Review of the Doctoral Dissertation

Candidate: Maria Miażdżyk

Title of the dissertation: *Estimation of corneal light scattering parameters which are independent of external factors and anterior eye geometry*

Institution: Faculty of Fundamental Problems of Technology, Wrocław University of Science and Technology

Supervisors: Prof. D. Robert Iskander; Dr Alejandra Consejo Vaquero

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Reviewer: Prof. Edward Wylęgała MD, PhD

1. General assessment

The dissertation addresses a well-defined and clinically relevant problem in biomedical optics: the fact that currently used measures of corneal backscatter - in particular Scheimpflug-based densitometry and, more recently, OCT-based densitometry - are confounded by factors that have little to do with the genuine microstructural state of the corneal tissue. The candidate builds a coherent narrative around a single research hypothesis ("creating objective estimators of corneal light scattering parameters independent of confounding factors will improve their diagnostic value") and pursues it across three internally consistent sub-projects:

1. Identification and compensation of confounding factors (anterior chamber depth, pupil size, central corneal thickness, image background) in Scheimpflug densitometry, culminating in a two-branch preprocessing algorithm that combines column-based normalization with the "second corneal shoulder" and contrast-limited adaptive histogram equalization (CLAHE).

2. Quantification of the confounding effect of the corneal epithelium on stromal OCT speckle, demonstrated on 11 porcine corneas imaged before and after epithelial debridement, with an estimation error attributable to the epithelium reported to exceed 20% depending on stromal depth.

3. Development of a digital OCT phantom of the corneal stroma based on an adapted Monte Carlo photon transport model coupled with an OCT signal-formation equation, and - building on this phantom - a novel statistical-matching method that estimates the scattering coefficient μ_s and the anisotropy factor g of porcine corneal stroma under in-vivo-compatible conditions, yielding $\bar{\mu_s} = 0.146 \pm 0.020\ \mathrm{mm}^{-1}$ and $\bar{g} = 0.893 \pm 0.021$.

The scientific output accompanying the dissertation is, in my view, outstanding for a PhD candidate in this field: three first-author papers in Biomedical Optics Express (2022, 2023, 2026), five conference contributions at high-profile meetings (EMBC, ARVO, EVER, VPO), and a successfully awarded PRELUDIUM-22 grant from the Polish National Science Centre based on the ideas developed in the third project. Each main research chapter (2, 3, 5–6) is tightly mapped onto one of these peer-reviewed articles, which is itself a form of external validation of the work.

The dissertation is well organized, logically structured (introduction: three projects in chronological order of both scientific logic and the candidate's maturation: final conclusions), and written in fluent, scientifically precise English. The candidate's single-author contribution is clearly declared and credible: the MATLAB implementation of all algorithms - including the manual re-implementation of the Monte Carlo photon-transport routine - is the work of the candidate, and the only non-retrospective data acquisition (the hypoxia pilot study in Chapter 4) was carried out by her personally.

2. Strengths

A genuinely novel methodological contribution. The statistical-matching method in Chapter 6 - in which a single, non-averaged experimental OCT B-scan is matched against a look-up map of 165 simulated digital phantoms via three complementary distance measures (ΔCR, D_{RMS}, D_{KL}) - appears to be the first OCT-based method that produces corneal μ_s values consistent in order of magnitude with independent ex-vivo integrating-sphere and spectroscopic measurements (Yust et al.; Regal et al.). Earlier OCT-attenuation-based approaches (Bocheux et al.; Ge et al. using Vermeer's method) yielded values one to two orders of magnitude higher. This is, in my assessment, the most important original result of the dissertation and a real contribution to the field.

A mature handling of confounders. The work in Chapter 2 is methodologically careful: the candidate does not stop at "we found a correlation with age" but systematically dissects which

correlations reflect biometry (ACD, PUP, CCT) and background pixel intensity rather than microstructural aging. The two-branch preprocessing pipeline (second-corneal-shoulder normalization for the Weibull scale and mean-intensity parameters, CLAHE for the Weibull shape parameter) is an honest engineering solution: rather than force a single method to do everything, the candidate acknowledges that different densitometry parameters respond to different preprocessing and documents this transparently.

Transparency about what did not work. Both Chapter 2 and Chapter 6 are presented in chronological order and explicitly describe failed attempts - the Kolmogorov–Smirnov p-value map producing values of order 10^{-8}, the instability under data pruning, the rejected non-linear two-variable fits. This kind of disclosure is uncommon in dissertations and is, I believe, genuinely useful for future researchers. The candidate also correctly identifies (citing Wasserstein & Lazar's 2016 ASA Statement on p-values, ref. [178]) the logical trap of drawing inferences from vanishingly small p-values on large samples.

Rigor in experimental design where it matters most. The porcine dataset used in Chapters 3 and 6 is notably well controlled: same breed and age, abattoir-sourced within 3 hours post-mortem, PBS moistening throughout, a custom rig maintaining IOP at 20 mmHg, and OCT imaging within the depth of focus. The remarkably low between-eye variability of the final μ_s and $\hat{g}$ estimates ($\sigma \approx 14\%$ and 2%, respectively) is, as the candidate correctly argues, evidence for the method's internal consistency rather than against - particularly because the minima values themselves of the three distance measures differ between eyes, which would not be the case under a purely systematic error.

Bridging clinic and physics. The dissertation successfully spans a range that most PhD theses do not: from clinically oriented image processing (Chapter 2) through physiological experiments (Chapters 3–4) to a genuinely physics-based simulation and inverse-estimation framework (Chapters 5–6). The closing vision of OCT as an "all-in-one" diagnostic platform is not merely rhetorical - the dissertation has delivered concrete building blocks toward it.

3. Weaknesses and issues requiring clarification

I identified the following issues that the candidate should address, either by clarification during the defence or, where appropriate, by minor editorial correction before archiving.

1. **The hypoxia pilot study (Chapter 4) is methodologically underpowered and its placement is somewhat awkward.** The study includes only two participants - one younger, one older - who also served as the experimenters themselves, with acquisitions cross-collected between them. The candidate herself acknowledges on p. 66 that "no strong conclusions can be drawn regarding the reported speckle statistic values." While I accept the author's framing as a "pilot," the chapter nevertheless occupies a full chapter of the dissertation and presents figures showing trends (e.g. differential recovery of anterior vs. posterior stroma) from which the reader is inevitably invited to draw conclusions. I would expect either (a) a stronger justification for devoting a full chapter to n=2 results, or (b) a clearer demotion of this material to an appendix or to a single figure within Chapter 3. This is, to my mind, the clearest methodological weakness of the dissertation as a whole.

2. **Non-correction for multiple comparisons in Chapter 2 is flagged but not resolved.** The candidate notes on p. 42 that multiple-comparison corrections (e.g. Bonferroni) were not applied and that "some may view [this] as a limitation." She then argues that all significant p-values were ≤ 0.005 and would survive a Bonferroni-adjusted threshold of $\alpha \approx 0.007$ for seven tests. This is a reasonable post-hoc defence, but given that the core claim of the chapter - that particular biometric variables confound densitometry - rests precisely on the statistical significance of correlations across multiple ROIs (T, C, N), groups (Y, Y and O, O), and parameters, I believe the dissertation would be strengthened by a formally corrected analysis rather than an appeal to "would have survived." A related concern: on p. 39 the residual significant correlation between β_M and CCT in the central ROI for the combined Y and O group is acknowledged but not fully explored - is this a methodological residual or a genuine biophysical signal?

3. **The digital phantom in Chapters 5–6 uses a time-domain OCT signal model to simulate a spectral-domain OCT instrument.** The candidate honestly acknowledges this on p. 83 ("the experimental corneal images were recorded with the SOCT REVO 80, which is an SD-OCT device, while the equation used in this study is dedicated to time-domain OCT") and points to alternative formulations (Lu et al.; Mao et al.). However, given that the central claim of Chapter 6 is quantitative agreement with ex-vivo reference values of μ_s, the question of how much of that agreement is a property of the statistical-matching machinery versus the specific signal model used is not fully

addressed. At minimum, a sensitivity analysis showing that the estimated μ_s and g are stable under a change of OCT signal model would greatly strengthen the claim.

4. **Minor editorial and technical points.** A few errors and inconsistencies should be corrected in the archival version: on p. 44 "the problem **od** decoupling" (should be **of**); on p. 87 "$\hat{F}_{k,\,EXP}$" in Eq. (6.4) should almost certainly read $\hat{F}_{k,\,SIM}$ given the surrounding text; on p. 87 "yelding" should be yielding; and the phrasing of the age groups ("141 young and 73 old subjects") in the English *abstract* does not match the Polish *streszczenie* exactly. These are small matters but worth tidying up.

4. Suggested questions for the public defence

1. **On the pilot hypoxia chapter (Chapter 4):** Given the n=2 design and the fact that the two subjects were also the experimenters, what specific conclusions of this chapter do you consider robust, and what would a properly powered follow-up experiment look like - in particular, how would you separate epithelial swelling from stromal swelling, which you rightly note cannot be done pharmacologically or physiologically?

2. **On the time-domain vs. spectral-domain OCT signal model:** Your simulated phantoms use the Kirillin et al. TD-OCT equation, but your experimental data come from an SD-OCT device (SOCT REVO 80). To what extent do the values $\bar{\mu_s} = 0.146$ mm^{-1} and $\bar{g} = 0.893$ depend on this choice? Have you performed - or can you sketch - a comparison with an SD-OCT-appropriate model (e.g. Mao et al.) showing that the group-mean estimates would remain stable?

3. **On the confounder compensation in Chapter 2:** The correction successfully decorrelates densitometry from ACD, PUP, and (via the 13-pixel ROI trick) CCT, but a residual age-correlation in $\hat{\alpha_M}$ (central and nasal) and $\hat{\beta_M}$ (nasal) remains. In your view, does this residual reflect genuine microstructural aging that the Corvis ST can just barely resolve, or is it a further confounder (e.g. eyelid shadow, iris pigmentation - the Alanazi 2024 and Consejo / Arizcuren findings you discuss on p. 43)? What experiment would discriminate between these two interpretations?

4. **On clinical translation and the Pentacam HR:** You are explicit that your preprocessing pipeline has been validated only on Corvis ST data and needs re-evaluation on the clinical gold-standard Pentacam HR. Given that Pentacam HR reports

densitometry on a rescaled 0–100 range rather than raw 0–255 pixel values, and given the different illumination geometry, do you expect your second-corneal-shoulder normalization to transfer directly, or will the method need structural adaptation?

5. **On the broader vision - the "all-in-one" OCT platform:** Your closing conclusion envisages OCT as a comprehensive diagnostic platform for the cornea. Concretely, what is the minimum set of extensions to the digital phantom (bilayered epithelium–stroma? corneal curvature? a Gaussian-beam source? non-zero μ_a?) that you consider necessary before the statistical-matching estimator could be trialled on in vivo human data, and in roughly what order of priority?

5. Overall recommendation

Subject to the minor editorial corrections listed above and a satisfactory defence of the issues raised in Chapter 3 and Chapter 4, the dissertation clearly meets - and in the originality of Chapter 6, exceeds - the standards expected of a doctoral dissertation in biomedical engineering / applied optics at a leading Polish technical university. The work is internally coherent, methodologically honest (including about its own failed attempts), externally validated by three peer-reviewed first-author publications in a reputable journal and by an awarded national grant, and delivers at least one genuinely novel scientific contribution (OCT-based statistical-matching estimation of μ_s and g for corneal tissue).

I hereby recommend MSc Eng. Maria Miażdżyk for admission to the further stages of the doctoral proceedings at Wrocław University of Science and Technology on the basis of the doctoral dissertation entitled "Estimation of corneal light scattering parameters which are independent of external factors and anterior eye geometry".