

A compact instrument for the objective Measurement Of Macular pigment Optical density (MOMENTO)

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ABSTRACT

The project focuses on the development of a compact instrument for the objective and in-vivo measurement of the optical density of the macular pigment, based on a laboratory prototype. During the project, the instrument was redesigned to reduce its form factor and its cost, as well as to increase its accuracy and speed of measurement, in order to meet clinical needs. A first compact prototype was developed and tested in a small cohort of healthy volunteers.

Keywords: Physiological Optics; Ophthalmology; Fundus imaging.

1. INTRODUCTION

The term macular pigment (MP) is a collective name for three carotenoids, of purely dietary origin, found at the central part of the ocular fundus [1]. Its role in ocular function is thought to be twofold: first, acting as an optical filter, protecting the photoreceptors from the phototoxic effects of high-energy blue light [2], and, second, as an anti-oxidant, quenching free radicals in the retina [3]. Studies have shown correlation between the macular pigment optical density (MPOD) and age-related macular degeneration, one of the leading cause of blindness in the western world [4], [5]. Since, there is currently no treatment able to fully restore lost vision, early detection is important to prevent the disease to progress further. The MP can prove to be an important biomarker and act as an early warning sign for the disease. Finally, due to its relation to diet and other lifestyle parameters, such as smoking or obesity, it could be used as an overall marker of how healthy one's lifestyle is.

Despite the potential importance of the MP, it has not yet been part of the standard eye exam. The reason for that is that there are currently only a small number of instruments that can measure it and they are either bulky and expensive, not accurate and take time. In this project, we developed an optical system that uses an innovating method, based on

1. the illumination of the ocular fundus with dual-wavelength, structured light using LED sources.
2. the collection of the reflected signal with a high-speed and high-sensitivity photodetector.
3. the processing of the harvested signal using analysis in the frequency domain.

This new technique allowed the development of an optical system, built specifically for the measurement of

MPOD. The use of LEDs, a single photodetector and low-cost optics allows for the construction of an overall low-cost instrument that can carry out the measurement accurately and within a few seconds.

During the project, a compact version of the laboratory prototype [6] was designed and built. The optics and the electronic parts of the system were redesigned. A user-friendly graphical user interface was developed in order for the instrument to be easily used by clinicians with very short training. A first validation of the clinical use of the instrument on a cohort of healthy subjects was carried out successfully in a clinical environment and the results were presented at conferences. In parallel, we worked on the development of a hand-held, stand-alone instrument featuring a raspberry-Pi and an on-board touch screen that could further reduce the portability, usability and significantly lower the cost of the instrument, making it apt for wider use.

2. STATE OF THE ART

Currently, there is only a handful of instruments used to measure MPOD. There are two methods to measure MPOD in vivo: one psychophysical, where the subject's input is required during the measurement and the optical, where no input is required by the subject. Both methods use the spatial and spectral properties of the macular pigment and the ocular fundus.

There are several different psychophysical techniques used for the measurement of MPOD, but the most used one is based on Heterochromatic Flicker Photometry (HFP)[7]. In this technique the subject is presented with a series of flickering light fields and the subject's task is to determine where the flickering becomes minimum or vanished completely. There are a number of commercial devices such as the MPSII (Elektron Eye Technology, Cambridge, UK) or the MPS

9000 (Tinsley Ophthalmic Instruments, Redhill, Surrey, UK). The technique is repeatable but makes a number of assumptions that can often lead to wrongly estimating the value of MPOD. Furthermore, the test itself is not easy for all subjects and can also be time consuming.

Optical methods illuminate the fundus with light of different wavelengths and analyse the reflected (or re-emitted in some methods) light from the fundus. These methods include reflectometry, autofluorescence and Rama spectroscopy. Currently, the only commercial instrument using this method is the fundus camera Visucam 200 (Carl Zeiss Meditec AG, Jena, Germany), which offers a module for the measurement of macular pigment. The instrument provides a quick measurement, yet it is not considered to be fully proven, the instrument is bulky and expensive, and therefore it is not considered apt for wide clinical use for MPOD measurements[8].

There is no golden standard in the measurement of MPOD, although it has been in the spotlight of research for more than two decades.

3. BREAKTHROUGH CHARACTER OF THE PROJECT

The project involved the development of an optical instrument for the in-vivo, quick, reliable and accurate measurement of MPOD. The instrument is based on the reflectometry method where light is delivered on the retina and the reflected light is captured by a light sensor, typically a camera. In the prototype instrument, LED sources of specific spectral, spatial and temporal properties were used and the reflected signal was captured using a high-speed, high-sensitivity photodetector. The instrument features a number of innovative elements:

- a specific spatial distribution of the source allowing to encode the spatial information in the illumination.
- the use of a photodetector to capture the reflected signal.
- the temporal modulation of the sources that allowed the analysis of the recorded signal in the frequency domain, hence the method was named Frequency Imaging (FI).

Tab. 1. Comparison of the current methods/instruments for the measurement of MPOD and the instrument developed in the project.

Name	Reliability	Accuracy	Validity	Cost	Time
<i>HFP</i>	High	Low	Medium	Medium	Long
<i>RE</i>	Medium	High	High	High	Medium
<i>AF</i>	Medium	High	High	High	Medium
<i>FI</i>	High	Medium	High	Low	Short

HFP = Heterochromatic Flicker Photometry

RE = Reflectometry

AF = Autofluorescence

FI = Frequency Imaging

The advantage of using a photodetector is two-fold: on the one hand the high-sensitivity compared to the traditional camera allowed fast, low-noise measurements with minimal retinal exposure to light, limiting the actual measurement to less than 200msec. A measurement below 200ms is faster than pupil reflex, and therefore there is no need for medically induced pupil dilation. The latter means that the measurement does not need to be performed by an ophthalmologist but, in most places, by non-medical health care professionals. Furthermore, since the analysis of the recorded is done in the frequency domain, the instrument is not affected by ambient light, leading to a more reliable measurement.

The optical design was such that the instrument was easy to construct and align, and reduce its cost, making large scale production possible.

A comparative table showing how each method/instrument performs in the measurement of macular pigment can be found below.

It is also important to note that the project refers to the application of a more generic method, that of Frequency Imaging, for the measurement of a specific ocular pigment. Once completed, it can act as a foundation for other applications of this technology in ophthalmology or elsewhere.

4. PROJECT RESULTS

The objective of the project was to develop a compact instrument for the measurement of MPOD, which would have the potential to become part of the standard eye exam. The instrument was based on a laboratory prototype [6] and an associated patented method [9]. The main focus of the project was to redesign the laboratory instrument and adapt the associated method, to be apt for clinical use and a potential scale up. As such, the first step of the project was to redesign the electronics of the instrument and more specifically the illumination (LEDs sources and drivers) and the imaging (photodetector and driver) electronics (WP1). Also, the optics were redesigned, focusing in reducing the form factor and the complexity of the instrument, and hence, the cost, without sacrificing its performance. The redesigned instrument was built on an optical breadboard. Furthermore, a user-friendly graphical user interface (GUI) was developed; the GUI was built so that it would be used by a person not involved in the development of the instrument and with limited knowledge of the method details. Subsequently a set of measurements was carried out on a healthy cohort of 51 volunteers to test the prototype instrument outside the laboratory environment. The measurements were carried out by a non-specialist,

after a short training in the use of the instrument. The results were presented at the Association for Research in Vision and Ophthalmology (ARVO) meeting 2020[10], which was meant to take place in Baltimore, USA, however, due to the CoViD-19 pandemic took place solely virtually.

Parallely to the development of breadboard version of the instrument, a fully portable, stand-alone instrument was designed, and a first prototype is being developed. The instrument has the same principle of operation but it uses custom electronics to carry out the measurement and the processing of the signal. Furthermore, the optical design was refined to further reduce the instrument's form factor, towards a handheld instrument. A single-board computer (raspberry Pi) is used to fully control the instrument, featuring a mini TFT touch screen. A pupil tracking algorithm was developed and used in the mini-instrument, in order to assist with the alignment of the subject during the measurement. The mini-instrument was presented at the ARVO – Imaging the Eye conference 2020 [11].

A series of outreach actions were carried out during the project. The focus audience of the actions at this stage of the project was ophthalmologists and optometrists. A mini lecture was given at the Athens Eye Hospital in Greece, one of Greece's leading clinics in ophthalmology, presenting the main principle of operation of the instrument, measurement details, as well as the current status in the macular pigment research. An invited lecture on the topic was also given at the South-Eastern European Ophthalmological Society meeting in Pristina in June 2019.

A website providing details on the project was built and it is being hosted at the partner's (Athens Eye Hospital) website (research.athenseyehospital.gr/momento).

5. FUTURE PROJECT VISION

5.1. Technology Scaling

The project was based on a laboratory prototype instrument built on an optical table at the Laboratorio de Optica at the Universidad de Murcia. Prior to the phase 1, the method was experimentally tested in the lab, presented at conferences, published in a scientific journal and the technology was patented (TRL1-3). During the project, the prototype was further developed in order to be more suitable for clinical use and preliminary tests were carried out at the partner (AEH) in a clinical environment on a cohort of healthy subjects (TRL4-5). In parallel, a handheld instrument is being developed that would significantly reduce the cost and the complexity. In phase 2 of the project the first step would be to produce a small number of prototype devices and send them to clinical partners at different locations. The clinical partners will carry out large scale measurements on volunteers and examine how various optical parameters

and specific ocular pathologies can affect the measurements (e.g. very high myopia, cataract). Also, a large cohort of healthy volunteers will be measured to establish a baseline value for MPOD. Development of the handheld, stand-alone version of the instrument will continue during phase 2 and will be tested by the clinical partners and further refined using their feedback. Other potential applications of the developed method will also be explored during phase 2 (eg. retinal oximetry). Furthermore, during phase 2 the preliminary work will be done to subsequently certify the instrument as a medical device, following the EU medical device regulation. Finally, an in-depth market analysis will be carried out, in order to determine the appropriate markets to initially launch the instrument. This will also examine legal matters on the use of the instrument by non-ophthalmologists (eg. optometrists or nutritionists).

5.2. Project Synergies and Outreach

Phase 2 of the project involves four distinct types of actions: scientific, clinical, technical and socio-economical. Currently, the consortium comprises of two partners: Laboratorio de Optica, Universidad de Murcia, Spain and the Department of Research, Athens Eye Hospital, Greece. The network will be expanded by including additional partners, and more specifically:

- two clinical partners specialised in ophthalmology
- a clinical partner specialised in nutrition
- a newly formed start-up company which will exploit the technology once finalised. The start-up, founded by the four inventors, will further advance the instrument technically, as well as be in charge of the preliminary steps needed for the certification of the instrument
- a commercial partner (medical device manufacturer) for the commercialisation of the instrument.

The current team has already canvassed the field and found a number of potential partners in the EU and the United Kingdom, as well as the United States and China. The main medium to disseminate the activities of the consortium will be the ophthalmology and vision science conferences. Past experience indicates that the instrument will be received positively by eye professionals and research groups. The instrument and clinical results will be presented at the ARVO conference in the United States and similar conferences in Europe and in Asia. Furthermore, a dedicate webpage of the consortium will be built, presenting the technology, results and the actions of the consortium. A series of seminars presenting the topic and the instrument will be given to clinicians in Greece and in Spain, acquainting them with the state-of-the-art and our technology. Finally, a brochure summarising the importance of MPOD in layman terms will be printed and distributed at the clinical partners.

5.3. Technology application and demonstration cases

A potential phase 2 will focus on developing a fully working compact prototype and a stand-alone, handheld prototype featuring the same principle of operation. The main objective of the instrument is to measure a biomarker (the macular pigment) that studies have shown that it has an importance in retinal health. Additionally, since it is directly related to a healthy diet and other environmental parameters such as smoking, obesity etc, it can be an index of a healthy lifestyle. As such the technology will be demonstrated to a number of different audiences; ophthalmology/optometry conferences where it will be presented to both researchers and clinicians, informing them about the new technology and convincing them of the use of the instrument in both clinical and research applications. The innovative aspects of the instrument will also be presented at engineering conferences (e.g. SPIE Photonics West) where the technology can be appreciated for its innovative elements and potentially explore new applications. The technology will also be demonstrated to investors to secure funding for a scale up in the technology. Finally, it will be presented to the general public, through outreach actions (see 5.2).

5.4. Technology commercialization

The commercialisation of the instrument is planned to be done through a start-up company, founded for the exploitation of the specific technology. The start-up company would be eventually founded by the four inventors in order to start more formal interactions with private investors. Additionally, preliminary contacts with companies from the medical certification field have been done to investigate the instrument's certification. Finally, a preliminary market analysis has been done for the EU and the UK market; a final market analysis and business plan will be done by an expert during a potential phase 2 of the project.

5.5. Envisioned risks

There are a number of risks involved in a potential ATTRACT phase 2 project. The risks, the associated likelihood, their impact and the actions to mitigate them are shown in tab. 2.

Tab. 2. Risk management of a potential ATTRACT phase 2

Risk	Likelihood	Impact	Mitigation action
<i>Failure to find partners</i>	Low	Low	There are already four partners who showed interested (UM, AEH, start-up company, Hospital Arritxaca). If no more partners are found, part of the budget will be allocated to

			outsource the needed actions.
<i>Failure to secure further funding for phase 3</i>	Medium	High	Efforts to secure private and public investment will be done by a dedicated team member from the start of a phase 2.
<i>Failure to complete handheld instrument</i>	Low	Low	Further develop current compact instrument.
<i>Delays due to CoVID-19 pandemic</i>	Low	Low	All involved partners have developed protocols to minimise delays due a potential new lockdown.

5.6. Liaison with Student Teams and Socio-Economic Study

The fundamental technology behind the instrument will be broken down by the inventors to MSc level and presented at the project's webpage. The presentation will include schematics of the system explaining the optical and opto-electronical components, explanation of how the signal processing is done with practical examples, animations on how the technology works, and a video by the inventors explaining the details of the instrument. One team member will be nominated to organise and carry out all dissemination and outreach actions as well as be the liaison with the MSc. Student teams. This team member will be also responsible to facilitated all needed information for the socio-economic study of the ATTRACT included but not limited to:

1. a report on the evaluation of different strategies for introducing new technologies into the clinical practice.
2. social media activity (facebook, twitter, ads) to outline the research findings on the role of nutrition and aging in the density of Macular pigment in the eye. We will assess the awareness level of our randomly enrolled patients following the afore-mentioned dissemination activities.

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