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## REVIEW REPORT

*on PhD Thesis of Clara Llorens-Quintana  
„Methods for non-invasive measurement and analysis of tear film quality”*

### General description of the Thesis

The submitted thesis is focused on the problem of assessment of the quality of tear film in the context of the dry eye disease (DED), which is an illness of the ocular surface leading to discomfort and various visual disorders. Due to the increasing prevalence of the dry eye syndrome, caused mainly by the use of viewing devices, much research effort has been devoted to the analysis of the tear film stability, which is regarded as an important diagnostic feature. The main problem in the evaluation of the tear film dynamics, which can be related to the dry eye syndrome, is the lack of standardized measurement protocols, which could reliably describe and diagnose the patient's condition. Many approaches have been proposed, however their accuracy and repeatability is unsatisfactory and therefore new, more precise and robust methods are being developed.

The main objective of the thesis was to develop new approaches aiding the assessment of the dry eye disease based on the visual analysis of the tear film stability and the features of the Meibomian glands morphology in relation to the tear film characteristics. The developed solutions should be also applicable for the in-vivo assessment of the performance of contact lenses and their biocompatibility.

The scientific hypothesis states that *“Advancing in robust and automated ways of tear film and Meibomian glands analysis would result in better estimation of tear film quality and lead to better diagnosis and understanding of DED”*.

In the thesis, a novel method of the analysis of the tear film stability based on the advanced techniques of image analysis has been proposed. Its efficiency has been proved on 39 subjects and the method can be applied in various videokeratoscopes used in the clinical practice. The



developed algorithmic framework is also of vital importance for contact lens wearers whose number is growing steadily. Despite the many advantages of contact lenses, about one third of their users discontinue wearing them because of discomfort symptoms caused by the physical and chemical interactions between the material of the lens and the ocular surface. Therefore, the research on the interactions between the contact lens and the eye surface, focused mostly on the analysis of the tear film instability, is an important research topic investigated also in the thesis. The obtained results can be useful in the development of new contact lens designs with minimized impact on the tear film stability and the homeostasis of the ocular surface. The developed algorithms can also help the optician to offer a lens adjusted to the structure of the ocular surface in order to reduce the risk of dry eye symptoms.

Another problem investigated in the thesis is the assessment of the morphometric structures of the Meibomian glands responsible for the supply of meibum. In the submitted work, an advanced automatic algorithm measuring their number and regularity has been constructed and its efficiency has been tested on 149 subjects with different level of Meibomian gland dysfunction. The obtained results show a good performance of the developed approach.

### **Layout and the content of the Thesis**

The submitted PhD thesis consists of three main chapters which are accompanied by acknowledgements, table of contents, an abstract in English, Polish and Spanish, list of author's publications, list of acronyms, figures and tables and ends with the list of references. The appendix contains 5 papers submitted to journals and 2 conference papers. The PhD candidate is the first author of all the presented publications.

The thesis structure is deliberate and transparent. In the first Chapter an extensive introduction to the problem of tear film quality and its relation to the dry eye syndrome is presented. First the tear film physiology and its stability together with the role of the Meibomian glands is thoroughly surveyed. Then the dry eye disease classification, symptoms and diagnosis is discussed. Next part is devoted to the tarsal glands dysfunction and the effects associated with the use of contact lenses. The introduction contains also a description of state-of-the-art methods used in the assessment of the tear film quality and analysis of tarsal glands morphology.

The first part should provide the reader with the background of the performed research. In fact it is too detailed in comparison with the second chapter whose aim is to summarize the performed research.

The second chapter (research summary) is divided into 2 parts. In the first part a novel method of tear film assessment using high speed videokeratoscopy is presented. The proposed framework is based on the analysis of the texture of images acquired with a videokeratoscope. To describe the temporal disturbance of the Placido disks reflections, the fractal dimension based approach has been adopted. First, the images of the eye surface were transformed into polar coordinates and processed to determine the indicators of the observed rings distortions. The temporal analysis of the introduced





quality metrics enables to calculate the non-invasive break-up time, which is used to describe the stability of the tear film.

The second part describes a method of the analysis of the Meibomian glands. Consecutive steps of image pre-processing are described and the index of gland's regularity is formulated. Its usability in the assessment of the tarsal glands dysfunction has been verified and future work needed to improve its efficiency is also discussed.

The summary of research is unfortunately rather short (18 pages with figures, tables and plots) and many details are to be searched for in the summarized publications. This is rather inconvenient for the reader who is forced to read carefully both the summary and the papers contained in the appendix to find some information about the details. In the view of the reviewer, it would be desired that the summary contains some additional plots, tables, illustrations instead of the repetition of the material already published in the paper. What is disturbing, the research summary contains errors not present in the summarized papers. For example: the basic equation 1, (p. 72) is not correct, volume element is called voxel (p. 72), pixels which are portions of the object and not image are counted, (p.72), the range of the index (p. 75) seems to be [0.88,1.12] . This errors are irritating and forces the reviewer to continuously compare the research summary with the referenced papers.

The third part of the thesis is the collection of 5 journal papers and 2 conference contributions:

C. Llorens-Quintana, D.R Iskander, *Assessment of tear film using videokeratometry based on fractal dimension*, Optometry and Vision Science, Sci. 2018 Jan;95(1): 32-42, IF=1.9

C. Llorens-Quintana, D. Szczesna-Iskander, D.R Iskander, *Supporting dry eye diagnosis with a new method for non-invasive tear film quality assessment*, Optometry and Vision Science, in press.

C. Llorens-Quintana, M. Mousavi, D. Szczesna-Iskander, D.R Iskander, *Non-invasive pre-lens tear film assessment with high-speed videokeratometry*, Contact Lens and Anterior Eye. 2018 Feb;41(1):18-22, IF= 1.988

C. Llorens-Quintana, D. Szczesna-Iskander, D.R Iskander, *A unified approach to tear film surface analysis with high speed videokeratometry*, submitted to J. Opt. Soc. Am. on October 24, 2018

C. Llorens-Quintana, L. Rico-del-Viejo, P. Syga, D. Madrid-Costa, D.R Iskander, *A novel automated approach for infrared-based assessment of Meibomian gland morphology*, submitted to Trans. Vis. Sci. Tech on August 2, 2018

C. Llorens-Quintana, P. Syga, D.R Iskander, *Automated image processing algorithm for infrared meibography*, Proc. of Imaging and Applied Optics 2018, OSA Technical Digest (Optical Society of America, 2018), paper IM3B.3

C. Llorens-Quintana, D. Szczesna-Iskander, D.R Iskander, *Efforts towards standardizing high speed videokeratometry based tear film assessment*, Proc. of Visual and Physiological Optics, 2018

Two publications have been already printed in journals with impact factor. The quality of the remaining papers makes their publication highly probable.

### Critical Remarks

The thesis is technically sound. The reviewer noticed some typing errors, however the thesis is very well written in clear and concise manner and nicely illustrated. The plots and tables were correctly prepared. The performed statistical analysis is also of excellent quality. However, the reviewer would like to make some remarks and suggestions:

1. The approach of the estimation of fractal dimension using the Fourier transform should be addressed in the thesis.
2. The influence of the transformation to polar coordinates on the fractal dimension is not discussed in the thesis.
3. The application of other measures describing the texture regularity has not been fully addressed in the thesis.
4. It is not clear if the indicators described on page 75 are calculated for the whole image as depicted in Fig. 12 or only in the region where the transformed area of interest is present.
5. The reference to the work of B. Mandelbrot should be corrected.
6. Image opening can be regarded as background estimation for large structural elements (SE) only, (rolling ball). If the SE is small, then it is used for the detection of local maxima (top-hat transformation).
7. Canny algorithm cannot be defined as the first derivative of Gaussian, (p. 120).
8. Edge detection, using first or second derivatives should not be used for the detection of edges in binary images, in which the contour is already created (p. 120, p. 190).

These shortcomings do not substantially affect the quality of the work and do not disqualify it in any way.

### Conclusions

The main goal of the thesis has been achieved. The Author correctly highlighted the contribution of the thesis and also noticed the limitations of the proposed methods. The thesis shows clearly that the PhD candidate has a comprehensive understanding of the context of her work. Thus the thesis, that "*Advancing in robust and automated ways of tear film and Meibomian glands analysis would result in better estimation of tear film quality and lead to better diagnosis and understanding of DED*" has been proved.

The obtained results are well presented and their interpretation is at a high scientific level. The candidate has an extensive expertise in the application of image processing techniques to the problems of pictorial data analysis and description. Therefore, I am of the opinion that the thesis fulfils the provisions of Art. 13, par. 1, of "The Act on academic degrees and academic title, and degrees and title in the field of art (Dz. U. z 2016 r. point. 882, 1311.)" and I recommend to admit Clara Llorens-Quintana to public defense of her thesis.

I would like also to propose to distinguish the doctoral dissertation due to the scientific novelty of the submitted work, an extensive range of research, meritorious presentation and discussion of obtained results already confirmed by two papers published in renowned journals.

Bogdan Smolka

