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Dr hab. Ireneusz Grulkowski, prof. UMK
Institute of Physics
Nicolaus Copernicus University
Torun, Poland
www.boelab.org

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Review of the PhD dissertation entitled
'Statistical modelling of corneal OCT speckle'
submitted by Marcela Niemczyk

Introduction

This review was prepared at the request of the Chair of the Council of the Scientific Discipline 'Biomedical Engineering' at the Wroclaw University of Science and Technology, Prof. Halina Podbielska, based on delivered hardcopy of the PhD dissertation. The research presented in the dissertation was carried out at the Department of Biomedical Engineering by Marcela Niemczyk, MSc Eng, under the supervision of Prof. D. Robert Iskander and Prof. David Alonso Caneiro.

Aim of the thesis and rational for the topic

Generally, the thesis is devoted to the development of novel functionality to optical coherence tomography data analysis that enables indirect assessment of intraocular pressure (IOP).

Precise IOP measurement is of great importance from the clinical point of view e.g. in the diagnosis of glaucoma. Goldmann applanation tonometry is regarded as a gold standard in IOP measurement. Current measurement paradigms for the IOP include also application of the mechanic force in a non-contact way like the air puff, and simultaneous non-invasive visualization of the tissue reaction to such a stimulus. The research presented in this thesis utilized determination of speckle statistics in OCT images of the cornea as a biomarker of IOP. The effects studied here are also important in fundamental research on exploration of information carried by speckle phenomena.

The Author formulated the aim of the presented study in Preface. The Author specified that 'the main goal of this thesis is to develop some statistical methods of speckle analysis to indirectly assess corneal properties, which may be influenced by the IOP. It is important to note here that Preface includes also a direct formulation of three research hypotheses that the research is based on and that form the structure of the

thesis. Accordingly, the Author follows rigorous scientific approach leading to provide the research aim. Therefore, in my opinion the research problem has been formulated correctly, and the title of the dissertation matches the assumed goals.

Structure of the thesis

The main part of the doctoral thesis presented for review contains 85 pages. This was preceded by 30-page initial part including abstracts, acknowledgements, list of publications and conference proceedings, contents, list of figures, tables, abbreviations and symbols as well as Preface. The main part of the dissertation has been divided into 4 chapters, 2 appendixes and a bibliography. The thesis contains 40 figures, 8 tables and 89 equations. The thesis is characterized by a regular and logical structure, typical for research articles in natural sciences, which makes it easy to read and follow.

The dissertation of Mrs. Marcela Niemczyk starts with Preface including the motivation, aim, hypotheses and short description of the all chapters. Chapter 1 – Introduction - presents optical coherence tomography as a coherent imaging modality. Three generations of OCT instruments are shown. The Author demonstrates also a brief summary of applications in biomedicine. Later on, the Author concentrates on fundamentals of speckle theory, where all the necessary terms are introduced. An important part of Chapter 1 is the demonstration of both parametric and non-parametric approaches to speckle modelling that were applied in this study. Finally, the properties of the object of the study – the cornea – is described along with the impact of IOP and age on its properties. Such design of the chapter clearly sells the background of the study. The Author proved that she is able to communicate the state-of-the-art in a synthetic way, and provided with accurate recognition of the current advances in the field.

Methodological aspects of the study are presented in Chapter 2. The Author shows the details of the experimental procedures namely: phantom study, ex-vivo study with porcine eyes and human subject study. Later on, the candidate demonstrates the details of the methods for extraction information from OCT images. In particular, parametric method and non-parametric method utilized in this study are given. Finally, statistical analysis tools are demonstrated.

Chapter 3 is the key section and includes the results of the studies completed by the PhD candidate. The structure of this chapter reflects the specific research questions raised in Preface. Therefore, this chapter is divided into three sections corresponding to

the objects (phantom, pig eyes or human eyes). Both ex-vivo and in vivo study possesses the results taken from parametric and non-parametric analysis.

Final fourth chapter of the dissertation is the most important section of the thesis that summarizes the most important facts and discusses the obtained results. Furthermore, the Author critically points out the limitations of the study, draws the main conclusions, and presents possible future directions. The thesis includes also two Appendixes. Appendix A presents how the speckle statistics is influenced by averaging the B-scans. Appendix B introduces a theoretical model of corneal OCT speckle as the product distribution of two gamma random variables. The author made also significant efforts to do accurate literature search during editing the text as 144 references are included in the reference list.

Editorial (technical) comments

The dissertation is written in English in a style meeting high standards of scientific papers. I have to admit that I do really appreciate an Author's eye for detail. Technical aspect of the thesis is definitely a strong point. Although I am quite picky and sensitive to editing the text and figures, I found only few places throughout the thesis that would require minor stylistic modifications. Another issue that may help in understanding the results is the style of inserting the figure references in Chapter 3. I would expect the Author to be more specific when referencing to particular figure (subfigure / plot) in the text while mentioning the observed facts. Finally, I have some doubts regarding the term 'pixel value' used through the entire thesis. I do believe that the Author debated on how to name it properly, but I would suggest using the term 'OCT image signal'.

The artwork consisting of 40 figures was prepared correctly. The quality proves that the Author took care on that technical aspect of the dissertation, which I also value very much.

Critical analysis & questions

In this section, I would like to raise the issues and questions that arose during reading the manuscript. The list below can be addressed by the Candidate during the defense:

1) Section 1.1.1, p. 1 – "(OCT) is particularly suitable in biomedical applications for in-vivo imaging of tissues, especially when the traditional microscopy in-vitro is

inconvenient or even impossible to be performed" – I do not understand the reasoning here. Usually in vivo applications are harder than in vitro. In addition, standard microscopy outperforms the resolutions of standard OCT systems. However, maybe the Author meant that OCT enables in vivo applications without any contact with the sample.

2) Section 1.1.1, p. 1 – 'axial measurement of time' ???
3) Section 1.2.4, p. 10 – please explain how r_2 (half width at 1/e amplitude of OCT signal) is defined.
4) Section 1.2.6 – please explain what 'inverse log-transformation' means
   Another issue is that you usually obtain OCT images in the digital form of 8-bit image (file). Therefore, to appropriately convert from log to linear scale of intensity, you need to know the levels of minimum (black, 0) and maximum (white, 255) signal in the OCT image unless raw data are used. Please specify how you converted the grey levels in OCT images during data post-processing.
5) Section 1.3.2, p. 18 – What is the wavelength at which the refractive indices of the cornea are provided in the text?
6) What was the absorption spectrum of the blue dye in the resin of the phantom? Can this affect the results?
7) Did you avoid the specular reflection from the cornea when analyzing the image?
8) What is the impact of signal-to-noise ratio on the results?
9) Figures 3.10 & 3.11 – Can you notice that gamma distribution shape parameter is linked to the SNR level (in peripheral parts of the corneal image)? The regions with lower signal give lower v values. If that is true, it will affect the study on differences between anterior and posterior part of the cornea.
10) Can CCT decrease be attributed to the dehydration?
11) Just noticed that some structural OCT images lack grey scale.
12) Can you compare the results of speckle analysis in inflation test with the studies on speckles from other modalities, such as Scheimpflug camera?

Evaluation of the dissertation

The PhD thesis is the result of theoretical (simulation) and experimental work and addresses an interesting and novel challenge in non-invasive clinical imaging. **The PhD candidate had to acquire several skills necessary to complete the research tasks and to**

achieve the goals, from experimental design, preparation of original experimental system, data processing (image analysis) and advanced modelling of speckle phenomena.

In my opinion, a unique achievement of the PhD student is the **demonstration of proof-of-concept methodology for non-invasive assessment of IOP from OCT data**. I particularly value attempts to extract information from regular OCT images by applying advanced statistical modelling. The theoretical studies used the experimental data. The experiments presented in this thesis involved different types of studies: with self-made phantom, ex-vivo porcine eyes and human subject studies. There is no doubt that all studies required acquisition extraordinary skills **and synchronization of research activities to address the challenges associated with in vivo imaging**. Ex-vivo study involved design and practical realization of the system for IOP control and eye positioning. In particular, in vivo study with human subjects would not be **completed successfully without proper planning and system preparation.** Comprehensive approach adopted by the Author proves that she is also aware of the limitations of the study.

In spite of my comments and raised questions, I have to admit that the proposed research constitute the **Author's contribution to the development of field of biomedical imaging and may have impact on the translational research**. As indicated in the thesis, the know-how and results acquired during Mrs. Niemczyk PhD project should be used in future experiments. Furthermore, the outcome of the PhD project is significant at the international level as three articles in peer-reviewed journals and four conference proceeding have been already published, with contribution of the Candidate as the first author in most cases. Conference proceedings / abstracts also show that the material included in the dissertation was presented at few international and most recognized conferences / congresses in the form of oral contribution or poster.

Final conclusions

In conclusion, all achievements demonstrated in this thesis represent consistent set of studies presented with high quality. The research problems addressed in this thesis demonstrate high level of skills and expertise acquired by the candidate. Comprehensive and integrated research methodology was applied to problems solved in this dissertation. All defined aims have been achieved.

I do declare that the PhD dissertation of Marcela Niemczyk, MSc Eng meets the requirements for doctoral dissertations specified in Art. 190 of the Act on Higher

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Education and Science of July 20, 2018 (Dz.U. 2021 it. 478; as amended) and in other relevant regulations. Accordingly, I do recommend that Mrs. Niemczyk's PhD thesis proceeds to the next stage of procedure and be admitted for public defense.

Finally, based on the arguments presented in previous section of the review (bold text), I would like to support the nomination of the thesis for distinction.

Prepared in the city of Toruń, on September 13th, 2022

dr hab. Ireneusz Grulkowski, prof. UMK

Dr hab. Ireneusz Grulkowski, prof. UMK
Associate Professor
Bio-Optics & Optical Engineering Lab
Institute of Physics
Nicolaus Copernicus University