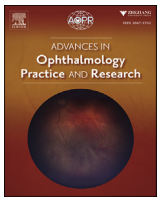
Advances in Ophthalmology Practice and Research 3 (2023) 101–102

Contents lists available at ScienceDirect

Advances in Ophthalmology Practice and Research

journal homepage: www.journals.elsevier.com/advances-in-ophthalmology-practice-and-research



Commentary

Image registration: Required for all ophthalmic imaging as demonstrated by optoretinography

Ronald A. Schachar [a], Ira H. Schachar [b], Andrzej Grzybowski [c,d,*]

[a] Department of Physics, University of Texas at Arlington, Arlington, TX, USA
[b] North Bay Vitreoretinal Consultants, Santa Rosa, CA, USA
[c] Ophthalmology, University of Warmia and Mazury, Olsztyn, Poland
[d] Institute for Research in Ophthalmology, Foundation for Ophthalmology Development, Poznan, Poland

1. Introduction

Ophthalmology focuses on relating structural changes to function and disease. From biomicroscopy, ophthalmoscopy and fundus photography, to electroretinography and visual evoked potentials the clinical purpose is to objectively assess visual function. However, these techniques are macroscopic and only grossly related to visual acuity. With the development of optical coherence tomography (OCT) *in vivo* histological resolution of the retina has become routine. OCT has revolutionized monitoring and treatment of retinal diseases. In addition, by measuring the density of photoreceptors and lengthening of photoreceptor outer segments (OS) in response to light phototransduction, Fig. 1., adaptive optics (AO) and optoretinography (ORG), respectively, have set the clinical foundation for objectively assessing a specific level of visual acuity.[1]

2. Optoretinograph

There are three types of ORG, phase optoretinography (pORG), intensity optoretinography (iORG) and spatio-temporal optical coherence-tomography (STOC-T). pORG combines adaptive optics (AO) and optic coherence tomography (OCT) to measure the initial photoreceptor OS transient decrease in length that is followed by a longer and larger nonlinear increase that occurs from phototransduction of a brief light flash.[2] Both the rate of the transient shortening and the sustained increase in OS length are related to the flash energy. These changes in OS length alter photoreceptor reflectance of individual cones that can be measured by both pORG and intensity optical retinography (iORG).

iORG combines a scanning laser ophthalmoscope (SLO) with AO to measure the reflectance of single photoreceptors.[3] pORG and iORG noninvasively, objectively and precisely quantify photoreceptor response that directly relates to visual function. The differences in timescale and change in cone OS length enable *in vivo* identification of cone spectral type that reveal the phototransduction cascade of the underlying photoreceptor neuroprocessing required to fully understand color vision and retinal disease. For example, in retinitis pigmentosa (RP) cone pORG responses decrease with increasing RP severity. Short--wavelength–sensitive cones are more vulnerable to RP than medium- and long-wavelength–sensitive cones. Decreases in cone OS length and reflectance arise earlier in RP than changes in cone density.[2]

STOC-T captures a flicker stimulated optoretinogram from a light adapted subject over an area of 1.7×0.85 mm^2 between the fovea and the optic nerve to measure the modulated photoreceptor optical path length (OPL) amplitudes that are related to the flicker frequency.[4] Moreover, STOC-T can map the photoreceptors OPL amplitudes in response to a spatial pattern of different frequency flickering light stripes that will potentially clinically enable objective *in vivo* assessment of the visual field and contrast sensitivity.

Similar to OCT, ORG will eventually be a paradigm changing clinical technique. Ophthalmologists will be able to objectively measure visual acuity, visual fields and contrast sensitivity *in vivo* at the photreceptor level. These marvelous advances rely on the speed of image acquisition and fundamentally image registration.

3. Image registration

Image registration is standard practice in medical imaging to minimize the effects of motion artifacts.[5] Image registration involves superimposing two images by precisely aligning reference features that are common to both images. Images from different modalities, for example, computer-axial tomography scan (CAT-scan), magnetic resonance imaging (MRI) and ultrasound, positron emission tomography (PET) and nuclear magnetic resonance imaging (NMRI) can be image registered as long as they have corresponding nonchanging features in common that

* Corresponding author. Ophthalmology, Head of the Institute for Research in Ophthalmology, Gorczyczewskiego 2/3, 61-553 Poznan, Poland.
E-mail address: ae.grzybowski@gmail.com (A. Grzybowski).

https://doi.org/10.1016/j.aopr.2023.03.001
Received 26 February 2023; Accepted 7 March 2023
Available online 8 March 2023

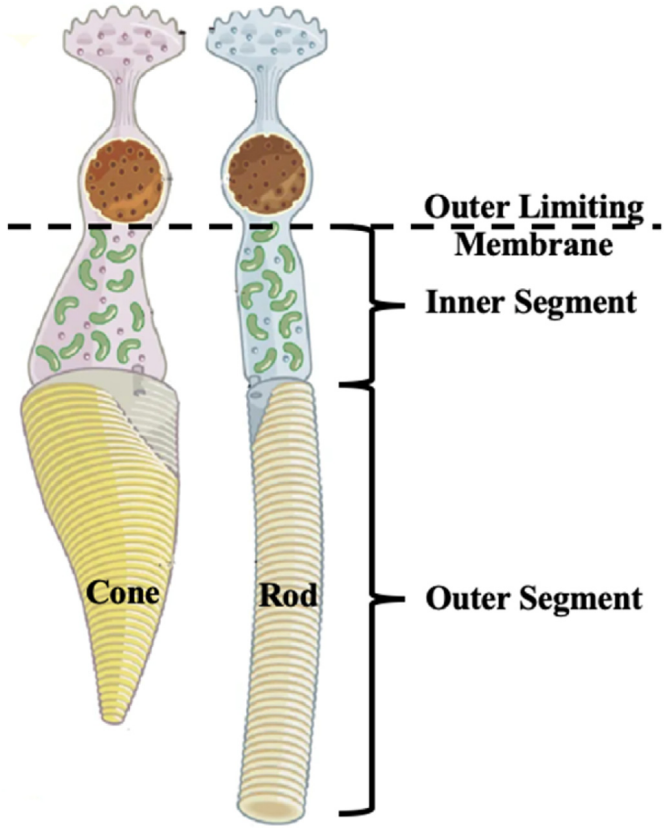


Fig. 1. Cone and rod photoreceptors. The outer segments lengthen when light phototransduces the photopigment.

do not change position or dimensions during the capture of each image. By aligning the unchanging reference features, differences between the compared images can be accurately detected.

Image registration has significantly improved measurement accuracy and detection of organ and tissue changes. This is especially important for ophthalmic imaging. Normal saccades, convergent and cyclo-torsional eye movements in addition to head and physiologically induced movements make image registration imperative for ophthalmic image comparisons. Image registration has become standard in OCT of the posterior segment of the eye and has led to significant improvements in resolution. Measurements of change in the retinal nerve fiber layer and central retinal thickness have become more accurate. Detection of subtle retinal and choroidal pathologies and disease progression, not visible in the past, are now routinely observed. Image registration continues to improve with fast computer algorithms.

4. Anterior segment image registration

Unfortunately, image registration of the anterior segment has lagged behind. For example, many have assumed monocular viewing can avoid extraneous eye movements during accommodation; however, even with monocular viewing the eye cyclotorts and translates.[6] Commonly the corneal reflex is used for aligning the eye. This is insufficient and has led to the incorrect belief that the cornea and sclera change shape during accommodation. When images were registered, there is no evidence that the cornea or sclera change shape during accommodation[7] as Thomas Young demonstrated in 1801. Another technique is to use the center of the pupil for eye alignment; however, as the pupil constricts its center shifts so it is not a non-changing reference for comparing images. Commonly statistical methods are used in the comparison of ophthalmic images; however, eye movements are not always random; e.g., convergent and torsional eye movements are directly related to the magnitude of accommodation as demonstrated by the accommodative/convergence (A/C) ratio.

The need for anterior segment image registration is exemplified by studies that evaluated accommodation without image registration. These studies reported exaggerated increases in anterior chamber depth, lens thickness and equatorial diameter of approximately three or more times greater than when image registration was performed.[8,9]

5. The future

Unexpected physiological and pathological subtle changes of the retina are now commonly observed with posterior segment OCT for the benefit of patient care.[10] ORG will potentially significantly add to these advances. All being made possible by image registration that itself will continue to improve. By simultaneously recording from at least 6 individual high speed imaging devices located in different spatial positions and including image registration, changes in the contour and dimensions of the eye and its components will be measurable with nanometer accuracy. This will lead to remarkable advances in imaging both the eye anterior and posterior segments resulting in improved diagnosis and treatment similar to the advances in tennis, cricket and golf made by Hawk-eye.

Study approval

Not Applicable.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Cheng H, Ciuffreda KJ, Jiang H, et al. Cone parameters in different vision levels from the adaptive optics imaging. *Medicine (Baltim)*. 2021;100, e25618. https://doi.org/10.1097/MD.0000000000025618. PMID: 33879731 PMCID: PMC8078260.
2. Lassoued A, Zhang F, Kurokawa K, et al. Cone photoreceptor dysfunction in retinitis pigmentosa revealed by optoretinography. *Proc Natl Acad Sci USA*. 2021;118, e2107444118. https://doi.org/10.1073/pnas.2107444118. PMID: 34795055 PMCID: PMC8617487.
3. Warner RL, Brainard DH, Morgan JIW. Repeatability and reciprocity of the cone optoretinogram. *Biomed Opt Express*. 2022;13:6561–6573. https://doi.org/10.1364/boe.471990. PMID: 36589578 PMCID: PMC9774868.
4. Tomczewski S, Wegrzyn P, Borycki D, et al. Light-adapted flicker optoretinograms captured with a spatio-temporal optical coherence-tomography (STOC-T) system. *Biomed Opt Express*. 2022;13:2186–2201. https://doi.org/10.1364/BOE.444567. PMID: 35519256 PMCID: PMC9045926.
5. Brown LG. A survey of image registration techniques. *ACM Comput Surv*. 1992;24: 325–376. https://doi.org/10.1145/146370.146374.
6. Buehren T, Collins MJ, Loughridge J, et al. Corneal topography and accommodation. *Cornea*. 2003;22:311–316. https://doi.org/10.1097/00003226-200305000-00007. PMID: 12792473.
7. Schachar RA. The cornea is stable during accommodation. *J Cataract Refract Surg*. 2006;32:376. https://doi.org/10.1016/J.JCRS.2005.12.087.
8. Grzybowski A, Schachar RA, Gaca-Wysocka M, et al. Image registration of the human accommodating eye demonstrates equivalent increases in lens equatorial radius and central thickness. *Int J Ophthalmol*. 2019;12:1751–1757. https://doi.org/10.18240/ijo.2019.11.14. PMID: 31741865 PMCID: PMC6848867.
9. Schachar RA, Mani M, Schachar IH. Image registration reveals central lens thickness minimally increases during accommodation. *Clin Ophthalmol*. 2017;11:1625–1636. https://doi.org/10.2147/OPTH.S144238. PMID: 28979092 PMCID: PMC5602687.
10. Vujosevic S, Parra MM, Hartnett ME, et al. Optical coherence tomography as retinal imaging biomarker of neuroinflammation/neurodegeneration in systemic disorders in adults and children. *Eye*. 2023;37:203–219. https://doi.org/10.1038/s41433-022-02056-9. PMID: 35428871 PMCID: PMC9012155.