High Resolution Imaging in Microscopy and Ophthalmology

Josef F. Bille
Editor

High Resolution Imaging in Microscopy and Ophthalmology

New Frontiers in Biomedical Optics

OPEN

Springer

Editor
Prof. Dr. Josef F. Bille
University Heidelberg
Heidelberg
Germany

This book is an open access publication.
ISBN 978-3-030-16637-3 ISBN 978-3-030-16638-0 (eBook)
https://doi.org/10.1007/978-3-030-16638-0

Cover Illustration: Courtesy Marco Lupidi, University of Perugia, Italy and Heidelberg Engineering GmbH

This Springer imprint is published by the registered company Springer Nature Switzerland AG.
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword 1

In Memoriam Dr. Gerhard Zinser

When I started my graduate work in the laboratories of Heidelberg Instruments GmbH in the Neuenheimer Feld, Gerhard Zinser was already an established senior scientist of the company. There was not a direct overlap in what we both worked on, and we did not work together. However, for a long stretch of time the optics laboratory in which I conducted my experiments was located right next to Gerhard's office. We therefore ran into each other every day.

Gerhard was a luminous example of dedication to his work. He was so passionate about what he was doing; it was a joy to see. I would say he was at the workplace even more than I was, and yes, I was there a lot.

So, one Sunday—it had seemed there was no one else there in the building when I had entered in the morning—I jumped out of the lab in the early afternoon, and there was Gerhard. Of course he was, never mind the Sunday. He was busy preparing a scientific poster for an ophthalmology meeting, describing a new laser scanner. And I couldn't but watch in awe: Gerhard was on the floor of the hallway getting the job done with spectacular efficiency. Note that in those days posters were still cut and pasted manually with glue. He was putting together the poster at lightning speed, a cigarette in the left corner of his mouth, and smiling at me. He then walked me through his poster, and I so clearly remember his joy and enthusiasm for the science. He enjoyed what he was doing, and this joy was exemplary.

Over the following 25 and more years, I got to know a lot of people in optics. I went to meetings in microscopy, sure, but met so many people from the adjacent fields, including ophthalmology. And whenever we talked and I would mention Gerhard, they knew right away who I was talking about. And I was so proud to know him.

Gerhard Zinser was a major player in applied optics and ophthalmology in particular. He made contributions of a lasting impact. I was not at all surprised when he so very successfully embarked on new scientific adventures and responsibilities with his key roles in Heidelberg Engineering. His vision and dedication to excellence will be missed by all who knew him.

Stefan W. Hell
Max Planck Institute for Biophysical Chemistry
Göttingen
Germany

Foreword 2

Memories

It was December 1991. The annual meeting of the American Glaucoma Society was taking place at the Hotel del Coronado, just south of San Diego. It was the fourth meeting of the Society that had been founded just several years earlier. And it was just 8 months after opening the Shiley Eye Center in La Jolla at the University of California San Diego, approximately 25 miles north of the meeting site. There was a surprising brief rain shower early that evening in San Diego, and a bus filled with 38 glaucoma colleagues was in transit to La Jolla. They had heard rumors for more than 1 year that there was a new medical imaging device that would enable quantitative and objective imaging of the optic nerve head. Moreover, it would soon be available at a reasonable cost and it would provide for practical patient testing in the office. I am told that those on the bus were excited because many of them thought that they might be viewing the future of glaucoma management. I had lectured and published on optic disc imaging, and hoped that our demonstration would justify the funding of a National Eye Institute grant that I had received several years earlier to study this technology, and validate much of what we had been doing. At the Shiley Eye Center, there was anxiety among almost all of those who had done research or developed the technology over the preceding few years. However, there was one individual who sat on the side, just near the front window, waiting for the bus. He was smoking one cigarette after the other and had his usual smile.

Actually, the idea for imaging the optic disc and retinal nerve fiber layer was not new. Several other technologies had been tested and employed, but never gained traction. Just a few years before the eventful December 1991 demonstration, a commercial confocal scanning laser ophthalmoscope (the Laser Tomographic Scanner (LTS) by Heidelberg Instruments) had been developed and commercialized by the brilliant Josef Bille and his team of engineers and students. At that time, Josef spent increasing amounts of time with us at UCSD and on many of his visits he was accompanied by his students. Uniformly, they were all hardworking, clever, and serious about their work. It was around that time that I first met Gerhard Zinser. Gerhard stood out among the many graduate and postdoctoral students that came to work

with Josef and us in San Diego. Not only was he the brightest star, but he was collaborative, insightful, visionary, and just a wonderfully warm person. Ask him a technical question and there always was a thoughtful and comprehensible response. In discussions in the laboratory and also in restaurants (where he would opine over his steak and potatoes and postprandial cigarettes), we spent hours discussing how this technology could be applied to both the optic disc and macula. So many of those hours, we spent just discussing reference planes and analyses.

Gerhard understood well the potential for confocal imaging of the eye. He also understood well the limitations of the ponderous and costly LTS that we were using in our research. So I was not surprised when he told me that he would be developing a next generation instrument. And, I also was not surprised when he said that it was ready for testing.

And that brings us back to December 1991. The new instrument, called the Heidelberg Retina Tomograph or HRT, was relatively compact and inexpensive. With improvements in hardware and software, it was capable of faster and better imaging. It was supposed to arrive well in advance of its demonstration to my glaucoma colleagues. However, it had been delayed at customs in Los Angeles. The instrument finally did arrive, but it did not work to our dismay. It was a fiber, tube, or electrical component that needed replacement. The only replacement would need to be shipped from Germany. We received notification that it was sent, but unfortunately it did not yet make it to La Jolla. A series of phone calls (there was no internet) confirmed its shipment. And, again, we discovered that it was in customs at the Los Angeles Airport. I do not remember who, but someone from Heidelberg Engineering raced to their car and drove 100 miles north to retrieve it. They then raced back again. It was well after midnight; our group, fueled by coffee and colas, were determined to have a functional device for the visitors. I do not remember exactly when the component arrived. But I distinctly remember what happened next. Gerhard jumped into action and began some serious tinkering.

It was afternoon when he said the HRT was ready for testing. What if it still did not image? Or, what if the imaging was not as expected? The only one in the room who had complete confidence that it would work as planned was Gerhard. And sure enough, he plugged in the instrument to an outlet and flipped the switch to turn it on. The room was silent as we waited. Gerhard pressed some buttons and adjusted some things at the keyboard. After being up all night, and waiting throughout the day for the delivery of the component, we learned that the bus had left the hotel and was on its way. And then I never will forget as he walked to the front window, took a seat, lit a cigarette, and then with a broad smile he calmly told us that it was working well.

Our colleagues arrived and to them all seemed just fine. Little did they know what had happened over the preceding 18 h and that we were without sleep. Imaging them one after the other, we could see their excitement. It was then that we knew that we had entered a new era of glaucoma manage-

ment. It was then that I knew, as well, that by changing the way that we examined the eye, we had entered a new era and there soon would be a new perspective not only for glaucoma, but retina diseases and other eye conditions as well.

Technology has moved forward considerably since then and over the next almost 3 decades. The imaging technologies, available today, particularly optical coherence tomography which was nascent at the time, were almost unimaginable then. And we always will remember Gerhard Zinser as a pioneer, a friend and colleague whose name is synonymous with excellence.

Robert N. Weinreb, MD
Shiley Eye Institute
La Jolla, CA
USA

Preface

To our knowledge, for the first time, this book provides a comprehensive overview of the application of the newest laser and microscope/ophthalmoscope technologies to the field of high-resolution imaging in microscopy and ophthalmology. Ophthalmologists, physicists, and engineers combine in an interdisciplinary approach to summarize the newest findings of cutting-edge technologies in microscopy and ophthalmology. The newest clinical results of retina and glaucoma diagnostics and therapy control are presented. New findings in the assessment of the anterior segment of the eye are elucidated, providing the basis to innovations in cataract surgery and refractive surgery.

Until recently, the resolution of far-field light microscopy was limited to about 200 nm in the object plane and 600 nm along the optical axis ("Abbe/Rayleigh limit"). These limits have been substantially overcome by various super-resolution fluorescence microscopy (SRM) methods. SRM allows linking the knowledge gained by molecular methods to cellular structures. In ophthalmology, adaptive optics (AO) has emerged as an empowering technology for retinal imaging with cellular resolution, providing diffraction-limited performance. Combining SRM and AO techniques, breaking the diffraction limit in retinal imaging may become feasible.

Since the first scanning laser ophthalmoscope (SLO) was introduced in the early 1980s, this confocal imaging modality has been adapted and optimized for various clinical imaging applications based on different contrast mechanism. Optical coherence tomography (OCT) has emerged to the forefront of ocular imaging because of the wide variety of information it can provide, its high-resolution images, and the complex 3-dimensional (3D) data it is able to gather.

For ophthalmology, OCT is of particular utility in glaucoma and retinal diseases, since it provides high-resolution objective, quantitative assessment of the retinal cellular layers affected by each disease. Especially since glaucoma is a slowly progressing disease, objective and quantitative measures could potentially provide a more accurate and precise method for the diagnosis of glaucoma and detection of its progression.

Swept-source OCT technology offers inherent characteristics that are suitable for high-resolution anterior segment imaging and analysis. Such capabilities allow for non-contact imaging, detailed visualization, and analysis of anterior segment structures of the human eye including the cornea, anterior chamber, iris, and lens with one device. Swept-source OCT technology can also serve as a tool to measure the axial length of the human eye.

The above-mentioned structures and parameters are used in ophthalmology for corneal topography, corneal tomography, anterior segment analysis, biometry, and calculation of intraocular lens power.

Adaptive optics has emerged as an empowering technology for retinal imaging with cellular resolution. This technology holds potential for noninvasive detection and diagnoses of leading eye diseases such as glaucoma, diabetic retinopathy, and age-related macular degeneration (AMD). Recent microstimulation techniques coupled with adaptive optics scanning laser ophthalmoscopy can produce stimuli as small as single photoreceptors that can be directed to precise locations on the retina. This enables direct in vivo study of cone activity and how it relates to visual perception.

The book is supposed to be positioned somewhere at the border between engineering and medicine/biology, i.e., it should address the MD/PhD, who has technical interest and wants to understand the equipment he/she uses, and on the other side the engineer, who wants to understand the applications and the medical/biological background.

The editor is grateful to the authors of this book who have made this multifaceted overview of basic science and engineering as well as clinical topics possible. It was our intention to provide the ophthalmological community with the most recent results in eye diagnostics and surgery.

Finally, I would like to express my special thanks to Agnieszka Biedka, Barbara Hallet, Dr. Bettina Olker, and Katrin Petersen from the Technical Writing department at Heidelberg Engineering GmbH for their continuous professional support in the fields of editorial work, linguistics, and graphics. The editor is also grateful to the editorial group at Springer Nature, London, for their strong support.

This book was made possible due to the initiative of Kfir Azoulay and the enthusiastic support by Arianna Schoess Vargas and Christoph Schoess, the managing directors of Heidelberg Engineering GmbH, honoring the scientific excellence and lifetime achievements of Dr. Gerhard Zinser, cofounder and former managing director of Heidelberg Engineering GmbH.

Heidelberg, Germany Josef F. Bille

Acknowledgment

The editor acknowledges that Heidelberg Engineering GmbH provided a grant to support the open-access publication of this book.

Contents

Contributors

Silke Aumann Heidelberg Engineering GmbH, Heidelberg, Germany

William H. Baldridge Department of Medical Neuroscience, Dalhousie University, Halifax, NS, Canada

Paul Bernstein Moran Eye Center, University of Utah School of Medicine, Salt Lake City, Utah, USA

Josef F. Bille University of Heidelberg, Heidelberg, Germany

Brett E. Bouma Wellman Center for Photomedicine, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, USA

Christopher Bowd Ophthalmology, Hamilton Glaucoma Center, Shiley Eye Institute, and Viterbi Family Department of Ophthalmology, University of California San Diego, La Jolla, CA, USA

Boy Braaf Wellman Center for Photomedicine, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Ralf Brinkmann Medical Laser Center Lübeck GmbH, Lübeck, Germany

Balwantray C. Chauhan Ophthalmology and Visual Sciences, Dalhousie University, Halifax, NS, Canada

Federico Corvi Eye Clinic, Department of Biomedical and Clinical Science "Luigi Sacco", Sacco Hospital, University of Milan, Milan, Italy

Johannes F. de Boer Vrije Universiteit Amsterdam, HV, Amsterdam, The Netherlands

François Delori Schepens Eye Research Institute, Harvard University, Boston, MA, USA

Rosa Dolz-Marco Heidelberg Engineering, Heidelberg, Germany

Unit of Macula, Oftalvist Clinic, Valencia, Spain

Sabine Donner Heidelberg Engineering GmbH, Heidelberg, Germany

Gerit Dröge Heidelberg Engineering GmbH, Heidelberg, Germany

Chantal Dysli Department of Ophthalmology, Inselspital, University of Bern, Bern, Switzerland

Spring RM. Farrell Department of Pharmacology, Dalhousie University, Halifax, NS, Canada

Oliver Findl Department of Ophthalmology, Hanusch Hospital, Vienna, Austria

Jörg Fischer Heidelberg Engineering GmbH, Heidelberg, Germany

Gesa Franke Institute of Biomedical Optics, University of Lübeck, Lübeck, Germany

Andreas Fritz Heidelberg Engineering GmbH, Heidelberg, Germany

Maximilian G. O. Gräfe Vrije Universiteit Amsterdam, HV, Amsterdam, The Netherlands

Rudolf F. Guthoff Department of Ophthalmology, University Medical Center Rostock, Rostock, Germany

Martin Hammer Universitätsklinikum Jena, Jena, Germany

Wolf M. Harmening Department of Ophthalmology, University of Bonn, Bonn, Germany

Stefan W. Hell Max Planck Institute for Biophysical Chemistry, Göttingen, Germany

Dierck Hillmann Thorlabs GmbH, Lübeck, Germany

Nino Hirnschall Department of Ophthalmology, Hanusch Hospital, Vienna, Austria

Frank G. Holz Department of Ophthalmology, University of Bonn, Bonn, Germany

Gereon Hüttmann Institute of Biomedical Optics, University of Lübeck, Lübeck, Germany

Medical Laser Center Lübeck GmbH, Lübeck, Germany

Airway Research Center North (ARCN), German Center of Lung Research (DZL), Gießen, Germany

Gopal Swamy Jayabalan Heidelberg Engineering GmbH, Heidelberg, Germany

Tschackad Kamali Heidelberg Engineering GmbH, Heidelberg, Germany

Yoshihiko Katayama Heidelberg Engineering GmbH, Heidelberg, Germany

Ralf Kessler Heidelberg Engineering GmbH, Heidelberg, Germany

Sasan Moghimi Ophthalmology, Hamilton Glaucoma Center, Shiley Eye Institute, and Viterbi Family Department of Ophthalmology, University of California San Diego, La Jolla, CA, USA

Frank Müller Heidelberg Engineering GmbH, Heidelberg, Germany

Philipp L. Müller Department of Ophthalmology, University of Bonn, Bonn, Germany

Moorfields Eye Hospital, NHS Foundation Trust, Bonn, Germany

Tobias Neuhann Augenklinik am Marienplatz, Munich, Germany

Tilman Otto Heidelberg Engineering GmbH, Heidelberg, Germany

Lucia Pace Department of Biomedical and Clinical Sciences, University of Milano, Milano, Italy

Clara Pfäffle Institute of Biomedical Optics, University of Lübeck, Lübeck, Germany

Melanie Polzer Heidelberg Engineering GmbH, Heidelberg, Germany

Boris Považay HuCE OptoLab, Berne University of Applied Sciences, Switzerland

Sebastian Rausch Heidelberg Engineering GmbH, Heidelberg, Germany

Roland Rocholz Heidelberg Engineering GmbH, Heidelberg, Germany

Steffen J. Sahl Max Planck Institute for Biophysical Chemistry, Göttingen, Germany

Ruth Sahler Perfect Lens LLC, Irvine, CA, USA

Lydia Sauer Moran Eye Center, University of Utah School of Medicine, Utah, USA

Stefan Schmidt Heidelberg Engineering GmbH, Heidelberg, Germany

Steffen Schmitz-Valckenberg Department of Ophthalmology, University of Bonn, Bonn, Germany

Lawrence C. Sincich Department of Optometry and Vision Science, University of Alabama at Birmingham, Birmingham, AL, USA

Jacqueline Sousa Asam Heidelberg Engineering GmbH, Heidelberg, Germany

Hendrik Spahr Institute of Biomedical Optics, University of Lübeck, Lübeck, Germany

Oliver Stachs Department of Ophthalmology, University Medical Center Rostock, Rostock, Germany

Giovanni Staurenghi Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, Milano, Italy

Markus Stoller Meridian AG, Thun, Switzerland

Helge Sudkamp Institute of Biomedical Optics, University of Lübeck, Lübeck, Germany

Medical Laser Center Lübeck GmbH, Lübeck, Germany

Hui Sun University of Chinese Academy of Sciences, Beijing, China

Ali Tafreshi Heidelberg Engineering GmbH, Heidelberg, Germany

Néstor Uribe-Patarroyo Wellman Center for Photomedicine, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Benjamin J. Vakoc Wellman Center for Photomedicine, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, USA

Julian Weichsel Heidelberg Engineering GmbH, Heidelberg, Germany

Robert N. Weinreb Shiley Eye Institute, La Jolla, CA, USA

Sebastian Wolf Department of Ophthalmology, University of Berne, Berne, Switzerland

Linda M. Zangwill Shiley Eye Institute, La Jolla, CA, USA

Martin S. Zinkernagel Department of Ophthalmology, Inselspital, University of Bern, Bern, Switzerland