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Optics in the Medical World

Seeing beyond

Michael Kempe, Rudolf von Bünau

Optical technologies have always played an important role for innovation in medicine. By extending and complementing these with digital technologies, optical solutions can become even more relevant for targeting the increasing and complex needs of medicine and health care. Therefore, this year's ZEISS Symposium "Optics in the Medical World" focused on the role, the challenges, and the potential of photonics in health care.

In particular, it illustrated how photonics can support some of the larger trends in health care like the trend towards more **precise and personalized medicine**. Photonic technologies are also essential for precision surgery, in that they provide essential information for surgeons and make devices more intelligent for **assisted or automated procedures**. Often, photonics enables simple-to-use and compact methods that support yet another important trend in medicine: **bringing care closer to the patient**, i.e. as remote care and point-of-care medicine. In-vitro diagnostics (IVD), often enabled by photonic technologies, is an essential tool not only for the diagnosis and management of many diseases, but also for **screening and prevention**.

The Symposium program was organized in three thematic strands, focusing on diagnostics, therapy, and the translational research field. It concluded with a panel discussion addressing trends in the healthcare sector and how technology can support these.

Optical Image Acquisition, Sensing and Interpretation for Diagnostics

Optical imaging and sensing support the trend towards more precise and personalized medicine by enabling earlier, more comprehensive, and functional diagnostics. In her keynote, Eva Sevick reported how near-infrared fluorescence lymphatic imaging has helped to understand the key role of the lymphatic system for the cardiovascular system, the immune response and the metastasis of tumors. Minimally invasive optical imaging enables the study of function, the diagnosis of pathologies e.g. during acute inflammation, lymphatic dysfunction due to lymph node removal and lymphedema, as well as the management and assessment of therapies. Lymphatic imaging is one of the rare and fortuitous situations where **minimally invasive optical whole-body imaging** is possible.

Photonics plays out its diagnostic advantages where high-quality, high-resolution **label-free imaging in tissue and organs** can be achieved. The progress in this area was shown by Paola Taroni and Stephen Boppart for breast tissue using diffuse imaging and optical coherence tomography (OCT), respectively, by Jochen Straub for the eye, and by Rob Adamson for the middle-ear, both using OCT.

With regard to precise, even personalized medicine, one challenge is to access clinically highly relevant, often **multi-factorial, functional information** via these non-invasive methods. The advancements achieved in this respect were made possible by multi-wavelength imaging for assessing tissue composition and physiological and microstructural information (Paola Taroni), combination of auto-fluorescence and multi-harmonic microscopy for the visualization of the molecular, metabolic, and structural composition of tissue (Stephen Boppart), and microscopic motion analysis in OCT to access metabolic and structural information (Claude Boccara). Functional imaging can also be achieved by combining optical imaging with specific tissue manipulation as shown by Rob Adamson for the middle ear.

The wealth of data provided by novel diagnostic tools makes it increasingly necessary and beneficial to support and **assist medical professionals in deriving diagnostical information** from it. This is obvious in the case of high-dimensional datasets as discussed by Stephen Boppart, but also needed to derive relevant information from structural and functional data as discussed for OCT by Claude Boccara and Niranchana Manivannan. Manuel Costa presented results in the assisted assessment of skin lesions resulting from another one of the rare scenarios for whole-body optical imaging.

Advanced Visualization and Automation in Surgery, and Light-Based Therapies

Photonic technologies are essential for precision surgery, in that they provide essential information for surgeons and make devices more intelligent for assisted or automated procedures. Jonathan Sorger described in his keynote how Intuitive's da Vinci, by far the most frequently used robotic-assisted surgical system, depends on excellent optical visualization. The addition of fluorescence imaging has improved outcomes through tumor margin visualization and by reducing adverse effects, e.g. nerve damage. In addition, the analysis of the surgical images helps in training surgeons and may support decision-making in the future.

Also, Rudolf Verdaasdonk and Ralf Brinkmann presented how optical and photonic technologies can be used both for diagnostics and therapy during surgical interventions. Smart imaging technologies, such as hyperspectral cameras or optoacoustic imaging, can be used to detect tissue properties or function, and **enable real-time guidance and assistance for the surgeon as well as potentially automation** of surgical tasks. In the fields of retinal laser therapies and in photodynamic therapy (PDT), **light** is used **for precise and selective therapy**. Luis Arnaut presented how PDT enables new personalized treatment options, e.g. for patients with low-risk prostate cancer. The presentation also demonstrated how medical devices, pharmaceutical drugs and clinical studies must be closely connected in order to establish PDT procedures as a standard of care.

David Reichert and Anja Britten presented fluorescence lifetime imaging microscopy (FLIM) and OCT as new **intraoperative visualization technologies** for surgery. Both technologies are well-known in microscopy and in the medical diagnostic field. Key to success in surgery are speed and real-time feedback to surgeons. Recent developments, mainly in the field of light sources and cameras, have increased imaging speed and are thereby allowing OCT and FLIM to be integrated as new visualization technologies in medical devices like endoscopes or surgical microscopes. Improved assistance functions as support during tumor resection, high resolution 3D visualization, or functional tissue assessment like perfusion and oxygenation can be realized.

Over the last years, the most frequent surgery, **cataract surgery**, has evolved from merely treating crystalline lens opacification, to a procedure aiming to achieve the best possible vision. This requires a personalized surgical approach combined with high precision regarding the desired refractive outcome. Harilaos Ginis showed how personalized eye models can be used to design optimized intra-ocular lenses (IOL) for peripheral quality of vision not yet achieved with current IOL designs. This is relevant for a range of daily tasks, such as navigation and driving. Applying machine learning to biometry data and including physical knowledge about the patient's eye into the model enable highly personalized surgical treatments, as discussed by Hendrik Burwinkel.

Emerging Translational Photonics Life Science Research Topics

There is a broad translational potential of photonics technologies used in research. In his keynote, Vasilis Ntziachristos pointed out the specific needs to bridge the difficult gap between scientific discovery and clinical solutions. Like in other areas, it requires – but often still lacks – **dedicated engineering and information science**, which is a focus of large health science centers, such as the Helmholtz Center Munich. One specific example is the ongoing development of clinical optoacoustics, moving from small animal

imaging to visualizing human metabolism, inflammation, and breast cancer, as well as in-vitro diagnostics of diabetes and cardio-vascular disease. In addition, the technology continues to be developed as research tool.

Photonics has a long tradition of helping **understand the mechanisms of** function and dysfunction **of life** as the foundation of medicine. Optical microscopy continues to be a key tool for investigations of cells as the building blocks of all organisms and their interaction, ideally live and in their natural environment. Monika Ritsch-Marte discussed technical advancements to improve the observation of living cells in tissue by fast 3D volumetric high-resolution imaging. Unraveling the structure and function of the complex network of connected nerve cells of the brain remains one of the largest challenges of biomedical research with far-reaching implications for medicine.

Closely associated with the working of the brain are the complex mechanisms of **perception and vision**, the most important human sense. Understanding these mechanisms in their function and dysfunction is of broad relevance for ophthalmology and optometry to preserve and restore vision, but also for society as a whole. Judith Ungewiß showed that using virtual reality and advanced simulation, vision can be studied, and intra-ocular lenses can be assessed with regard to various measures of vision in specific situations. This assessment can be used to improve and tailor IOL design to specific needs.

In-vitro diagnostics (IVD) is an essential tool not only for the diagnosis and management of many diseases, but also for screening and prevention. New photonics research insights extend its potential and enable further development of IVD methods. This includes very high sensitivity, as demonstrated by Valerio Pruneri and Jutta Toscano, specificity up to the level of molecular bonds, as shown by Mihaela Zigman, and an intrinsically high degree of parallelization in data acquisition, as demonstrated in the implementation of the biomarker detection platform by Valerio Pruneri. Sensitivity is important in working with minimal amounts of tissue or fluid that are easily accessible through minimally-invasive procedures. Using gases in the breath, discussed by Jutta Toscano, is one case in point. Often, photonics enables simple-to-use and compact methods that support yet another important trend in medicine: bringing care closer to the patient, i.e. point-of-care devices.

In the trend towards better assistive technologies for physicians, **robotics** with full autonomy can be considered the ultimate goal. Much research will be required to approach this goal, and collaborative action between humans and robotic systems is likely to be an important milestone. Balazs Gyenes demonstrated that multi-agent reinforcement learning is a well-suited paradigm for the training of decentralized policies on cooperative surgical tasks. Intelligent systems and their successful training are key requirements for the clinical use of more autonomous robotic solutions.

Panel Discussion

The panel discussion highlighted the importance of technological innovation, and photonic technologies in particular as discussed in the scientific track of the Symposium, in enabling and driving change in the medical system. One trend in particular was taken in focus: Data-driven medicine.

One barrier to progress that was identified by the panelists is non-uniform regulation for data privacy and patient consent. The concept of a “universal consent agreement” was proposed and found much support. Panelists also highlighted the need for understandable rules instead of pages of “fine print” to increase patient acceptance for research use of their medical data. Several participants pointed out that there are political as well as ethical dimensions to the balance between data privacy and research benefit. In addition, the benefits for the patients, including indirect ones, must be in focus and made transparent.

Another barrier that was discussed is lack of connectivity and data aggregation. Fragmented, local data repositories and too much free text in patient records were identified as obstacles to better research use of data. Patient registries were seen a possible solution, yet governance of registry data was seen as an area in which progress needs to be made. Both the approach of large multi-stakeholder registries managed by professional societies and bilateral industry-hospital data sharing agreements had supporters on the panel.

In general, increased collaboration between the stakeholders was considered a key for acceptance, to select and connect technologies with clinical need and reimbursement, including but not limited to collaboration between fundamental research, applied clinical research and industrial R&D – in the field of photonics and beyond.Program

Optical Image Acquisition, Sensing and Interpretation for Diagnostics

- Eva Sevick-Muraca, The University of Texas (keynote):
  Discovery in the translation of diagnostic, near-infrared fluorescence lymphatic imaging
- Paola Taroni, Politecnico di Milano (invited):
  Diffuse optical imaging and spectroscopy for medical diagnostics
- Stephen Boppart, University of Illinois (invited):
  Label-Free Intraoperative Imaging of Tumor Margins, Microenvironments, and Markers
- Claude Boccara, ESPCI Paris:
  Optical Coherence Tomography Revisited: high resolution in vivo, cellular activity and artificial intelligence
- Manuel Costa, University of Minho:
  Skin Neoplasia Early Detection by Fractal Analysis of Images and 3D Inspection
- Niranchana Manivannan, Carl Zeiss Meditec:
  The Past, Present and Future of AI applications in Ophthalmic Diagnostics
- Jochen Straub, Carl Zeiss Meditec:
  Widefield and ultra-widefield retinal imaging in ophthalmic diagnostics
- Rob Adamson, Audioptics Medical:
  Ossiview - Changing the Standard of Care in Otology with Optical Coherence Tomography Doppler Vibrography

Advanced Visualization and Automation in Surgery and Light-Based Therapies

- Jonathan Sorger, Intuitive Surgical (keynote):
  How advances in visualization have contributed to intelligent (robotic) surgery
- Rudolf M. Verdaasdonk University of Twende (invited):
  Improvement of light-based surgical interventions using ‘smart’ imaging techniques
- Luis Arnaut, University of Coimbra (invited):
  Perspectives of Photo-dynamic Therapy in Oncology and Infectious Diseases
- Ralf Brinkmann, MLL Luebeck:
  Optoacoustics for real-time feedback controlled retinal laser therapy
- Anja Britten, Medical University Vienna:
  Four-dimensional Optical Coherence Tomography for enhanced visualization in ophthalmic surgery
- Hendrik Burwinkel, Carl Zeiss Meditec:
  Next level in IOL calculation using domain-specific physical learning
- Harilaos Ginis, Athens Eye Hospital:
  Optical advantages of the meniscus intraocular lens
- David Reichert, Medical University Vienna:
  Fluorescence Lifetime Imaging for Enhanced Protoporphyrin IX Guided Surgery

Emerging Translational Photonics Life Science Research Topics

- Vasilis Ntziachristos, Technical University Munich (keynote):
  Engineering as the driver of medicine and life sciences
- Monika Ritsch-Marte, University of Innsbruck:
  Focus-tunable diffractive Moire lenses for biomedical and atomic optics applications
- Qingming Luo, Hainan University:
  Visualizing brain-wide networks at single neuron resolution with micro-optical sectioning tomography
- Judith Ungewiß, University Aalen:
  Benchmarking of refractive lenses and procedures using a nighttime driving simulator
- Mihaela Zigman, MPI Garching:
  Electric-field molecular fingerprinting of blood-based liquid biopsies: new prospects for probing human health
- Valerio Pruneri, ICFO Barcelona:
  Lens-free interferometric technologies for point-of-care label-free biomarker detection
- Jutta Toscano, JILA Boulder:
  Ultra-sensitive multi-species spectroscopic breath analysis for real-time health monitoring and diagnostics
- Balazs Gyenes, KIT Karlsruhe:
  Cooperative Multi-Agent Reinforcement Learning for Next-Generation Cognitive Robotics in Laparoscopic Surgery

Conclusion: Panel Discussion

Panelists:

- Nicole Eter, University of Muenster
- Ludwin Monz, ZEISS
- Vasilis Ntziachristos, Technical University Munich
- Eva Sevick-Muraca, The University of Texas
- Jonathan Sorger, Intuitive Surgical
- Christoph Straub, BARMER
- Stefan Vilsmeier, Brainlab

Skin Neoplasia Early Detection by Fractal Analysis of Images and 3D Inspection

Manuel F. M. Costa*

Center of Physics, University of Minho, Portugal
** Corresponding author: mfcosta@fisica.uminho.pt*

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Abstract

Early detection of skin cancer is fundamental to a successful treatment. Changes in the shape, including the relief, of skin lesions are an indicator of a possible malignity. As well and image processing optical microtopographic inspection of skin lesions can be used to identify diagnostic patterns of benign and malign skin lesions. Statistical parameters like the mean roughness (Ra) may allow the discrimination between different types of lesions and degree of malignity. Fractal analysis of bi-dimensional and 3D images of skin lesions can validate or complement that assessment by calculation of its fractal dimensions (FD). On the study herein reported the microtopographic inspection of the skin lesions were performed using the optical triangulation based microtopographer developed at the Physics Department of the University of Minho, MICROTOP.03.MFC. Images of the skin lesions were digitized and processed in order to calculate fractal parameters. The patients that participated in this research work were men and women older than 15 years with the clinical and histopathology diagnoses of: melanoma, basocellular carcinoma, epidermoide carcinoma, actinic keratosis, keratoacantosis and benign nevus. The combination of the rugometric evaluation and fractal geometry characterization, both 2D and 3D, provides valuable information about the malignity of skin lesions and type of lesion.