Clinical near-infrared spectroscopy and imaging

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The *Journal of Biomedical Optics* (JBO) was founded in 1996. In the fourth issue of 1996 and in the subsequent first issue of 1997, JBO published a Special Section on Near Infrared Spectroscopy and Imaging of Tissues, guest edited by Marco Ferrari, David T. Delpy, and David A. Benaron.[1] The special section included 12 articles on fetal- and infant-brain oximetry, muscle oximetry, and breast spectroscopy. In 2016, JBO celebrates its 20th anniversary. Throughout these two decades, JBO papers have reported the tremendous progress in this field. A new Special Section on Clinical Near-Infrared Spectroscopy and Imaging in JBO, and a parallel Special Section on Clinical Near-Infrared Spectroscopy and Imaging of the Brain in the new SPIE journal *Neurophotonics* (NPh), highlight these achievements.

The discovery of medical near-infrared spectroscopy (NIRS) goes back to 1977,[2] when Frans Jöbsis reported that the relatively high degree of transparency of brain tissue in the near-infrared range enables real-time noninvasive detection of hemoglobin (Hb) oxygenation using transillumination spectroscopy. Brain and muscle oximetry and functional NIRS[3] (fNIRS) represent the most established clinical and/or basic research areas, but additional applications to other tissues and organs are emerging.

This JBO special section includes 7 reviews and 8 original articles that report on major developments and applications in various fields of clinical NIRS and imaging. They illustrate the significant impact of this noninvasive methodology on diagnosis and treatment of diseases and promotion of health.

In the last 20 years the clinical applications of brain and muscle oximetry consistently increased. Muscle oximetry has been largely utilized. On the basis of an extensive literature, Grassi and Quaresima review how muscle oximetry offers insights into the physiological and pathophysiological adaptations to conditions of increased oxygen demand in different organs and systems of the body. NIRS measures of muscle reactive hyperemia have the potential to evaluate the pathophysiology of the microvascular perfusion. Willingham et al. report methods for accurately measuring reactive hyperemia using NIRS signals in the calf and foot. As reviewed by Bailey and Mally, the oximetry of the visceral organs (splanchnic oximetry) is an emerging method for its ability to monitor patient oxygenation status and to detect disease states of the liver and kidney in humans, especially in pediatric populations.

Different NIRS approaches have been utilized to investigate skin pathophysiology. Wound management is a challenging and costly problem. Sowa et al. review the NIRS methods for wound assessment that can be utilized along the entire healing trajectory of a wound. In addition, human brown adipose tissue is a recognized therapeutic target of obesity. Nirengi et al. first utilized a commercial time-domain oximeter to demonstrate the increase of the brown adipose tissue vascularity (total Hb) after daily ingestion of capsinoids.

The cover of the JBO 1996 special section was dedicated to the Carl Zeiss optical breast imager prototype. The original expectation to develop optical mammography as a screening tool for breast cancer was not fulfilled, yet optical breast imaging and spectroscopy is an area of active research to date. Grosenick et al. provide a comprehensive review on this topic that gives an overview of the pathophysiology of breast diseases, major developments in methodology, and results of numerous clinical studies. Monitoring neoadjuvant chemotherapy and breast cancer risk assessment are considered as promising applications with high potential for translation into clinical routine. In a specific multimodal investigation, Michaelsen et al. apply the combination of near-infrared spectral tomography and x-ray tomosynthesis to study the effects of breast density and compression on normal breast tissue hemodynamics.

Since Jöbsis' report,[2] the clinical NIRS measurements of cerebral cytochrome-c-oxidase have been considered to have the potential to yield crucial information about cerebral metabolism at the patient bedside. Almost 40 years from his article, this signal continues to hold significant interest in our understanding of the human brain in health and disease. Bale et al. discuss the new methodologies for obtaining NIRS measurements of cerebral cytochrome-c-oxidase in the clinic and review studies in neonates and adults.

Consistent progress has been made in diffuse optical tomography (DOT) techniques for synthesizing collections of individual NIRS measurements into images. Hoshi and Yamada provide an overview of the DOT technical and clinical progress. They first summarize NIRS, and then describe various approaches in the efforts to develop accurate and efficient DOT algorithms and present some examples of clinical applications. The future prospects of DOT are also discussed. Hu et al. report the application of an ambulatory 64-channel DOT prototype for muscle monitoring integrated with the simultaneous acquisition of synchronized auxiliary data such as electromyography or electrocardiography. More advantages are expected by time-domain DOT. Pifferi et al. review the most recent developments in time-domain diffuse optics that rely on physical concepts (e.g., time-gating and null distance) and advanced photonic components (e.g., vertical cavity source-emitting laser as light sources, single-photon avalanche diode, and silicon photomultipliers as detectors, fast-gating circuits, and time-to-digital converters for acquisition). These tools could lead on one hand to compact and wearable time-domain devices for point-of-care diagnostics, and on the other hand to powerful systems with exceptional depth penetration and sensitivity.

In 1993, papers from four different groups were published demonstrating the ability of fNIRS to noninvasively measure Hb concentration responses to functional brain activation in humans.[3] In 2014, *Neuroimage* dedicated a special issue to commemorate the first 20 years of fNIRS research including 9 reviews and 49 contributed papers.[4] The present special section in JBO contains three papers related to fNIRS; more fNIRS papers can be found in the parallel NPh special section. Hwang et al. report a novel approach to a brain–computer interface for implementing more intuitive and user-friendly communication systems for patients with motor disabilities. Holper et al. find that short-term pulse rate variability is better characterized by fNIRS than by photoplethysmography under conditions in which respiration and temperature changes are present. Si et al. investigate the correlation between electrical and hemodynamic responses to visual stimuli, especially focusing on the relationship between the latencies of the visual evoked potential and the hemodynamic response.

Fluorescence imaging has been considered for over a half-century as a modality that could assist surgical guidance and visualization. Phantoms play an important role in providing a ground truth and to validate fluorescence imaging systems and results. Anastasopoulou et al. discuss requirements to phantoms and present a universal phantom design suitable for interlaboratory system performance evaluation that includes features to address characteristics like sensitivity, spatial resolution, and depth dependence.

The guest editors believe that this special section and the parallel special section in *Neurophotonics* are valuable reading for scientists both inside and outside the biomedical optics community. Readers will get a glimpse of how NIRS technologies impact medicine today and what can be expected from developments of tomorrow's technologies. In the coming years, current generations of NIRS instruments will migrate along the translational path toward clinical adoption as both the product engineering and use protocols are refined. However, while many aspects of NIRS technology have been tested for limits such as resolution, quantitative accuracy, field-of-view, depth sensitivity, wearability, portability, and integration with other modalities—many of these individual demands are at odds with other performance measures. For example, the solutions to several performance specifications positively correlate with instrument weight and thus work against wearability. Thus the phase-space for optimizing and engineering real-world NIRS instruments remains immense. In summary, NIRS has already provided many valuable insights in clinical research. While NIRS is on the verge of entering everyday clinical routine, the innovation yet to come is still brighter.

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Marco Ferrari is a biochemistry professor in the Department of Physical and Chemical Sciences, L'Aquila University, Italy. He has pioneered clinical applications of NIRS of the adult and infant muscle and brain, and has made substantial contributions to the wider NIRS scientific community. His recent research activity is focused on the study of the cerebral cortex hemodynamic changes upon cognitive and motor tasks of different complexity by using functional near-infrared spectroscopy (fNIRS). He has been a member of the editorial board of *Journal Biomedical Optics* since 1996.

Joseph P. Culver is a professor of radiology at Washington University. He obtained a PhD in physics at the University of Pennsylvania for work in ultrafast infrared laser spectroscopy. As a postdoc, he developed diffuse optical tomography systems for imaging breast cancer and imaging cerebral hemodynamics in animals. His lab explores ways of leveraging optical measurements for neuroimaging, with a focus on development of diffuse optical tomography techniques for mapping human brain function.

Yoko Hoshi is a professor in the Department of Biomedical Optics in Hamamatsu University School of Medicine. She graduated from Akita University School of Medicine and got her medical license in 1981, and received a PhD at Hokkaido University in 1990. She is a pediatrician (a child neurologist), while she has also been participating in developing NIRS and research in cognitive neuroscience, mainly

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