracking with optical coherence tomography (OCT). Currently, it is difficult to perform rheology on small volumes of heterogeneous and shear-dependent biofluids. To address this challenge, the Oldenburg group is developing a microparallel plate rheometer (MPPR) amenable to OCT to track depth-resolved lateral displacement in fluids in real time while under dynamic shear. To test the functionality of the MPPR, the group used Newtonian fluid samples. Presented results showed direct proportionality between lateral velocity of particles and depth in a Newtonian fluid, confirming ideal performance by the MPPR, and extracted shear rate in good agreement with shear rate applied by the MPPR. Extension to non-Newtonian fluids will enable studying biofluids, such as mucus, to assess shear-dependent properties in a geometry relevant to the mucus layer in lung epithelium.

Dr. Zaitsev from the Institute of Applied Physics of the Russian Federation[10] presented on phase-sensitive OCT used for monitoring of slow-rate strains in laser tissue reshaping. This is particularly relevant for laser-assisted modifications of collagenous tissues (e.g., for fabrication of cartilaginous implants). The imaging modality is based on estimating interframe phase-variation gradient using a developed "vector" method. This technique allows for mapping both fast and large, as well as small strains, slowly varying on intervals ~tens of minutes. The stability of strain estimation with the designed OCT setup was experimentally estimated using stable phantoms; examples of spatially resolved maps of slowly varying strains were demonstrated. The developed methods can be used in emerging techniques of compression elastography for tumor characterization.

Antonio Fiore from Dr. Scarcelli's group at the University of Maryland, USA, pointed out that the Brillouin shift, which is measured in Brillouin spectroscopy experiments, is related to high-frequency elastic modulus via the refractive index.[11] Thus Dr. Scarcelli's group advocated for high-precision refractive index measurements and discussed a newly developed confocal microscopy technique that can map the refractive index of samples in an absolute manner, with three-dimensional (3-D) resolution.[12] The unique experimental arrangement permits the same optical axis to be probed with two scattering geometries for Brillouin and elastic scattering, within a confocal voxel. In the proof-of-principle experiments, Dr. Scarcelli's group has achieved a refractive index accuracy of 0.001 and micron scale spatial resolution. The authors stated that their approach can provide an alternative to quantitative phase imaging microscopy in 3-D asymmetric samples and decouple mechanical and optical properties in Brillouin microscopy, which should improve the specificity of such measurements.

Dr. Brian Pogue and his group at Dartmouth College, New Hampshire, USA, in collaboration with their colleagues at Wellman Center for Photomedicine and University of Rochester, are developing a more traditional approach for assessing local tissue stiffness through a 300-μm-diameter fiber-optic pressure sensor, whose position was computer-controlled through a 3-D translational stage.[13] The developed system was first calibrated with the assistance of an US elastography system for a series of gelatin phantoms and then employed to map out pressure values per each location over 10- to 15-mm diameter *ex vivo* pancreatic tumors. The dense stroma of pancreatic tumors is considered a barrier to drug delivery due to collapsed vasculature and reduced perfusion, thus making such information critically important for a successful clinical outcome. The acquired tumor stiffness data were found to be strongly correlated with collagen content at regional levels for two different pancreatic tumor cell lines, which highlight distinctive collagen patterns.[14]

Light scattering can be used in a different manner to get local viscoelastic properties of tissues. Dr. Seemantini Nadkarni's group at Harvard Medical School, Massachusetts, USA, is using laser speckle imaging,[15] which they developed for noninvasive evaluation of tissue stiffness. In their presentation, they demonstrated the accuracy, sensitivity, and dynamic range of laser speckle microrheology in phantoms[16] and investigated its utility for micromechanical evaluation of human breast tissue specimens. They also developed an improved algorithm for enhancing the resolution of laser speckle microrheology, which they applied for the stiffness assessment of the extracellular matrix as a key regulator of cancer cell proliferation and migration and demonstrated the capability of their technique to address important questions related to mechanobiology.[17,18]

Dr. Ruikang Wang and Dr. Matthew O'Donnell, from the University of Washington (Seattle), USA, suggested to replace optical trapping with acoustic microtapping (AuT).[19] By employing focused, air-coupled US to induce mechanical displacement at the boundary of a soft material and combining it with high-speed phase-sensitive OCT, it is possible to achieve high-resolution quantitative elastography of soft tissues.[20] In their recent report, they focused on more accurate description of the above so that a straightforward method for elastic modulus reconstruction can be developed independent of tissue thickness and boundary properties.

3 Optical Coherence Elastography

The part of the conference devoted to OCE was divided into two sessions and featured two invited talks (Dr. Assad Oberai and Dr. Karol Karnowski) and nine contributed talks.

In the opening talk to this session, Dr. Assad A. Oberai from the University of Southern California, USA, described a new class of iterative algorithms that use strains from 3-D compression elastography as data input to generate volumetric maps of linear elastic properties of biological specimens.[21] The main idea behind these algorithms is to pose this inverse problem as a constrained minimization problem and use adjoint equations, spatially adaptive resolution and domain decomposition techniques to solve this problem. The authors demonstrated the ability to infer linear and nonlinear elastic properties on tissue phantom, and *ex vivo* and *in vivo* tissue samples.

In the other invited presentation, Dr. Karol Karnowski from the Institute of Physical Chemistry of the Polish Academy of Sciences and the University of Western Australia outlined the challenges and strategies for imaging the anterior segment of the human eye. Pathological changes of the anterior segment may severely impair vision. Quantifiable methods to assess those changes are greatly important. He showed that methods based on OCT imaging can be valuable for revealing the structure and the intraocular pressure, which is closely related to corneal biomechanics.[22,23]

Myocardial infarction (MI) is a leading cause of death and decrease of quality of life in the United States. An immense amount of research and development has been focused on the molecular mechanisms associated with MI, which have led to numerous therapies for treating and repairing cardiac tissue after MI. The presentation by Dr. Singh from Dr. Larin's group at the University of Houston, Texas, USA, outlined recent progress made in noncontact dynamic measurements of the changes in cardiac biomechanical properties 6 weeks after MI in a mouse model using elastic-wave optical OCE.[24] The results show that the left ventricle cardiac tissue became more isotropic and softer after six weeks in the MI-affected mice as compared to the sham mice. These preliminary results show that OCE can be a powerful tool for understanding the dynamics in biomechanical changes in cardiac tissue and could potentially reveal diseased areas for targeted genetic therapies.[24,25]

Dr. Liu from the same group at the University of Houston introduced the first clinical application of OCE technology to quantitatively and objectively assess systemic sclerosis (SSc) disease in the dorsal forearm of 12 patients and control group. SSc is an autoimmune disorder with high mortality due to excessive accumulation of collagen in the skin and internal organs. An accurate and early diagnosis is crucial to ensure effective treatment. The results from this study demonstrate the effectiveness of using OCT/OCE for monitoring the disease severity of SSc, outperformed the assessment by an experienced physician. This work is the first successful translational adaptation of OCE technology as the clinical diagnostics tool.[26,27]

In another study, Mr. Rowan Sanderson from the University of Western Australia introduced a finger-mounted OCE probe for quantitative microelastography (QME). This finger-mounted probe is designed to preserve the dexterity of manual palpation while providing quantitative, high-resolution images. High accuracy of the finger-mounted probe in measuring the elasticity of tissue mimicking phantoms and kangaroo muscle tissue has been demonstrated.[28]

Brecken J. Blackburn from the group of Dr. Andrew M. Rollins at the Case Western Reserve University, Ohio, USA, demonstrated the use of OCT to generate micrometer-scale strain maps of articular cartilage (AC) under compressive and shear deformations. Three-dimensional OCT images and elastograms of AC were obtained as the sample was loaded at constant rate of displacement. The authors conclude that the described compression OCE technology could be applied for high-throughput screening to nondestructively determine the functionality and failure modes of engineered AC as compared to native tissue.[29]

Dr. Duo Zhang from the University of Dundee, United Kingdom, presented results from an analytical study on the effect of excitation frequency on tissue mechanical properties characterization using vibrational OCE. Real OCE experimental data were used as input in transient model of ANSYS to simulate vibrational pattern of the sample stimulated by frequency ranged from 100 to 1000 Hz. The results suggest that the frequencies below 800 Hz excitation will be the best for the vibration OCE applications.[30]

Toward the goal of translating compression OCE technology into clinics, Dr. James Anstie from Harry Perkins Institute of Medical Research (Australia) introduced possibility of QME using a hand-held probe. The authors presented results from QME of structured phantoms and freshly excised human breast tissue, validated by histology. This hand-held technology has a great promise toward improved intraoperative margin assessment in real time.[31]

Dr. Matt Hepburn, from the same group at Harry Perkins Institute of Medical Research, presented a rigorous framework for analyzing axial and lateral resolutions in compression OCE. This was achieved by combination of finite-element analysis of mechanical deformation with a model of the OCT system and signal processing, based on linear systems theory. The results demonstrate that axial and lateral resolutions in OCE are directly related to inclusion size and mechanical contrast rather than resolution of underline OCT system.[32]

Current methods for clinical evaluation of colorectal diseases usually lack the sensitivity or resolution to detect diseased tissue at early stages. Achuth Nair, a graduate student in Dr. Larin's lab (University of Houston), evaluated the capability of both OCT structural imaging and OCE biomechanical assessment of healthy, cancerous, and colitis tissues from mouse models.[33] The results show that OCT structural imaging combined with OCE can detect minute changes in colon tissue optical scattering and elastic properties, which may be useful for detection various colon diseases, such as colitis and colon cancer.[34]

Finally, a group of researchers from Zhongping Chen's lab at Beckman Laser Institute and Medical Clinic, Irvine, California, USA, developed a piezoelectric transducer-OCE system that enables real-time measurement of viscosity in a drop of blood during coagulation process. The described technology can greatly assist point-of-care testing for diagnosis of coagulation disorders and monitoring of therapies.[35]

4 Cell Biomechanics

In the invited talk for this session, Dr. Kandice Tanner from the U.S. National Institutes of Health discussed the applications of local viscoelastic properties of tumors and extracellular matrix surrounding those tumors.[36–38] Her group is searching for the understanding of mechanisms of metastasis, which were linked to local mechanical properties of cells and tissues. To quantify those small mechanical forces, they use optical tweezers and fluctuation correlation analysis. To achieve *in vivo* characterization, Dr. Tanner's group designed and built a special microscope that employed active microrheology optical trapping, which uses small-size beads trapped by a focused laser beam as local probes of viscoelastic properties. When used *in vivo*, this system allows to quantitate mechanical heterogeneities with micrometer spatial resolution. Dr. Tanner's group employed well-defined extracellular matrix ligands to mimic physiological tissue and combined microrheology setup with other powerful approaches, such as multiphoton fluorescent microscopy and mathematical modeling of complex cell dynamics in thick 3-D tissue structures, to reveal the mismatch between tumor cell cytoskeletal and extracellular matrix biomechanics. Their findings not only help to discover the new insights on cancer specific cell heterogeneity but also provide a possible guidance for future therapeutic treatments.

Similar ideas related to understanding and quantitatively assessing biomechanics of tumor cells were presented by Dr. Steven Adie's group from Cornell University, New York, USA. When using a closely related approach of using small particles to measure local forces exerted on those particles, they used optical coherence microscopy to track the time-varying positions of those scattering particles and, from this information, using computational image analysis techniques, derived the 3-D distribution of mechanical forces at microscopic scale level.[39] With the accuracy of defining particle location of the order of 10's of nanometers, forces as small as micro-Newton can be experimentally measured.

Dr. Giuseppe Antonacci from Istituto Italiano di Tecnologia (Italy) used yet another optical approach to assess local mechanical properties of cells and subcellular structure.[40] His group has recently developed what they called "background deflection" Brillouin spectrometer, which uses a specially designed rhomboidal-shape mask within a spectrometer to improve by >40 dB the rejection ratio of elastic scattering versus Brillouin signal, which serves as an indicator of local elasticity. In doing this way, the high-fidelity Brillouin spectra with a contrast of 70 dB were collected with a diffraction limited spatial resolution allowing for high-sensitivity imaging of HeLa cells and evaluating the effect of FUS proteins on the elasticity (Brillouin shift) and viscosity (Brillouin linewidth) of those cells, as cells were responding to such external stress.

Dr. Malte Gather's group at the University of St. Andrews (United Kingdom) explored the effect of mechanical forces on invadopodia, actin-rich protrusions of the plasma membrane associated with degradation of the extracellular matrix in metastasis. This was accomplished with yet another new development in optical instrumentation aimed at measuring mechanical forces, elastic resonator interference stress microscopy (ERISM).[41] ERISM technique offers highly versatile approach to measure forces exerted by single cells by interferometrically detecting deformations of an elastic microcavity, with which the cells are in contact. This approach enables fast displacement mapping with nanometer accuracy, which transfers in to sub-Pa stress resolution. The developed microcavities, which were utilized for ERISM, have shown excellent long-term stability and the optical readout avoids any phototoxic effects. This allowed not only to measure the local forces but also to observe the real-time dynamics of protrusions. It was found that miR-375 overexpression, which interferes with invadopodia, reduces the applied force and degrading ability of invadopodia and may become a therapeutic route against cancer invasion and metastasis.

5 Keynote and Computation and Modeling Sessions

The keynote session, supported by Thorlabs Inc., is the flagship event of the conference. The keynote presentation is given by the most prominent researchers of elastography and biomechanics field, broadly interpreted. The previous keynote speakers include Ronald Ehman, a founder of the field of MR elastography, Dennis Discher in cell mechanics, James Greenleaf, a leading figure in US elastography, and Roger Kamm in tumor biomechanics. This year, Professor Ross Ethier from Georgia Institute of Technology (USA) was delivering the keynote lecture on using different optical tools to understand biomechanics of glaucoma disease. Professor Ethier holds the Lawrence L. Gellerstedt, Jr. Chair in Bioengineering and is a Georgia Research Alliance Eminent Scholar in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Institute of Technology and Emory University School of Medicine. Prior to joining Georgia Institute of Technology, he was the head of the Department of Bioengineering at Imperial College, London, for five years, and director of the Institute of Biomaterials and Biomedical Engineering at the University of Toronto for two years before that. He received his PhD from MIT in 1986, his S.M. degree from MIT in 1983, his M. Math. Degree from the University of Waterloo in 1982, and his

B.Sc. degree from Queens University in 1980. His research is in the biomechanics of cells and whole organs, with specific emphasis on ocular biomechanics. He works on developing treatments for glaucoma, the second most common cause of blindness, and for SANS, a syndrome affecting astronauts, which is a major NASA human health concern. Among other activities, he has developed a new paradigm of how pressure within the eye is regulated and how the sclera plays a major and unexpected role in influencing vision loss in glaucoma.

Following the keynote seminar, three contributed talks continued highlighting the computational and modeling themes of elastography research.

The Nadkarni group from the Wellman Center for Photomedicine, Massachusetts, USA, presented modeling effort to derive a biomechanical stress equation for identification of the propensity of coronary plaque rupture.[42] Rupture of mechanically unstable plaque is the major cause of acute stroke and MI. Plaque rupture occurs when the peak stress in the plaque exceeds the material strength. Although finite-element modeling (FEM) can successfully be used to calculate the tensile stress, it is computationally intensive and impractical as a clinical tool. In this study, a faster method was presented that derives a multifactorial stress equation (MSE) to compute peak stress in necrotic core fibroatheromas. Over 60 samples were used to validate the novel protocol and showed excellent correlation and high concordance with the FEM-measured peak stress. This demonstrates that the MSE tool can be used interchangeably to replace FEM, without compromising the accuracy of peak stress calculations.

Dr. Salavat Aglyamov from the University of Houston presented an analytical model of laser-induced dynamic thermoelastic deformation of the viscoelastic half-space.[43] Laser-induced thermoelastic deformation can be an effective way to induce disturbances in soft biological tissues: a laser pulse results in rapid temperature increase, thermoelastic expansion, and generation of compressional and shear waves in the tissue. After the expansion and wave attenuation, a quasisteady state is reached. For several medical applications of elastography, laser-induced thermoelastic deformation has been proposed to produce strain in the tissue to assess tissue mechanical properties. In combination with measuring tissue response using OCT, such an approach could be an effective method for noncontact measurement of tissue mechanical properties. In this work, the dynamic tissue response immediately after the laser pulse was considered and an analytical expression was derived for the thermoelastic displacements and stresses. Such expression could be used to model mechanical and photoacoustic tissue response to laser excitation, as well as to investigate the mechanism of photomechanical laser ablation.

To close the session, the Higgins group at the University of Michigan, USA, reported elasticity measurement by strain-photoacoustic imaging. The measurement of elasticity involves the quantification of strain and stress in a tissue volume. The uncertainty of stress propagation, however, makes the elasticity measurement in deep tissue a challenge. Based on the observation that vasculature collapsing is a function of the stress exerted on a tissue volume, the Higgins group is investigating strain-photoacoustic correlation as an alternative to the strain–stress correlation for elasticity measurement. The group reported an analytical model mapping the change of hemoglobin content in tissue to the stress and a validation study using rabbit ears *in vivo* and a stress sensor and a PA–US imaging system. Both the strain–stress and strain–PA correlations agreed with the mechanical measurements performed *ex vivo* on harvested tissues.

6 Poster Session

Poster session is one of the most interactive and well-attended session of the conference. This session had several exciting presentations that expanded on the material presented at the regular sessions.

Several posters were devoted to further refinement of OCE and exploring its new applications. For example, Dr. Kevin Parker's group at the University of Rochester[44] presented their preliminary studies of reverberant shear wave fields to characterize brain tissue elasticity of mice in OCE. Those experiments were performed on mice brains *ex vivo* with a portion of the skull replaced by glass windows to allow for optical imaging and demonstrated promising potential of OCE for quantitative brain imaging. Dr. Matthew O'Donnell's group from the University of Washington (Seattle), USA, evaluated the lateral mechanical resolution of OCE in gelatin phantoms of varying stiffness to explore the apparent differences between OCT and OCE image resolution. By varying the bandwidth of mechanical pulse, it was found that frequency reduction of the mechanical wave results in degradation of the lateral resolution.

Dr. Gijs van Soest's group (Erasmus MC, The Netherlands) together with several collaborating institutions is exploring the applications of optical coherence for intravascular tissue elasticity assessment. They presented results on capturing the strain, which was induced by modifying the infusion rate using a programmable pump and was independently monitored by a pressure transducer, with a phase-resolved intravascular OCE system running at 3000 frames/s. They estimated the tissue elasticity in phantom and human coronary arteries *in vitro*. The results show that their system can capture a strain smaller than 0.022% induced by just a couple of mmHg pressure difference. The elastic modulus was measured to be 460 kPa in coronary artery, in good agreement with previous measurements.[45]

Dr. Yoshiaki Yasuno's group (University of Tsukuba, Japan) explored an application of OCE for imaging of the porcine carotid artery and esophagus tissues. The tissues were actively compressed by a glass coverslip attached piezoelectric transducer, and OCT system was used to image those tissues. The digital-shift and complex-correlation-based displacement analysis method was applied to average the displacements of four channels, and the depth-resolved in-plane lateral and axial displacements were obtained.[46] OCT also allowed to visualize the microstructural decorrelation map of the tissue.

Several presentations were devoted to the applications of OCE to eye imaging. Dr. Zhihong Huang's group from the University of Dundee (United Kingdom) presented their recent results on imaging and mechanical evaluation of human corneal ulcer's healing process.[47] They pointed out that corneal injury often leads to ulceration. In their preliminary study, they established a successful human corneal 3-D model and mimicked corneal injuries with adjustable lesion size and depth. A phase-sensitive OCT system with a spectral-domain configuration[48] probed the structure and mechanical strength of the wounded corneal tissues. Two presentations by Dr. Kirill Larin's group (University of Houston) were related to quantification of biomechanical properties of the eye.[49] Hongqui Zhang evaluated the effects of storage medium on the biomechanical properties of porcine lens for *in vitro* measurements.[50] He utilized a focused micro air-pulse and phase-sensitive OCE to quantify the changes in lenticular biomechanical properties when incubated at different temperatures for 12 h. His findings showed that stiffness increases when incubated at lower temperatures. In a separate report presented by Wu,[51] lens elastic properties were evaluated as a function of the intraocular pressure. Changes in lenticular biomechanical properties have been implicated in conditions and diseases such as presbyopia and cataract. However, the relationship between eye-globe intraocular pressure and lenticular biomechanical properties is relatively unknown. Chen Wu using the above-described setup was able to measure biomechanical properties at various intraocular pressures. The results indicated a nonmonotonic increase in the lens stiffness when the intraocular pressure was raised from 10 to 40 mmHg.

Dr. Stephen Boppart's group from the University of Illinois at Urbana-Champaign, USA, presented results on high-speed magnetomotive OCE based on iron oxide nanoparticles embedded into tissues. The advances in nanoparticles' delivery allowed to provide a uniform nanoparticles' distribution in the tissues. Significant advancements in image acquisition speed, where a B-M scan is performed after one chirp excitation, demonstrated that a magnetomotive OCE image can be acquired in 2 s, which is orders-of-magnitude faster than the previous approach.[52,53] Dr. Pierre Bagnaninchi's group from the University of Edinburgh (United Kingdom) presented their results on image analysis for OCE.[8] OCE can be performed through estimating local displacement maps from subsequent acquisitions of a sample under different loads.[54] This displacement estimation is limited by noise in the images, which can be high in dynamic systems due to the inability to perform long exposures or B-scan averaging. Dr. Bagnaninchi's group proposed a framework for enhancing both the image quality and displacement map by motion compensated denoising with the block-matching and 4-D filtering, followed by a re-estimation of displacement.[55] They adopted the interferometric synthetic aperture microscopy method to enhance the lateral resolution away from the focal plane and used subpixel cross-correlation block matching for nonuniform deformation estimation. Such approach leads to an enhancement of both image and displacement accuracy of up to 33% over a standard approach.

Dr. Xuan Liu's group from New Jersey Institute of Technology, USA, presented their analysis for a handheld fiber-optic OCE instrument.[56] However, the variable speed within a deformed sample under manual compression can substantially affect those measurements. Dr. Liu's group presented an adaptive Doppler analysis method to guide the choice of the time interval between signals involved in Doppler phase calculation to accurately track the nonconstant motion speed. In another presentation by the same group,[57] they proposed a novel method to quantify the Poisson's ratio by simultaneously tracking axial and lateral motion using speckle imaging and experimentally validated its capability on samples with different degrees of compressibility.

Dr. Jürgen Czarske's group at the Technical University of Dresden (Germany) evaluated stimulated Brillouin microscopy for microscopic viscoelastic imaging.[58,59] Although Brillouin microscopy offers noninvasive access to the elasticity of biological specimens, the often-used spontaneous Brillouin signal suffers of a low signal strength and is hidden in a high background of Rayleigh scattering. These hurdles are not present for stimulated Brillouin scattering. The presentation evaluated the technical challenges and information content of the impulsive Brillouin scattering and demonstrated performance of a prototype system using hydrogels. Another presentation on Brillouin microscopy dealt with the signal-to-noise enhancement. A joint effort of Imperial College of London (United Kingdom) and Nanyang Technological University (Singapore) is led by Dr. Peter Török who discussed two spectral reconstruction methods, maximum entropy and wavelet analysis, which were applied to Brillouin spectroscopy. Brillouin measurements are typically limited by low signal-to-noise ratio, and information is usually extracted by the Lorentzian fitting, without the consideration of noise. When applied to simulated and experimental Brillouin data, both numerical methods were successful in overcoming this limitation.

7 Biomechanics of the Eye

The cornea, the transparent tissue in front of the eye, is responsible for almost 80% of the light focusing into the retina. Thus any abnormalities in the shape of the cornea could lead to dramatic changes in the vision quality. This session was devoted to understanding the importance of corneal (and scleral) mechanical properties to maintain eye globe shape and their alternations during various degenerative diseases and surgical procedures.

In the invited talk of the session, Dr. Brad Randleman from the University of Southern California, USA, provided the clinical perspective of why quantifying the mechanical properties of the cornea is of utmost importance.[60] Corneal morphologic imaging (topography and tomography) is currently used to identify corneal ectatic disorders such as keratoconus and to appropriately screen patients to determine suitability for corneal refractive surgery. Despite many devices and strategies being used for this task, there remains a gap in identifying ectatic corneal disease at its earliest manifestation, and there remains significant controversy and discrepancy in the literature about the relative value of different evaluations in distinguishing keratoconus suspect eyes from normal populations. The need for accurate identification of subclinical ectasia has never been greater as the status quo results in some patients incorrectly receiving refractive surgery while others lose vision before cross-linking treatment is initiated. The clear next step in corneal imaging will address direct biomechanical measurements in an accurate, reproducible way.

Dr. Matthew R. Ford from Cole Eye Institute, Cleveland Clinic, USA, presented results from compression OCE assessment of corneal biomechanical properties in keratoconus patients before (<1 week) and after corneal cross-linking (CXL) treatment (3 to 6 months). Obtained results demonstrated the effectiveness of this method to quantify the distribution of compressive mechanical properties in all three patient types.[61] The described technique can greatly assist in assessing CLX procedures and contribute to development of more effective therapeutic procedures.

Noncontact estimation of corneal biomechanical properties is the key for fast clinical adaptation of new technologies. Like the previous talk but using noncontact AuT excitation, Mitchell A. Kirby from the University of Washington (Seattle), USA, presented results of using dynamic OCE to assess the effect of CLX *ex vivo*. The results suggest that changes in corneal structure and wave speed over time may infer rates of CLX to refine UV illumination protocols and improve clinical outcomes.[62]

A group of researchers from Nicolaus Copernicus University (Poland) presented a new comprehensive biomechanical model to predict biomechanical properties of all ocular tissues and to compare the simulations with air-puff swept-source OCT data.

This model was effectively predicting air-puff induced dynamics of the eye through its entire length and can be used in future modeling of the whole eye biomechanics.[63]

Abby Wilson from the University of Cambridge (United Kingdom) and John Marshall from the University College London (United Kingdom) presented results from using speckle interferometric techniques to measure the full-field displacement of the cornea in response to intraocular pressure changes equivalent to those that occur during the cardiac cycle. This method could potentially use cardiac cycle as a tissue loading mechanism to assess the effect of CLX on spatial distribution of corneal biomechanical properties.[64]

To close the session, Antoine Ramier, a PhD student from Dr. Seok-Hyun Yun's lab at Massachusetts General Hospital, USA, demonstrated unique advantages of a contact-based approach to stimulate elastic waves in the cornea. A piezoelectrically vibrating tip induced traveling wave velocities at frequency range of 1 to 15 kHz, improving the resolution of traveling wave elastography and enabling measurements of stiffer tissues such as the sclera.[65]

8 Brillouin Elastography

In the invited talk of the session, Dr. Darryl Overby from Imperial College London, United Kingdom, discussed Brillouin spectroscopy to stiffness after correcting for the influence of water content in hydrogels.[66] Although prior studies have shown that the longitudinal elastic modulus M measured by Brillouin spectroscopy correlates with the Young's modulus E of cells and tissues, both M and E for hydrated materials are both influenced by water content. Using hydrogels as a model for hydrated biological materials, Dr. Overby's group designed experiments to separate the effects of E and water content on M and showed that both M and E decreased over time due to swelling, but no single relationship could describe how M changed in terms of E. This work cautions against the straightforward application of Brillouin spectroscopy for optical elastography but suggests that Brillouin spectroscopy and microscopy may be useful also to investigate mechanisms involving changes in local water content.

Professor Yakovlev from Texas A&M University, USA,[67] reported on the latest advances in instrumentation, which result in much higher speed of Brillouin spectroscopy and imaging while providing better discrimination against the background scattering and better sensitivity of Brillouin microscopy measurements. Such improvements in instrumentation are critical for the translation of Brillouin microscopy into a number of applications, namely the assessment of tissue mechanics using Brillouin microscopy and the characterization modifications of tissues in response to a certain treatment procedure, which advocated for the use of Brillouin microscopy as an essential component of broader medical protocols.

Dr. Jitao Zhang from the University of Maryland, USA, presented a collaboration work between Scarcelli–Larin and Finnell groups for noncontact quantification of tissue biomechanics during embryo development with Brillouin microscopy and OCT.[68] Embryonic development involves the interplay of driving forces that shape the tissue and the mechanical resistance that the tissue offers in response. However, quantifying the stiffness of tissue *in situ* with 3-D high resolution and in a noncontact manner has so far been difficult to achieve. The groups at Maryland and Houston collaborated to combine two all-optical technique, OCT and Brillouin microscopy, to map the longitudinal modulus of the neural tube tissue of mouse embryo *in situ*.[69] Measurement of tissue stiffening during neural tube closure was reported as well as spatial gradients in modulus that have been suggested as critical mechanical cues for cell migration.

Dr. Elsayad, Vienna Biocenter Core Facilities, Austria, presented new setups of Brillouin microspectroscopy to measure mechanical anisotropy. Current Brillouin spectrometers measure the Brillouin signal from a single (scattering) geometry at a time, thereby only accessing a single component of the stiffness tensor. The mechanical properties of a sample are however rarely isotropic. Dr. Elsayad introduced an imaging spectrometer capable of single-shot measurement of the spectra from a range of different scattering geometries at a given point in the sample. Simulations as well as experimental results were presented for different model samples. Different approaches for surface enhanced Brillouin spectroscopy were also discussed highlighting to what extent it can be used to extract information not accessible in conventional Brillouin spectroscopy.

The Texas A&M University group reported on a new protocol, sequentially shifted excitation (SSE) Brillouin spectroscopy, to recover signal contaminated with strong scattering, absorption, or fluorescence. The method is particularly useful to correct spectral distortions caused by a molecular filter's absorption, fluorescent background, or ambient room light. Due to the weak intensity of the Brillouin signal, a distortion of the baseline or a partial absorption of Brillouin peak can have strong impact on data analysis. The idea behind the proposed method is the observation that the Brillouin and elastically scattered light strongly depend on the wavelength of the incident light while the fluorescence background or distortions due to molecular filter absorption remain the same for small changes in incident wavelength. The new proposed protocol acquires multiple Brillouin spectra using slightly offset excitation wavelengths and computationally separates the signal and distortion/background components, thus recovering the Brillouin signal. The application of SSE Brillouin spectroscopy in highly scattering sample was presented using sample of cream.

The group of the University of Maryland, USA, presented adaptive optics (AO) methods for Brillouin microspectroscopy. Brillouin spectroscopy performances are rapidly degraded by optical aberrations and have, therefore, been so far limited to homogenous transparent samples. Thus correcting sample aberrations to enable mechanical characterization within inhomogeneous medium remains the current barrier on the versatility of this emerging technique. The Maryland group developed an AO configuration designed for Brillouin scattering spectroscopy to dynamically correct aberrations induced by interrogated samples and optical elements.[70,71] Using wavefront-corrected Brillouin spectrometer in aberrated phantoms and biological samples, a 2.5-fold enhancement in Brillouin signal strength and 1.4-fold improvement in axial resolution was demonstrated.

To close the session, Tijana Lainović from the University of Novi Sad, Serbia, presented work in collaboration with the group of Dr. Dehoux at the University of Claude Bernard, Lyon, France, to map the mechanical properties and structure of dentin by a combination of Brillouin spectroscopy and nonlinear optical microscopy. Mechanical and optical properties are the main criteria for assessing the health of dental tissue in contemporary dentistry. Maps of the Brillouin frequency shift and linewidth can be interpreted as maps of sound velocity and viscosity and were co-localized with two-photon excitation fluorescence microscopy and second harmonic generation. Presented results showed significant changes between healthy tissues and pathological lesions. Such results can help to precisely delineate destructed dentin during clinical procedures, paving the way to minimally invasive strategies.

9 Summary and Outlook

Optical elastography is the use of optical imaging techniques to characterize tissues and cells based on their elastic and viscoelastic mechanical properties. The Optical Elastography and Tissue Biomechanics VI conference featured several presentations and posters regarding the biomechanics of cells and tissues as measured by exciting novel methods for biomedical optics, US, MRI, and optical microscopy. As mechanical forces and their distribution, mediated by tissue/cell stiffness, are recognized to play a critical role in the development of biological systems, their physiological behavior, and the emergence of disease, the technologies showcased in the conference promise to complement established methods for biomechanics to investigate biomechanical phenomena in a wide range of spatial scales, from submicron (cells and their constituents) to millimeter and beyond (tissue and organ). Each of the presented techniques and methods has distinct advantages and limitations for the different applications and readers are further directed to the following reviews, which thoroughly discuss this topic: Refs. 2 and 72–74.

Disclosures

The authors have no relevant financial interests in this article and no potential conflicts of interest to disclose.

Acknowledgments

We would like to acknowledge generous support provided by Thorlabs Inc. to bring most prominent researchers to make keynote addresses during this conference. The authors would like also to acknowledge the support of their work by the following agencies/grants: 2R01EY022362 (K. L.), 1R01HL130804 (K. L.), 9R01HD096335 (K. L. and G. S.), 1R01HD095520 (K. L.), 1R01GM127696 (V. Y.), R01EY028666 (G. S.), R33CA204582 (G. S.), and 1R21CA231561 (K. L.) from the U.S. National Institute of Health, Bethesda, Maryland; DBI-1455671 (V. Y.), DBI-1532188 (V. Y.), ECCS-1509268 (V. Y.), CMMI-1826078 (V. Y.) from the National Science Foundation; FA9550-15-1-0517 (V. Y.), and FA9550-18-1-0141 (V. Y.) from the U.S. Air Force Office of Scientific Research; the N00014-16-1-2578 (V. Y.) from the Office of Naval Research; and RP180588 from Cancer Prevention and Research Institute of Texas.

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Vladislav V. Yakovlev: Biography is not available.