Pupillometry in clinical settings

Abstract

Assessment of pupil size and the pupillary light reflex (PLR) are critical for neurological examination. Pupillometry is a powerful diagnostic tool in diverse clinical settings (ER, OR, ICU), ranging from anesthesiology and critical care, through endocrinology and drug addiction, to psychiatry and sleep medicine. However, at present, pupillometry at the patient's bedside is intermittent, qualitative, and performed manually using a penlight and a ruler. Such practice is akin to 19th-century cardiology using manual pulse palpation without medical devices. It is inevitably time-consuming, inaccurate, subjective, non-continuous, and limited to open eye situations. Conversely, laboratory pupillometry systems are cumbersome and inappropriate for clinical applications due to their sensitivity to ambient light changes. To address this unmet need and 'bring pupillometry to the 21st century', we will develop and validate a compact automatic pupillometry system for clinical settings. First, (aim1) we will achieve pupillometry with a compact real-time apparatus by improving data acquisition and processing. We will further (aim2) incorporate mid-infrared imaging to overcome ambient light sensitivity. Finally, (aim3) we will improve SNR and resolution by active diode illumination and light polarization. The new developments will be compared with simultaneous gold-standard video-based pupillometry used in basic research. Our proposal ideally fits this year's Zimin focus on medical equipment and sensing. It builds upon our combined interdisciplinary expertise in Pupillometry (Nir) and Biophotonics (Gannot). Our research will harness technology to advance humanity and contribute towards a better world by transforming neurocritical care and could help prevent intra-operative awareness and pain during surgery.

Keywords: Pupil, Pupillometry, Neurological disorders, Pupil light reflex, midIR Imaging, Polarization imaging.

Research project description

Introduction

The human eye can be described as an optical system; The eye focuses and processes incoming light through the lens and the retina (Fig. 1a). The pupil, an opening in the ring-shaped iris, optimizes retinal illumination. Pupil size is modulated by two factors: by the level of ambient light, and by arousal. Mydriasis (dilation) occurs in conditions of low light intensity and high arousal and is caused by the dilator pupillae muscle. Miosis (contraction) occurs in illuminated conditions and low arousal and is caused by the sphincter pupillae muscle. Pupil diameter varies from 1 to 8 mm and is largely symmetric between two eyes in healthy individuals [1, 2].

The measurement of pupil size (or diameter) as a function of time is referred to as pupillometry or pupillography. Pupillometry is often used to evaluate neurological function by measuring the pupil light reflex (PLR), a time-course of pupil size dynamics around brief light stimulation (Fig. 1b) [3]. Pupillometry and PLR are useful for clinical diagnosis in many medical disorders. For example, pupil functional abnormalities occur in psychiatry, neurodegenerative disorders, drug overdose, and autonomic neuropathies in diabetes [4]. Furthermore, pupillometry can be used to monitor anesthesia depth and analgesia, head injuries, and clinical status following cardiac arrest [5, 6].

The PLR has stereotypical dynamics that allow to readily detect any abnormalities as clinical indications. When light is presented to the eye, the pupil automatically constricts, whereas stimulus termination leads to pupil re-dilation (Fig. 1c). The PLR response is mediated by concerted action of the sympathetic and parasympathetic systems. An important PLR feature for clinical diagnosis is that light stimulation in front of one eye causes a symmetric reaction in both eyes whenever the brain pathway is intact. PLR dynamics follow a pattern consisting of four phases: response latency, maximum constriction, pupil escape, and re-dilation. When light stimulation is brief, pupil changes are characterized by a sharp, "impulse response"-like profile (Fig. 1c).

Physicians have long recognized the enormous clinical potential of pupillometry in medicine, and have been checking the pupils of patients with suspected brain injury (e.g. suspected stroke) or impaired consciousness for over 100 years [2]. To detect pain (e.g. during surgery), the pupil is a more sensitive measure than commonly used variables of

arterial blood pressure and heart rate, and even EEG [7, 8]. Therefore, pupillometry can provide a novel, sensitive, and effective measure to address the growing public concern of intraoperative conscious awareness, a topic of increased attention that significantly contributes to PTSD [9]. In the context of traumatic brain injury, pupil size and PLR alterations are correlated with clinical outcomes; therefore, the American Association of Neurological Surgeons recommend evaluating and documenting PLR in clinical records [10-12]. In critically injured patients, anisocoria (pupil asymmetry) indicates neurological dysfunction. A dilated, sluggishly-reactive pupil suggests transtentorial herniation. [12].

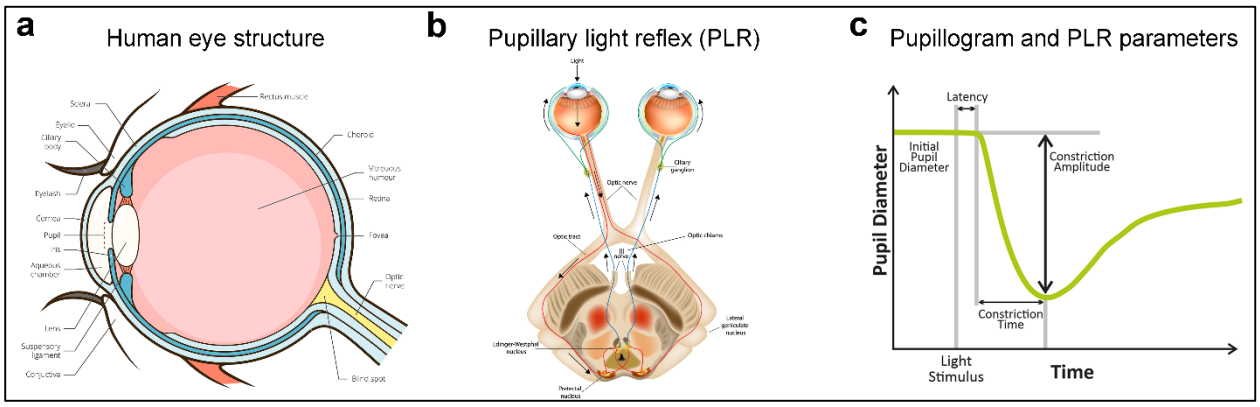

Figure 1. The human eye, pupil and the pupillary light reflex (PLR). (A) Human eye structure, as seen from mid-sagittal section**.** Light enters through the cornea, through the aqueous humor, through the pupil (an opening in the ring-shaped iris), through the lens (which modulates illumination and focus and is controlled by ciliary muscles), and through the vitreous humour. The retina on the interior back of the eye transduces light to electrical activity that is then relayed through axons of ganglion cells via the optic nerve to further processing in the brain. (**B**) **Pupillary light reflex (PLR).** The PLR is an autonomic reflex that constricts the pupil in response to light via iris sphincter muscles. After light impinges on the retina, ganglion cells send impulses through the optic nerve and the optic chiasm, and through the optic tracts (where nasal fibers cross to the contralateral side, and temporal fibers continue on the ipsilateral side). Signals travel further to the pretectal nucleus in the midbrain, where they send signals to the parasympathetic Edinger-Westphal nucleus. Efferent (output) parasympathetic preganglionic fibers travel on the oculomotor nerve and synapse with the ciliary ganglion, which sends postganglionic axons to directly innervate the iris sphincter muscles. The contraction of the iris sphincter muscles leads to pupil constriction (miosis). This structural and functional integrity of this pathway is typically tested by a light shined on the eyes. (C) **Pupillogram and PLR parameters.** PLR in response to brief (e.g. 100ms) light stimulation: the pupillogram shows the time-course of pupil diameter (y-axis) as a function of time (x-axis) around light stimulation (time zero, when a brief light stimulus is presented). After an initial response latency (~0.4s delay), the pupil gradually constricts from its baseline to a minimal diameter (maximum constriction). The difference between baseline diameter and the maximum constriction is termed the constriction amplitude (vertical arrow), and the time interval between constriction onset to maximum constriction is termed construction time. In the absence of further illumination changes, the pupil slowly returns to its baseline diameter.

However, at present, quantitative automatic pupillometry is limited to laboratory settings and is not used regularly at the patient's bedside in the clinic. While the basic science

community has recognized the huge potential of *quantitative* pupillometry (~5000 publications (!) in the past 5 years when searching for 'pupil' in PubMed), amazingly, this has remained outside clinical practice, largely due to the absence of a reliable device for pupillometry in clinical settings. Instead, pupillometry is performed intermittently rather than continuously, and involves a manual check with a pen flashlight to evaluate reactivity, and a 'pupil gauge' to estimate pupil size. Such practice inevitably relies on subjective terminology (e.g. "brisk", "sluggish", "nonreactive pupils") and leads to high inter-examiner disagreement as high as 39% [13-15]. We aim to address this major unmet clinical need by developing a compact accurate pupillometry system for clinical settings. Our working hypothesis is that midIR and polarization imaging could aid such development.

Mid Infrared (midIR) and polarized light imaging. midIR imaging has a number of features that could potentially improve existing methods for pupillometry. MidIR imaging (at the 8-12 μm spectral range) captures the natural radiation generated by an object and represents a safe, tolerable, non-invasive non-contact modality to collect information using an IR camera in real time [16]. In contrast to visible light imaging (video), it not affected by ambient light and is therefore well suited for measurements at the patient's bedside. Another imaging modality that could improve sensitivity and applicability of pupillometry is polarization imaging. It builds upon differences between the polarization of light that is reflected back from tissue versus the polarization of the light penetrating through the tissue (its polarization is largely random due to interference) [17]. The polarized image reveals any inclusion that breaks the structure of the surrounding tissue (e.g. melanoma in comparison to benign nevus). A thorough updated review of clinical and pre-clinical applications can be found here [18].

Expected significance, innovation, and impact

The proposed research has the potential to transform neurocritical care, prevent intra-operative awareness and pain during surgery, and change sleep medicine. Despite its massive clinical utility, a technological barrier prevents pupillometry and PLR tests from being as useful and widely used as they should be. A device that would enable continuous automatic assessment of pupil size and reactivity at the patient's bedside can transform neurocritical care by significantly improving the monitoring of patients in ICU and during anesthesia, quickly identifying cases in need of immediate attention, therefore saving lives. By combining engineering and medicine, we aim to address this unmet clinical need

towards better clinical care and a better world. We are confident that our collaboration constitutes an ideal fit for this year's Zimin award focus (medical equipment and medical sensing), and one that brings together the necessary interdisciplinary expertise to succeed: Prof. Nir being an expert in arousal and pupillometry research [19-21] , and Prof. Gannot being an expert in Biophotonics and Theranostics who developed midIR and NIR, nanoparticles based methods for cancer early detection and treatments [22-26].

Research objectives and specific aims

Until now, we have performed preliminary work to put together the experimental setup and provide proof-of-concepts for the potential of using midIR imaging and polarized light imagining to obtain ***static*** pupil information (Fig. 2). We now seek to perform the actual research and test for PLR/pupil ***dynamics***.

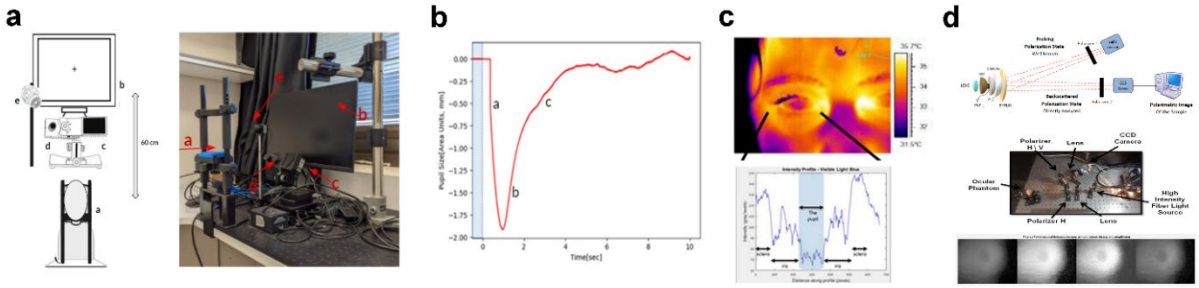

Figure 2. Experimental setup and proof-of-concepts. (a) schematic (left panel) and actual (right panel) illustration of experimental setup to be used to compare gold-standard commercial pupillometry simultaneously with novel imaging modalities. Setup includes (a) chinrest and forehead post used for placing subject face in fixed position, distance, and angle from illumination sources and cameras, (b) screen used to present bright stimuli for PLR measurements (c) Mid-infrared imaging of the eye, (d) Commercial "Eyelink" visible light (video) camera, and suggested position for midIR camera. (b) with this setup, we can reveal typical PLR dynamics and obtain a time course of pupil size (area in mm, y-axis) as a function of time (seconds, x-axis) around brief light stimulation. The PLR consists of (a) a fast (lasting ~60ms) constriction shortly after the eye has been exposed to light stimuli, (b) an early fast re-dilation of the pupil (lasting ~1s), and (c) An additional slow pupil dilation to original baseline size. (**c**) Top, static (still) midIR imaging of eye area reveals robust differences in temperature across center of eye. Bottom, Quantification of temperature across a horizontal eye section reveals distinct temperature values for sclera, iris, and pupil. (**d**) Top, schematic of suggested setup for polarized light imaging with a broadband light source, polarizers, an ocular phantom and a mechanical aperture. Middle, actual implementation of experimental setup for polarized light imaging. Bottom, gray levels of polarization images reveal central aperture serving as a mock pupil.

Overall goal: To develop an accurate and portable method for real time and continuous pupillometry at the patient's bedside.

Approach and experimental design: We will evaluate and validate new methods by comparing our development to a 'gold-standard' EyeLink® system for pupillometry in lab settings. We will build around a previous PLR study [27] that used a computer monitor as

the light stimulus and controlled its brightness via software. With this experiment and our setup, we have successfully obtained a robust PLR in response to brief (200ms) light stimulation (Fig. 2b).

To work towards clinically-suited assessment of pupil size and the pupillary light reflex (PLR), we will address the following specific aims:

Aim 1. Achieve pupillometry with a compact real-time apparatus that has comparable performance to lab settings. To this end, we will (1a) improve data acquisition with superior optics compared to current commercial systems, and (1b) improve image processing by employing advanced spatio-temporal filtering [28] and segmentation tools [29]. We anticipate that these improvements will allow us to **reduce** the image and temporal resolutions and move towards a compact solution.

Aim 2. Make compact pupillometry robust to changes in ambient light. Visible-light-based pupillometry, which is the norm in lab settings, relies on carefully controlled ambient light conditions (typically involving curtains or light meters, which are not feasible in clinical hospital settings). To go beyond this limitation, we will incorporate midIR imaging which is insensitive to ambient light. We obtained exciting proof-of-concept results for pupillometry with midIR imaging for *still* images (Fig. 2C), and will systematically establish such imaging and extend it to *dynamic* PLR measurements.

Aim 3. Improve SNR and resolution by active diode illumination and polarization. Pupillometry fundamentally detects a contrast between the pupil and surrounding tissue, which have different optical and thermal properties. We will take active measures to increase this contrast by (3a) combining visible & midIR optics, (3b) adding diode illumination, and (3c) adding structured illumination and polarization imaging.

Existing facilities. The proposed project leverages a new collaboration between the Nir and Gannot labs. We have recently put together a setup for pupillometry R&D in a dedicated room at TAU medicine. The facility includes an optical setup with breadboard frame and control of ambient light, synchronization of midIR and pupillometry devices, and low energy-density LED illumination systems (Fig. 2). Thus, the proposed project can build upon this infrastructure to achieve rapid progress of device development.

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Budget and justification

Category	Subcategory	Sum ($)
Personnel	(stipend) Postdoctoral fellow	37,710
	(stipend) Ph.D. student (Engineering; 50% Zimin, 50% TAU)	16,090
	(stipend) Master student (Medical sciences; 50% Zimin, 50% TAU)	8,500
	(salary) Programmer	12,000
Equipment	**Hardware**: light sources, optical, mechanical, and electronic components for midIR / polarized light imaging / hi-res. CCD video.	11,000
	High-performance PC workstation for data analysis (64G RAM, 2TB SSD hard-drive, multi-core GPU for machine learning)	4,200
Travel	Participation in workshops/conferences	5,000
Other	Combined server and cloud data backup solutions	2,500
	Software licenses (Matlab, Zemax, Comsol, Adobe CS)	2,000
	Office and administrative expenses	500
	Publishing costs	1,000
Total budget		**100,000**

We acknowledge that 25% matching is required by the University, IN KIND.

Personnel

A postdoctoral fellow will lead the project together with an engineering PhD student focusing on biomedical imaging (50% support from Zimin, 50% support from TAU). They will be assisted by a M.Sc. medical science student (50% support from Zimin, 50% support from TAU). A professional programmer will assist with image processing and with video stream synchronization between video (gold-standard pupillometry) and other imaging modalities.

Equipment

Required equipment Includes low-intensity LED light sources, optical components (filters for polarization, MidIR lenses), mechanical components (XYZ stages, tripods and holders), electronic components (e.g. photodiode, video stream converts), compact midIR imaging devices (research grade “thermal” cameras), and high-resolution CCD video.

In addition, a dedicated PC workstation will support precise experimental control and data analysis (64G RAM, 2 TB SSD hard-drive, multi-core GPU for machine learning).

Travel

Expenses will support presentation of research in international conferences and workshops to collect expert input before publication and disseminate knowledge.

Other

Other costs include data backup, software for experimental control and data analysis, office and administrative expenses and publishing costs.

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23. Hoffer, O.A., et al., *Thermal imaging as a tool for evaluating tumor treatment efficacy.* J Biomed Opt, 2018. **23**(5): p. 1-6.
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Yuval Nir, PhD

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Personal

Born: December 17th, 1974 | Married + 3 | Nationality: Israeli
ORCID: https://orcid.org/0000-0002-5433-6349

Education

2008 Weizmann Institute of Science, Israel
- PhD in neurobiology (laboratory of Prof. Rafael Malach)

2004 Tel Aviv University, Israel
- M.Sc. in computer science, magna cum laude
- Interdisciplinary program for outstanding students including topics in computer science, psychology, cognitive science, biology and philosophy

Research positions

2019-present. *Associate Professor*, Tel Aviv University, Department of Physiology and Pharmacology, Sackler School of Medicine and Sagol School of neuroscience
2012-2019. *Assistant Professor*, Tel Aviv University, Department of Physiology and Pharmacology, Sackler School of Medicine and Sagol School of neuroscience
2008-2012. *Postdoctoral Fellow*, Center for sleep and consciousness of Prof. Giulio Tononi, University of Wisconsin-Madison

Honors & awards

2019 Stanford Wu Tsai Institute visiting scholar award
2019 Tel Aviv University Best Publication Award in Biomedicine
2017 Tel Aviv University Rector's Prize for outstanding teaching achievements
2016 Adelis Prize in Neuroscience
2015 Teva Founders Prize for basic biomedical research
2014 Marguerite Stolz Research Fellowship for Junior Faculty in Medicine
2013 Sieratzki Prize for Advances in Neuroscience
2009 Human Frontier Science Program (HFSP) long term fellowship
2008 European Molecular Biology Organization (EMBO) long term fellowship
2008 Brainpower for Israel (BFI) postdoctoral award
2007 Travel Award, Human Brain Mapping Organization
2005 Fulbright Doctoral Student Fellowship
2003 Travel Award, Human Brain Mapping Organization
1998 Rector's Award for Achievements (TAU Psychology)
1998 Dean's Award for Achievements (TAU Computer Science)

Mentoring

2012-today. Supervised 3 postdocs, 6 Ph.D. students, and 7 M.Sc. students. Trainee awards include EU Career Integration Grant , HFSP fellow, Sagol school postdoc award, ISF "Clinical-Scientist" Award and Grant, and Azrieli Fellow

Publications

- 39 peer-reviewed publications cited 7150 times (G. Scholar) + 3 book chapters
- Publications in *Nature*, *Science*, *Nature Medicine*, *Molecular Cell*, *Nature Neuroscience* (2), *Neuron* (2), *Science Advances*, *Nature Communications*, *PNAS*, *Current Biology* (4), *NeuroImage* (2), *Human Brain Mapping* (2), *Journal of Neuroscience* (6), *Cerebral Cortex* (3)
- 3 additional papers currently in revision at Nature Neuroscience
- 2 additional papers under review at Science Advances, Cell Reports

Invited talks & seminars

- Over 55 invited international talks and seminars
- Invited talks at "Falling Walls" (Berlin), Stanford, Berkeley, Weizmann Institute, Italian Institute of Technology, Neuroscience School of Advanced Studies (Venice), Bristol Neuroscience, Pisa Sleep Conference, European Institute for Theoretical Neuroscience (Paris), Leopoldina (Berlin), Caltech, Bern Center for Sleep and Epilepsy (Switzerland), Lyon University Hospital, Associated Professional Sleep Societies (Baltimore, USA), Washington University St. Louis (WUSTL) Center for Neuroimaging, NYU, School of Medicine (Napoli), Department of biomedical engineering (Technion).
- Chaired symposia at the World Sleep Meetings (Prague, Rome), annual Society for Neuroscience Meeting (Washington DC, >35,000 attendees)

Teaching

2021-present. "Cellular Biophysics"
2016-present. "Sleep and consciousness: from neuronal basis to cognition"
2015-present. "Scientific Writing"
2014-present. "Introduction to Systems Neuroscience"
2013-present. "Introduction to Cell Physiology"
2002-2007. "Physiology of Behavior"

Organization of scientific meetings

2019. "Neural Correlates of Sleep & Anesthesia", International Symposium at the Israeli Society for Neuroscience annual meeting (600 participants), Eilat, Israel
2018. "Stability and plasticity of neural circuits", International Conference (380 participants) at Tel Aviv, Israel, https://www.sagol-synaptic-circuits.org/

Selected duties & commissions of trust

2021-today. Institutional Research Student Committee, TAU
2021-today. Chief Science Officer: Center for Sleep Medicine, Ichilov
2018-today. Editor "Frontiers in Neuroscience: Sleep & Circadian Rhythms"
2017–today. Scientific advisory panel, Australian research center on sleep & aging
2017–today. Sackler faculty of medicine, graduate school teaching committee
2017-today. Editorial board, "sleep spindles and up states"
2016-today. Israeli Society for Neuroscience, elected treasurer & executive board
2015–2019. Sagol School of Neuroscience, school postdoc committee
2014–today. Scientific advisory panel, R&D consortium on brain stimulation, office of chief scientific officer to the Israeli government

Selected grants

2021-2023. (PI) Aufzien Family Center grant on REM sleep in Parkinson's disease
2020-2025. (PI) ERC Consolidator Grant: sleep and episodic memory consolidation
2018-2020. (Subcontract PI) NIH UO1 (Sleep and memory)
2018-2022. (PI) NSF-BSF grant in Cognitive Neuroscience
2016-2019. (PI) Adelis Prize in Neuroscience
2015-2020. (PI) ISF grant #1326/15 (Anesthesia)
2015-2017. (PI) EU-Horizon2020, MC-IF # PCIG14-GA-2013-630974
2015. (PI) Teva Founders Prize and Research Grant
2014-2018. (PI) EU Marie Curie CIG# PCIG14-GA-2013-630974
2012-2017. (PI) Israeli "I-CORE Program" in Cognitive Sciences

BIOGRAPHICAL SKETCH (February 2022)

NAME: Israel Gannot

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Technion, Haifa, Israel	B.Sc.	1977-1981	Electrical Engineering
Tel-Aviv University, Tel-Aviv, Israel	M.Sc.	1987-1989	Biomedical Engineering
Tel-Aviv University, Tel-Aviv, Israel	Ph.D.	1989-1994	Electrical Engineering
American Academy of science fellowship			
For post-doctoral training		1994-1997	Biomedical Optics

A. Personal Statement

Over the course of my career, several recurring central themes have emerged. The first theme is multi-modal imaging, where two or more imaging modalities are used to characterize the same tissue site. A second theme is the development of probes for endoscopic imaging. One of my main contributions to the field is the use of thermal imaging bundles and waveguides, which can be coupled to sources and/or probes and used in a trans-endoscopic manner, within body cavities. A third theme is Theranostics: "image, treat and monitor" where the same technology (nanoparticles based) is used to treat the target tissue while simultaneously imaging it.

My research interest has expanded through the years into practical ethics. Ethical issues in advanced technology. Autonomous devices, Ethics in AI specifically in Medicine and ethically aligned design. I am active in translational sciences: How to transfer ideas from the laboratory into an effective successful tool for the sake of human healthcare. This expands and include also team science and implementation science. The current proposal incorporates my research interest and activities.

B. Positions and Honors

1997–2001 Lecturer, Department of Biomedical Engineering, Faculty of Engineering, Tel-Aviv University
2001-2007 Senior Lecturer (tenured), Department of Biomedical Engineering, Faculty of Engineering, Tel-Aviv University.
2002-2005 On sabbatical - Senior guest scientist, National Institutes of Health, Bethesda, MD, USA.
2005-2009 Visiting Professor, Department of Electrical and Computer Engineering, School of Engineering and Applied Sciences, George Washington University, Washington, DC
2007-2013 Associate Professor, Department of Biomedical Engineering, Faculty of Engineering, Tel-Aviv University.
2009-2011 Chair; Department of Biomedical Engineering, Faculty of Engineering, Tel-Aviv University.
2013- Professor.

C. Professional societies:

AIMBE - American Institute for Medical and Biological Engineering - Fellow

SPIE - The International Society for Optical Engineering - Fellow
ASLMS - The American Society for Laser Medicine and Surgery – Fellow

Students' supervision:

50 Doctorate and full research master students.

Publications (last 15):

1. O. Harbater and I. Gannot, "Fluorescent probes concentration estimation *in vitro* and *ex vivo* as a model for early detection of Alzheimer's disease*" J. Biomed. Opt*. 19(12), 127007 (Dec 29, 2014). doi:10.1117/1.JBO.19.12.127007.
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SACKLER FACULTY
OF MEDICINE
TEL AVIV UNIVERSITY
OFFICE OF THE DEAN

הפקולטה לרפואה
ע"ש סאקלר
אוניברסיטת תל אביב
לשכת דקאן

Friday, February 4, 2022

Endorsement of Zimin application by Profs. Nir (Medicine) and Gannot (Biomedical engineering)

To whom it may concern,

I heartily support and endorse the application entitled "**Pupillometry in clinical settings**" submitted to The 'Zimin Institute for Engineering Solutions Advancing Better Lives' by Prof. Nir (Department of Physiology and Pharmacology, Faculty of Medicine) and Prof. Gannot (Department of Biomedical Engineering, Faculty of Engineering).

Beyond my position as Dean at the Faculty of Medicine, I am also the director of the internal medicine division and the hypertension institute at Sheba Tel-Hashomer hospital. I am well familiar with the potential of pupillometry as a powerful diagnostic tool in diverse clinical settings, and enthusiastically support research that will develop a compact automatic pupillometry system for clinical settings, to go beyond the limitations of current practice.

I wish the investigators best of luck with their application.

Sincerely,

E Grossman

Prof. Ehud Grossman
Dean
Sackler Faculty of Medicine
Tel Aviv University

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Department of Biomedical Engineering

המחלקה להנדסה ביו-רפואית

Iby and Aladar Fleischman Faculty of Engineering Tel Aviv University

הפקולטה להנדסה ע"ש איבי ואלדר פליישמן אוניברסיטת תל-אביב

February 7, 2022

Endorsement of Zimin application by Israel Gannot (Biomedical engineering) Yuval Nir (Medicine)

To the Zimin Institute review committee

Dear Committee members;

I heartily support and endorse the application entitled "**Pupillometry in clinical settings**" submitted to The 'Zimin Institute for Engineering Solutions Advancing Better Lives' by Prof. Gannot (Department of Biomedical Engineering, Faculty of Engineering) and Prof. Nir (Department of Physiology and Pharmacology, Faculty of Medicine).

The proposal ideally fits this year's Zimin focus on medical equipment and sensing. It builds upon the combined interdisciplinary expertise in Pupillometry (Nir) and Biophotonics (Gannot). Such research can harness technology to advance humanity and contribute towards a better world.

I wish the investigators best of luck with their application.

Sincerely,

Prof. Mickey Scheinowitz

Chair; Department of Biomedical Engineering

The Iby and Aladar Fleischman Faculty of Engineering

Tel Aviv University

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