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Review of Ph.D. thesis "Anatomical and Structural Changes of Anterior Eye with Age" by Danilo Andrade de Jesus

In the submitted thesis Mr. Danilo Andrade de Jesus presents a number of methods to assess important parameters of the anterior part human eye in vivo. The Author focuses mainly on the human cornea and the eye surface. The obtained results linking macro- and microstructural features of the human cornea imaged by optical coherence tomography with short- and long- term changes occurring in the eye as well as with the intraocular pressure, will be in my opinion, valuable for the scientific society.

Layout and organization of presented thesis is sound and clear. The dissertation is divided in 8 chapters: Introduction, 6 main chapters and conclusions. The main text is preceded by Abstract, lists of acronyms used in the text as well as lists of tables and figures. Additionally, the separate list of Author's publication containing the results presented in the dissertation is provided.

The first introductory chapter ("Introduction") explains the needs of performing the research the Author decided to follow and points out the specific research goals he aimed to solve. It also presents a clear outlook of the organization of the thesis greatly improving the navigation in the text. I personally like figure 1.1 that provides the reader with a map of problems addressed by the Author in the dissertation that links chapters with publication and conference proceedings.

The second chapter ("Anterior Eye") provides the reader information about the human eye globe and more specifically about the anatomy of the anterior segment of the eye. It also discusses the current knowledge of changes that occur in the ageing cornea focusing on corneal thickness and structural changes. The chapter also gives a glance on the current attempts to understand corneal biomechanics and its impact on intraocular pressure measurements or pathogenesis. This chapter is well written and gives comprehensive overview of concepts relating to the scope of the dissertation.

I have only one minor concern about this chapter:

- I find it surprising that, regarding the fact that a great part of the work is related to cornea, there is no figure depicting the anatomical structure of the cornea. A figure between

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current Figure 2.2 (showing the whole anterior chamber of the eye) and Figure 2.3 (presenting organization of collagen lamellae in the stroma) would be very helpful to understand OCT images of the cornea presented in the following chapters.

The third chapter ("Structural Changes") focuses on possibility to observe the short-term and age-related structural changes in the cornea using images obtained with Optical Coherence Tomography (OCT). The assumption made by the Author is that the intensity distribution of OCT images of corneal stroma can deliver useful information about corneal structure. To prove this assumption a number of distributions is fit to experimental data and goodness of fit is analyzed for each of them with Kolmogorov-Smirnov test followed by Akaike's Information Criterion. As a result of this procedure the Generalized Gamma distribution (GG) was selected as the distribution best fitting to corneal data. Next, the parameters of GG were presented to show statistically significant difference for different age groups and for statistically significant change as a function of time during relaxation after inducing corneal swelling. Additionally, age dependence of the recovery speed after induced swelling was observed with use of one of the GG parameters, but the test group was too small to assess its statistical significance. The results described in this chapter may be, in my opinion, of great practical usefulness for OCT and ophthalmology communities. Nevertheless, I have several concerns about the assumptions and procedures used in this chapter:

- The first one is the assumption that intensity fluctuations in the stroma are caused by the speckle. In my opinion, only part of the fluctuations is caused by the signal degrading speckle. Important part of the fluctuations is caused by the layered structure of the stroma formed by the collagen lamellae (as described in chapter 2). This layered structure can be easily observed provided a speckle reduction technique is used (as in ref. 171), but is also present in standard OCT imaging of cornea (i.e. Fig. 3.2 and following). However, it has to be admitted that the procedure of finding the best distribution to fit the experimental data is in fact independent on assumptions concerning the nature of intensity fluctuations.
- Minor concern is about inconsistency in critical value plotted in Figure 3.6 (~0.075), and mentioned in the text (0.05). It seems that for the reasoning in the subsection 3.5.2 the Author used methods that were below level 0.075 what made the Rayleigh distribution to undergo Akaike's Information Criterion testing, while it evidently should be rejected.
- Another minor concern is about the procedure of calculating Akaike's Information Criterion. If I understand correctly equations 3.5 and 3.6 (the parameters n, L_k and p_k are not precisely defined – I guess that n is the number of points in the ROI, L_k in Eq. 3.6 is calculated from Eq. 3.5 and p_k is a number of parameters specific for a distribution), for ROI consisting of 67500 points the first term of Eq. 3.6 is in the range of thousands (what is proven by Fig. 3.7). In such a case cannot the second term be neglected? A table summarizing the parameters and AIC values for all the distributions would also be useful.

The fourth chapter ("Scleral Radius Estimation") explores the possibility to precisely measure the scleral radius using data from Eye Surface Profiler, a Fourier domain profilometer that acquires two images of projected fringes only from the surface of the eye. Corneal and scleral surface from are separated using a simple routine and two spheres are fit to the surfaces using least-squares estimation. The obtained results for both artificial eye and human eyes showed high precision and repeatability of the presented approach. The method was later on use to find correlation between calculated corneal radius and other eye biomarkers as axial length, anterior chamber length, corneal thickness and white-to-white diameter and the only significant correlation was found with axial length.

I have following concerns about the methodology used in this chapter:

- The Author utilizes in this chapter two methods: one with use of additional information about axial length of the eye (from IOLMaster 700) and the second without this additional information. As shown in Table 4.1, the results obtained with the two techniques differ significantly. Only the first method is used to search correlations with other parameters, except the comparison for Table 4.1. However, only the second method is described in detail in 4.4 section. A clear description how to introduce the additional knowledge about axial length to the model is missing.
- Figure 4.7(a) presents axial length form IOLMaster (I assume that as it is not explicitly mentioned) as a function of calculated scleral radius. Strong correlation is not surprising since the axial length should be twice the scleral radius (assuming spherical model) plus the distance between corneal apex and interpolated scleral surface. However, this correlation does not necessarily mean that the scleral radius is correctly retrieved, since the scleral radius is also dependent on the axial length. In my opinion, similar correlation plots should be presented for the second method (with no additional axial length measurement), and both methods should be analyzed in terms of goodness of fit to the experimental data.

The fifth chapter ("Corneoscleral Demarcation") introduces two techniques to estimate the limbus position using data from the Eye Surface Profiler and compares them with two techniques that use only intensity of the anterior eye image. In the first technique scleral and corneal surfaces are separately fit with Zernike polynomials while in the second the raw elevation data was weighted by the normalized intensity data from anterior eye image. The comparison provided by the Author indicates that all of the techniques give results that significantly vary between each other. This is explained by the Author in the summary as being the result of different physical criteria used by topographical and image methods. Additionally, the limbus is a transition zone and there is no agreement how to estimate its exact position.

In this chapter I only have minor concerns about the notation:

- Equation 5.1 should have subscripts in functions $f(r,\alpha)$ on the right-hand side of the equation as they are fits to inner and outer segments. In Eq. 5.8 the variable r is not present on the right-hand side of the equation.
- There are inconsistencies in notation between this chapter an previous ones. For example "inner" and "outer" segments in chapter 4 are named "corneal" and "scleral" segments. Same notation should also be kept in Eqs. 4.3-4.5 and Eqs. 5.5-5.7.

The sixth chapter ("Intraocular pressure") explores the influence of micro- and macrostructural properties of the cornea on the intraocular pressure assessed by applanation tonometry. It has been found that parameters of Generalized Gamma distribution fit to intensity structural OCT tomograms using methodology introduced in second chapter of the thesis correlate with IOP. A two parameter model of the IOP as a function of central cornea thickness (macrostructural parameter) and the scale parameter of the GG distribution (microstructural parameter) was proposed.

The seventh chapter ("Ray Tracing") describes a procedure to perform ray tracing using Chebyshev polynomials fit to surfaces in the model eyes and human eyes measured with videokeratoscope. The proposed technique expands the one-dimensional method of Gagnon et al. to two dimensions by fitting experimental data with two-dimensional Chebyshev polynomials.

I have the following concerns about the results presented in this chapter:

- The refracted ray in Figure 7.2 is erroneously placed on the same side of the vector normal to the surface. Although this seems to be only a drawing mistake as the result are apparently correct, this should be corrected.
- In figure 7.2 the Author should add the definition of x and z axes.
- Although the whole chapter is about using two-dimensional Chebyshev representation of surfaces no definition of the 2D Chebyshev polynomials is given.
- The Eqs 7.13 and 7.14 should be explained in more detail as their derivation is hard to understand. For example what is symbol N in equation 7.13? where is the result of Eq.7.14 used in Eqs. 7.15-7.16?
- Figure 7.4 that presents the flowchart of the algorithm should be described more exhaustively at least with the numbers of equations that are used in each step. Additionally, it seems to lack one step after "Intersection" which should be calculating the new propagation direction (Eqs.7.15-7.16). If the new direction is calculated in the step "Ray's direction" then a relation between Eqs. 7.7 and 7.16 should be explained. I also do not understand what "diff surface" means.

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In conclusion, I am convinced that the thesis fulfils the provisions of Art. 13, par. 1, of "Ustawa o stopniach naukowych i tytule naukowym oraz o stopniach i tytule w zakresie sztuki (Dz. U. z 2016 r. poz. 882, 1311.)".

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