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Review of the doctoral thesis by Aleh Sudakou

The evaluated dissertation of Mr. Aleh Sudakou, entitled "Depty-resolved assessment of tissue oxygen saturation using time-domain near infrared spectroscopy" was carried out under the supervision of Prof. Dr. hab. Adam Liebert, at the Nałęcz Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences. The dissertation consists of four thematically consistent scientific articles published in peer-reviewed journals well recognized globally by experts in the field. Original papers are accompanied by short introduction. The research presented was conducted over the past five years. In addition, Mr Sudakou is co-author of another 5 publications which indicates his strong commitment to the collaborative work of the research group.

Mr Aleh Sudakou's PhD thesis is computational in nature with experimental elements. The work presented relates to Time-domain near-infrared spectroscopy (TD-NIRS), which has emerged as a promising technique for non-invasive brain imaging, particularly in assessing cerebral oxygenation and blood flow. However, despite its potential, the method faces several significant challenges that impact its effectiveness, precision, and broader application. One of the primary hurdles NIRS encounters is the complexity of light behavior in the human head. The brain is surrounded by various layers—scalp, skull, cerebrospinal fluid, and brain tissue—all of which scatter and absorb photons. This scattering phenomenon elongates the path of photons, making it difficult to accurately determine where they've traveled. As a result, localizing brain activity becomes a challenge, and separating signals from superficial layers, such as the scalp and skull, from deeper cortical activity is particularly difficult. The limited depth sensitivity of NIRS further restricts its scope. While the technique can provide some depth-resolved information by measuring the time it takes photons to pass through the tissue, the penetration depth is still quite shallow, only reaching a few centimeters. This means that NIRS is predominantly useful for imaging the brain's surface, leaving deeper structures so far beyond its reach. Consequently, researchers and clinicians are still left with incomplete views of brain function when using this method. Physiological noise, such as fluctuations in heart rate, respiration, and systemic blood pressure, adds another layer of complexity. These natural bodily rhythms often interfere with the signals NIRS is designed to detect, masking the brain's hemodynamic responses. While there are techniques to filter out or account for these physiological noise sources, they are not perfect, and removing this noise can sometimes reduce sensitivity to small changes in brain activity. Another area where NIRS faces significant difficulties is quantification of brain signals. Accurately measuring the absolute concentrations of key chromophores—like oxyhemoglobin, deoxyhemoglobin, and cytochrome-c-oxidase—remains problematic. Tissue properties, calibration issues, and uncertainties in photon pathlengths make it difficult to derive precise, reliable measurements. This hinders the clinical utility of NIRS, where precise quantification is critical for diagnosing and monitoring conditions.

Despite these challenges, TD-NIRS remains a valuable tool due to its non-invasive nature and the possibility of portable, real-time monitoring of brain function. The candidate work also addresses some of above-mentioned limitations through novel computational advances and improved data processing techniques. His contribution to overcoming the limitations of quantifying brain signals could be an important element in unlocking the full potential of NIRS in both research and clinical settings.

In the first publication, the candidate described his contribution to the development of a new method for determining changes in tissue chromophore concentrations for time and wavelength through error propagation analysis. An advantageous characteristic of the statistical moments of DTOFs is that their uncertainties, arising from photon noise (which is assumed to follow Poisson statistics), can be derived from the higher-order moments. This enabled author to identify the optimal wavelength range for his measurement system that minimizes the uncertainty in detecting changes in concentrations of oxyhemoglobin, deoxyhemoglobin, and the enzyme cytochrome-c-oxidase (CCO), while accounting for the spectral responsivity of the detector. In his experimental work, Mr Aleh Sudakou used a time-domain multi-wavelength NIRS system that uses a supercontinuum light source, and the spectral range of the emission is selected using appropriate filters. Using a Monte Carlo (MC) method, he simulated DTOF signals at 25 different wavelengths for a three-layer model imitating scalp, skull and brain tissues according to data available in the literature. MC simulations were necessary to study the influence of various parameters, such as the choice of wavelength or the source-detector distance, on signals measured in diffuse reflection geometries. The uncertainty in the variation of chromophore concentrations is related to noise associated with the Poisson statistics. Therefore, the use of error propagation allowed the identification of several wavelengths for which the variation of chromophore concentrations is minimized. The detection performance, given here as the responsivity of a specific experimental system, was also taken into account here. This work has allowed the practical optimization of measurement systems giving important information necessary for the design of efficient DTOF systems with quantitative readout of chromophore concentrations.

In the second paper presented by Mr Aleh Sudakou, he was describing the development of a method to analyze, quantitatively compare and rank the performance of different measurands for NIRS in the time domain, which can be used to determine absorption changes at different depths in the measured medium. Time-domain optical brain imaging techniques have introduced a number of different measurement quantities to measure absorption changes located deep in the tissue, the accuracy of which is related to true physical absorption changes and pervasive noise. In this work, the candidate has shown an analysis that allows quantitative comparison and ranking of the performance of measurement quantities under different conditions - including different values of layer thickness, reduced scattering coefficient, and source-detector separation. The analysis included three objective metrics: relative contrast, contrast-to-noise ratio (CNR) and a measure of extinction susceptibility. The candidate examined the product of CNR and depth selectivity to quantitatively rank the overall performance of the measurement devices in the context of determining extinction coefficient changes at greater depths. All simulation results were confronted experimentally with DTOF measurements carried out on two-layer liquid phantoms, obtaining a high degree of consistency. Publication II provides a better understanding of the advantages and disadvantages of the different quantities that characterize the measurement of extinction coefficient changes in deep tissue layers. It was pointed out that the highest depth selectivity can be achieved with photon count ratios in different time windows, but with low CNR. In contrast, the highest CNR can be achieved with total photon count ratios, but its depth selectivity is low. Therefore, the choice of the appropriate measurement size can depend on the conditions - where the optical properties of the surface layer are constant, it is advantageous to use the total photon counts for data analysis, ignoring the high susceptibility to changes. Where there are strong changes in the surface layer, the photon count ratio may better reflect changes in the deeper layer, although the signals have a low CNR.

In the third paper presented, Mr. Sudakou introduced a novel approach to NIRS spectroscopic measurements utilizing two 16-channel spectrometers (referred to as polychromators, though somewhat outdated) with supercontinuum light serving as the illumination source, covering the 650 to 850 nm wavelength range. This system is specifically designed for monitoring muscle and brain oxygenation in clinical settings. It captures distributions of photon transit times (DTOFs) for 16 spectral channels (with a resolution of 12.5 nm per channel), resulting in a total of 32 DTOFs at frequencies up to 3 Hz. The candidate thoroughly validated this system using all the most advanced performance evaluation techniques available. He incorporated wavelength optimization data from earlier research (referred to as Paper I) and applied some of the performance evaluation methods detailed in Paper II. Collaborative, multi-center testing was conducted on well-characterized homogeneous solid phantoms and one dynamic heterogeneous solid phantom, leading to the standardization of performance evaluation for time-domain diffusion optics instruments. Additionally, Monte Carlo simulations were performed and compared with experimental data from two inhomogeneous phantoms. The presented 3D distributions confirmed and visually clarified the observed depth sensitivity profiles of changes in the three statistical moments calculated from the measured DTOFs. This research ultimately confirmed the translational potential of these methodologies for clinical applications.

In the final publication of the series, Mr. Aleh Sudkaou presented the results of his work on measuring blood oxygen saturation in two distinct layers through controlled experiments using a specially designed phantom. To achieve this, he developed a new data analysis method based on the Levenberg-Marquardt algorithm, a well-established technique for solving non-linear iterative least-squares minimization problems using an analytical diffusion solution. The candidate then tested his method for determining oxygen saturation in two layers through a series of three experiments. Measurements on the two-layer substrate demonstrated the anticipated impact of the surface layer, confirming the method's ability to accurately assess saturation in both layers. The phantom proved to be robust, easy to use, and produced reproducible results. The calculations aligned with experimental findings, assuming prior knowledge of the medium's extinction coefficient. However, this reliance on a known extinction coefficient presents a significant limitation, as in vivo measurements can be affected by changes in scattering due to haemodynamic fluctuations. Nevertheless, this method marks a significant advancement in addressing surface layer contamination, which is particularly advantageous for NIRS applications, improving the accuracy of oxygen saturation measurements in the brain from intracranial readings. The advanced phantom could contribute to ongoing efforts to create more realistic and standardized performance tests for NIRS tissue oximetry.

Given my limited expertise in the specific details of NIRS methodologies, I am unable to fully evaluate the merits of the publications included in this dissertation. However, considering the rigorous editorial standards of Biomedical Optics Express, where all the papers in the series were published, it can be reasonably assumed that the reviewers identified and addressed any significant methodological issues and limitations in the research before its final publication. In my view, a notable shortcoming of the presented dissertation is the lack of connection between the specific aims and objectives of the research and the broader challenges facing NIRS technology, the resolution of which will define its future role in neuroscience and medical diagnostics. Specifically, I am concerned about how the results presented in the thesis contribute to solution of overcoming key obstacles faced by NIRS, including structural complexity, low signal-to-noise ratio (SNR), physiological noise, spatial resolution limitations, calibration difficulties, and operational complexity of the instruments. I hope that the candidate will address these issues in a manner that is more accessible to a broader audience, beyond just experts in the field, during his PhD defense.

In conclusion, I affirm that the doctoral thesis of Mr. Aleh Sudakou fully satisfies the requirements set forth for doctoral theses by the Act on Academic Title and Degrees, and I hereby recommend it for public defense. Based on the Principles for Distinguishing Doctoral Theses, I also propose that this thesis be recognized for distinction due to the introduction of new universal computational methods that significantly improve the quantification of functional NIRS data, thereby advancing the clinical implementation of this technique.

Sincerely yours,

Maciej Wojtkowski