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Review of Ph.D. thesis

by **Saeed Samaei**

title: Assessment of depth-resolved blood flow changes in biological tissues based on time-domain diffuse correlation spectroscopy (TD-DCS) technique

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Introduction

In recent years, there has been significant development of optical technology able to non-invasively assess microvascular blood flow. One of the promising methods is time-domain diffuse correlation spectroscopy (TD-DCS). It offers an assessment of the Blood Flow Index (BFI) with path-length resolution. However, the TD-DCS setup must meet high requirements in terms of the performance of its components. The proper characteristics of the laser source (power, pulse width, coherence, stability) are of particular importance. With the time-of-flight (TOF) resolution TD-DSC theoretically decomposes the blood flow at different sample depths. However, photons with a similar TOF can be scattered from structures that move at different speeds. Accounting for unequal speeds of scattered moves might improve the accuracy of blood flow quantification with depth discrimination. The thesis takes into account all the above-mentioned issues and investigates the feasibility of accurately quantifying blood flow. The results of performed research may lead to better treatment assessment and an improved fundamental understanding of microvascular blood circulation in human tissue. Thus, this thesis addresses the highly relevant areas of current research in non-invasive blood flow monitoring.

Structure and the content of the thesis

The Dissertation of Saeed Samaei is organized as a monographic thesis (the classic book format). It contains 83 pages, 6 chapters, 45 figures, 5 tables, and a list of abbreviations and symbols. The Abstract of the thesis is written in two languages (Polish and English). The research is based on a large number of references (171), related to the topic. A list of publications associated with the thesis is presented at the beginning of the dissertation and it

contains 3 papers published in international scientific journals from the Journal Citation Reports (JCR) list.

In Chapter 1 Mr. Saeed Samaei introduces the reader to different techniques used for blood flow measurement. The chapter ends with the formulation of the hypothesis and a description of the study scope and the structure of the dissertation. Chapter 2 describes diffuse optics theory. It starts with an introduction to the optical properties of tissue. Then, the theoretical description of photon migration in turbid media is presented. Next, Mr. Saeed Samaei explains the theoretical basis of diffuse correlation spectroscopy and discusses the drawbacks of the standard model conventionally used to estimate the BFI. Finally, a new theoretical model for BFI estimation with depth discrimination proposed by Mr. Samaei is described. In Chapter 3 the experimental setup of TD-DCS with a data processing approach is discussed. The performance of three different laser sources for TD-DCS was compared and investigated in a series of phantom measurements. The results of in vivo studies were also presented. Chapter 4 shows the results of experiments on phantoms (homogenous and layered), human forearm (cuff occlusion test), and forehead (with pressure applied to reduce superficial blood flow) performed to test the capability of the novel model to distinguish different speeds of moving particles in layered media and to calculate BFI with depth discrimination. At the end of the dissertation the obtained results are discussed (Chapter 5) and the general conclusions of the performed research are presented (Chapter 6).

The structure of the dissertation is correct with minor remarks described below.

References

The thesis contains a comprehensive bibliography (171 references) of all the relevant papers for the discussed field.

Hypothesis

The aim of this thesis was to obtain depth-resolved blood flow information by applying a comprehensive model describing the relationship between the movement of particles at different depths in human tissue. The author posed the hypothesis that the time-gated intensity autocorrelation function obtained from layered multiple scattering media using TD-DCS carries information on the movement of particles contained at different depths in this medium.

The hypothesis is well formulated based on valuable and actual literature.

Novelty of the thesis

Two goals, which are closely related to the proposed hypothesis were achieved. The first one is related to the assessment of the influence of TD-DSC setup components on the feasibility of BFI measurement with depth discrimination. The second goal was to propose a new theoretical model for TD-DSC, enabling separate various blood flow in human tissue. A series of experimental measurements in tissue-mimicking phantoms and in-vivo studies were

successfully performed proving the achievement of the goals. The strength of the doctoral thesis is the combination of theoretical considerations with experimental and purely engineering work. The originality and novelty of the thesis have been confirmed by published papers in highly-ranked scientific journals (Biomedical Optics Express, Scientific Reports, APL Photonics). In my opinion, these works constitute an important contribution to modern optical technologies' state of the art and extend our knowledge about microcirculation in human tissue.

Remarks and Comments

Although the thesis is generally very well written, I think that Chapter I is the weakest part of the dissertation. The introduction should familiarize the reader with the subject of the work and clearly explain the motivation for undertaking the research. The goals related to the hypothesis should be also clearly defined. Reading the introduction, I could not find an answer to the question of why discrimination in blood flows in different layers is so important. What would be the advantages of applying the newly developed approach to patients' treatment? A review of the existing solutions regarding blood flow measurement is more than correct, although for me such a review should be presented in a separate chapter. Also, it would be interesting and useful to summarize the pros and cons of each technology in a table.

I also think that since the thesis concerns blood flow in human tissue, the physiology (and pathophysiology) of microcirculation should be briefly presented. Here I have a question regarding the assumption of different speeds of scattered moves in human tissue. What would be the reason, from the physiological point of view, that the cells in the tissue move at different speeds? Can diseases related to microcirculation, e.g. diabetes affect the speed of movement of particles in muscle tissue? What may be the clinical benefits of the proposed approach for BFI estimation?

Performed experiments are well arranged and measurement techniques and methods are correctly applied. However, my criticism concerns the small number of volunteers included in the in-vivo studies. With the experiment carried out on 3 people I have doubts if we can talk about the validation of the model. This is a nice showing of a potential of the proposed approach rather than a verification of the model. I wonder why so few volunteers were tested. Considering the simplicity of the cuff occlusion test and having already the appropriate approval of the bioethics committee, performing more tests should not be difficult and time-consuming.

Minor comments

The work contains many nice drawings that are very helpful. However, the size of the font and the often merging similar colors used in the figures make the readability and interpretation of these graphs difficult (e.g fig 4.10, 4.11).

List of acronyms and symbols: units should be given where applicable. Some frequently used abbreviations are missing: DTOF, TOF, TCSPC

Conclusions

To sum up, the dissertation represents high-level scientific work. The results achieved in the thesis enhance understanding of blood flow circulation in human tissue and provide a useful tool for blood flow measurement with depth selectivity. The topic of the thesis is unique and important for science and potential for clinical use. The methodology and methods are correct and appropriately used. The results are derived logically and well described. The conclusions correspond to the aim of the thesis.

The comments presented above are not critical and do not diminish the high scientific quality of the dissertation.

In my opinion, the reviewed thesis fulfills all requirements posed on theses aimed at obtaining a Ph.D. degree. Considering the high rank of published papers, extensive range of performed experiments, and scientific novelty of the thesis, I would like strongly recommend to the scientific committee to reward Saeed Samaei's dissertation.

M. Kosmová