1

Let There be Light Sheet

Pavel Tomančák[1,2] and Emmanuel G. Reynaud[3]

[1] Max Planck Institute of Molecular Cell Biology and Genetics, Pfotenhauerstrasse 108, 01307 Dresden, Germany
[2] Central European Institute of Technology (CEITEC) consortium, Žerotínovo nám. 617/9, Brno, 601 77, Czech Republic
[3] UCD Conway Institute, University College Dublin, School of Biomolecular and Biomedical Sciences, Belfield, Dublin 4, Ireland

COPYRIGHTED MATERIAL

The central and essential element of light sheet fluorescence microscopy is the use of a plane of light AKA light sheet to illuminate one plane of the sample at a time. Interestingly, a sheet of light creates not only a plane of light that optically slices the space but also a line of light when it interacts with surfaces (Figure 1.1). This second property of light sheets is extensively used to scan surfaces in industry (e.g. line scan cameras), commerce (e.g. bar code scanners), cleaning (e.g. Dyson V15 Dyson Absolute), architecture and art (e.g. 3D photogrammetry of buildings and sculptures). It also finds practical everyday applications in levelling systems for construction. However, this book revolves around the use of light sheets in microscopy.

1.1 Historical Context of Light Sheet Microscopy – Ultramicroscopy

The use of a plane of light in Selective Plane Illumination Microscopy (SPIM) was a great idea that resonated with the needs of biological imaging community. However, it was not new. In fact, already in 1903, Henry Siedentopf and Richard Zsigmondy utilized a planar sheet of light to image colloids in solution. They called their instrument the Ultramicroscope presumably to reflect its superiority over a conventional microscope.

Richard Zsigmondy worked as a scientific researcher at the Schott AG, a well-known glass manufacturing company in the German town Jena. Schott was a long-time partner providing optical glass to the famous Zeiss Werke, established just on the other side of the town. Zsigmondy apparently grew tired of studying colored and opaque glass and after three years left Schott. He however stayed in Jena and became a private teacher, a profitable position at the time. He married

Light Sheet Fluorescence Microscopy, First Edition. Edited by Emmanuel G. Reynaud and Pavel Tomančák.
© 2024 WILEY-VCH GmbH. Published 2024 by WILEY-VCH GmbH.

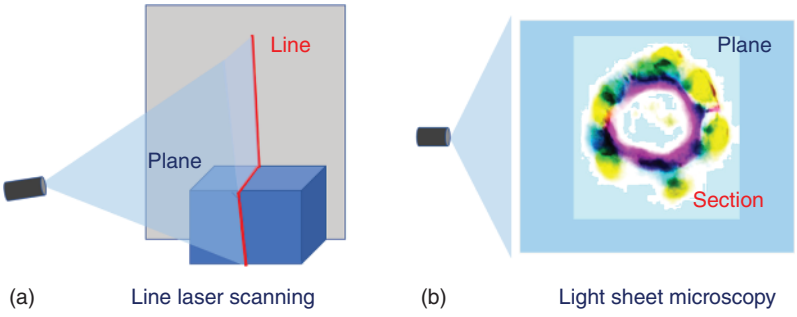

Figure 1.1 A plane of light. (a) can scan a surface or (b) scan a volume.

the daughter of a professor of anatomical pathology and established himself as a free, institutionally independent colloid chemist in Jena. Jena was a well-connected academic town with industries such as Zeiss Werke and Schott alongside a well-known university. Zsigmondy was looking for a way to see microscopic gold particles in colloid solutions (e.g. ruby glass). Colloid chemistry was seen as a very dynamic research field with far-reaching potential to understand the foundations of matter and life.

Zsigmondy managed to get recruited in the Zeiss Werke where he met Henry Siedentopf, a physicist with whom he worked on the development of the Ultramicroscope [1, 2]. They discovered that it was possible to observe very small particles by illuminating the preparation being studied in a direction that is perpendicular to the viewing angle on a dark background (i.e. in a dark field) [3].

The instrument allowed Richard Zsigmondy to prove the heterogeneous nature of colloidal solutions for which he was awarded the Nobel prize in Chemistry in 1925 [4]. Moreover, the Ultramicroscope helped establish the experimental foundations of the kinetic theory (and hence of atomism) by allowing studies of Brownian motion. The advances in colloid chemistry brought about by Ultramicroscopy meant that it played an indirect role in the awarding of the Nobel Prize to Einstein (Physics, 1921), Perrin (Physics, 1926), and Svedberg (Chemistry, 1926).

Henry Siedentopf was appointed Director of the Zeiss Werke' microscope laboratory until he retired in 1938. Together with French physiologist Jean Commandon he modified the Ultramicroscope to enable time-lapse imaging at the time referred to as "Ultramicroscopy microcinematography" [5]. The ultramicroscope was then extensively used as a dark field microscope in microbiology, parasitology, and plant biology until 1935, but then the instrument vanished form the Zeiss Werke catalogue and consequently from the radar of researchers in life sciences.

Interestingly, the term Ultramicroscopy was first revived at the end of 1960 and early 1970 to describe electron microscopy technologies. A journal titled *Ultramicroscopy* was established in 1975 and is defined as *ultramicroscopy deals with the application of all manner of radiation and utilization of any new principles that results in an improved state of the art*.

1.2 Light Sheet Imaging Across the Twentieth Century

The use of light sheet for imaging however did not disappear with the demise of the Ultramicroscope. It moved to different fields. Photosculpture, a technology developed in between 1859 and 1861 by the French sculptor and photograph François Willème (1830 and 1905), used a series of pictures of a subject to create a series of silhouettes to accurately reproduce it in plaster. The principle is rather like the modern Optical Projection Tomography. In 1935, two British Jeffreys Sidney Thomas and Petty Henry John also of Photosculpture Ltd, patented a new photosculpture system using a plane of light to scan the surface of the person and reproduce it with a better precision. It was the first use of line scanning to create a 3D model of the human subject in pictures and reality (plaster) [6]. This use of light sheet imaging for surface monitoring and generation of 3D volumes was further refined during the next 80 years and is now a main element of 3D scanning technology in industry, art, and architecture as well as mundane tasks such as bar code scanning. It finds however also uses in science for instance for macroscopy imaging of insects (3DLSM; [7]).

In the 1970s, groups of researchers investigated the possibility of using the method of laser speckle already developed in solid mechanics and showed that it could be applied to the measurement of fluid velocity fields. In 1977, three different research groups [8–10] independently demonstrated the feasibility of applying the laser speckle phenomenon to fluid flow by measuring the parabolic profile in laminar tube flow. They used a light sheet and established Particle Image Velocimetry (PIV) as an optical method to visualize flow dynamics not only in water but also in gas. Fundamentally, the system used a single fixed illumination plane without 3D capacity, an approach also used in modern Light Sheet Fluorescence Microscopy [11]. PIV became a dynamic field and introduced also 3D imaging (e.g. 3D PIV). Its simplicity made it suitable for extreme environments, for example in underwater systems capable of imaging sea creatures such as larvaceans at great depths (e.g. DeepPIV).

1.3 And here Comes the Flood

The light sheet microscopy winter ended in the last decade of the twentieth century. The revival began with relatively modest contributions whose impact remained confined to the microscopy technology development community. In 1993, light sheet microscopy was for the first time applied to 3D imaging of biological samples - the mouse cochlea [12]. Meanwhile, Ernst H.K. Stelzer and colleagues were developing a theta confocal microscope which used an orthogonal light sheet to illuminate specimens. They published their investigations in two papers that cited the historical Siedentopf [13] and the more recently published Voie [14] work. A few years later, Huber and colleagues presented a portable light sheet-based system for the non-invasive digital and photographic documentation of small objects such

as complete insects without loss of texture, color, or transparency – the 3D light scanning macrophotography (3DLSM) [7]. Building on the use of light sheet-based instruments in fluid mechanics studies, the Jaffe group designed a Thin Light Sheet Microscope (TLSM) for the studies of marine bacteria and larger particles [15].

However, the true revival of the light sheet technique came with the spectacular demonstration of the capabilities of SPIM (Selective and sometimes Single Plane Illumination Microscopy) in imaging of living model organism embryos [16]. It was soon followed by an impressive demonstration of *in toto* recording of an early development of zebra fish [17]. It opened the floodgates. Microscopy is an old and mature research field, and the introduction of a conceptually new design is a rare occurrence. When it happens, the new space becomes quickly populated by the microscopy technology developers who apply older concepts to the new paradigm. This happened in a big way with light sheet microscopy. Since 2004, every component of the light sheet microscope has been re-imagined. Innovation in light sheet formation, scanning, sample mounting, realization of multi angular imaging, and signal detection has led to an explosion of new microscopes [18]. This rapid evolution changed almost everything about the original SPIM set-up. The remaining synapomorphy, a feature shared by all evolutionary descendants of an ancestral species, was the use of light sheet and the physical separation of the illumination and detection. Even systems that rely on a single lens use light sheet and implement this separation [19, 20]. The downside of this Cambrian explosion in the light sheet field was the overproliferation of impenetrable acronyms for the various flavors of the light sheet technology. The paragraph below lists the ever-growing line-up of different realizations of the light sheet microscopes and the associated abbreviations. For a novice consumer of the technology, this menu can be daunting, and it is one of the reasons for putting together this book.

1903 – Ultramicroscope; **1960 – LSP** (Light Scanning Photomacrography); **1980s – PIV** (Particle Image Velocimetry); **1993 –** orthogonal-plane fluorescence optical sectioning (OPFOS); **2002 – TLSM** (Thin Light Sheet Microscopy); **2004 – SPIM** (Selective Plane Illumination Microscopy) or **SPIM (**Single Plane Illumination Microscopy); **2007 – UM** (Ultramicroscope), **mSPIM** (Multidirectional Selective Plane Illumination Microscopy); **2008 – DSLM** (Digital Scanned Laser Light Sheet Fluorescence Microscopy), **OCPI** (Objective Coupled Planar Illumination), **OPM** (Oblique Plane Microscopy), **HILO** (Highly Inclined Laminated Optical); **2009 – TSLIM** (Thin Sheet Laser Imaging Microscopy), **PLIF** (Planar Laser Induced Fluorescence); **2010 – DSLM-SI** (DSLM-Structured Illumination), **MISERB** (Microscopy Self Reconstructing Beam), **SPIM-FCS** (SPIM-Fluorescence Correlation Spectroscopy), **miniSPIM** (obvious!); **2011 – LSFM** (Light Sheet Fluorescence Microscopy), **BBPI** (Bessel Beam Plane Illumination), **iSPIM** (Inverted SPIM), **2P-SPIM** (2 photon SPIM), **IML-SPIM** (Individual Molecule Localization SPIM), **FLIM-SPIM** (Fluorescence Lifetime Imaging Microscopy SPIM); **2012 – 2P-DSLM** (2 photon DSLM), **CSLM** (Confocal Light Sheet Microscopy), **SiMView** (Simultaneous MultiView imaging), **Lightsheet Z.1** (Carl Zeiss GmbH), **OLSM** (Oblique Light Sheet Microscope), **iSPIM** (Inclined SPIM), **MuViSPIM** (Multi View SPIM, Luxendo GmbH), **WAO-SPIM** (Wavefront sensor Adaptive

Optics SPIM), **AO-SPIM** (Adaptive Optics SPIM); **2013 – RSLM** (Reflected Light Sheet Microscopy), **LSBM** (Light Sheet Bayesian Microscopy), **PCLSM** (Prism-Coupled Light Sheet Microscopy), **LST** (Light Sheet Tomography), **OpenSpin**, **OpenSPIM**, **2PE-SPIM** (Two Photon Excitation SPIM), **diSPIM** (Dual view inclined SPIM); **2014 – 2P3A-DSLM** (Two Photon 3 Axis DLSM), **COLM** (Clarity Optimized Light-sheet Microscopy), **MSLM** (Multiple Light Sheet Microscopy), **APOM** (Axial Plane Optical Microscopy), **TC-LSFM** (Tissue culture – LSFM), **LLS** (Lattice Light Sheet), **BTLSM-II** (Bi-directional Triple Light Sheet Microscopy), **SPIM-FCCS** (SPIM Fluorescence Cross Correlation Spectroscopy), **OPTiSPIM** (Optical projection Tomography I SPIM); **2015 – ASLM** (Axially Swept Light Sheet Microscopy), **LEGOLish** (LEGO Light Sheet), **SCAPE** (Swept Confocally-aligned planar excitation), **mu-SPIM**, **oSPIM** (Oblique SPIM), **AdaptiveSPIM** (Obvious!), **doSPIM** (Dual Oblique SPIM), **LatticeSPIM**, **OpenTopSPIM**, **SPIM-Fluid** (Well!); **2016 – diaSLM** (diagonally Swept Light-sheet Microscopy), **CSLM** (Curtailed light sheet microscopy), **RESOLFT** (REversible saturable/Switchable Optical Fluorescence Transitions light-sheet nanoscope), **2PLS-SOFI** (two-Photon super-resolution Light-Sheet imaging via Stochastic Optical Fluctuation Imaging), **STED MISERB** (Another obvious one!), **soLSM** (Single Objective Light-Sheet Microscopy), **cLSFM** (Cardiac LSFM), **PLST** (Polarized Light Sheet Tomography), **PIP** (Plane Illumination Plugin), **SVI-LSM** (Selective Volume Illumination – Light Field Microscopy), **SPIDDM** (Selective Plane Illumination Differential Dynamic Microscopy), **eduSPIM** (Educational SPIM), **2PE-iSPIM** (Two-Photon inverted Selective Plane Illumination Microscopy), **SPIM**, **QuviSPIM** (Quantitative View SPIM, Luxendo GmbH), **TLS-SPIM** (Tiling Light-Sheet SPIM); **2017 – FL-DSLM** (Frequency domain-FLIM DSLM), **HT LSFM** (High Throughput LSFM), **csiLSFM** (coherent structured illumination LSFM)**, aLSFMM** (Augmented Line-Scan Focal Modulation Microscope), **OLST** (Oblique Light Sheet Tomography), **pLSFM** (parallelized LSFM), **sideSPIM** (Easy!); **2018 – 4D LSFM** (like x, y, z, and t?), **3p LSFM** (how many photons?), **3P BB LSFM** (BB for Bessel Beam), **3D LSM** (Why?), **HILO *f*CT** (fluorescence computed tomography), **HILO LCCT** (HILO Live-Cell CT), **hLCTT** (HILO LCCT), **eLCCT** (epi Live-Cell CT), **HLTP** (high-throughput *light-sheet* tomography platform), **SOPI** (scanned oblique plane illumination), **TILT3D** (*Tilted light sheet* microscopy with 3D point spread functions), **LEMOLish** (LEGO Motorized Light Sheet), **LCS-SPIM** (Large cleared sample SPIM), **SPIM-mPIV** (SPIM-micro Particle Image Velocimetry), **socSPIM** (single objective cantilever SPIM), **SLM-SPIM** (Spatial Light Modulator-SPIM), **2019 – AFM-LS** (single objective cantilever SPIM), **AO-LSFM** (single objective cantilever SPIM), **APOM**, **DOPM** (single objective cantilever SPIM), **LSLFM** (single objective cantilever SPIM), **OTLS** (single objective cantilever SPIM), **SCAPE 2.0**, **eSPIM** (SPIM), **Mars-SPIM** (SPIM), **2020 – dOPM** (Dual-view OPM), **LLSM** (Live-cell Lattice *light-Sheet* Microscopy), **LLSDM** (Lattice *Light-Sheet* Difference *Microscopy*), **compactLSFM** (No comment!), **di2CLSFM** (dual-view inverted confocal *light sheet* fluorescence *microscope*), **AFM-SPIM** (Yes!), **2021 – 4D CMLS** (four-Dimensional Cuboid Multiangle illumination-based Light-sheet Super-resolution), **3D LSRM** (*cubic spline algorithm-based depth-dependent fluorescence-free three-dimensional*

light-sheet super-resolution microscopy), **daoSPIM** (Dual-view adaptive optics SPIM), **DMx-LSFM** (Dual arm Multi-level magnification Light Sheet Fluorescence Microscopy), **IHLLS 1L** (Incoherent Holography Lattice *Light-Sheet Single Lens*), **IHLLS 2L** (Incoherent Holography Lattice *Light-Sheet Dual Lens*), **ICHLLS** (Incoherent Color Holography Lattice Light-Sheet), **DO-DSLM** (Deep-learning On-chip-DSLM), **NIR-II-SIM** (Near-InfraRed II Structured-Illumination light-sheet Microscopy), **COMPASSLSM** (Compact Axially Swept Scanned Light Sheet Microscope), **LIC** (Light sheet Imaging Cytometry), **iLIFE** (Integrated Light-sheet Imaging Flow-based Enquiry), **OTAS-LSM** (Open-Top Axially Swept LSM), **sLSM** (Scattering-based LSM), **BLIM** (Bi-directional *Light-sheet* Illumination Microscope), **DC-APOM** (Digital Confocal-APOM), **3D-iLLS** (3D interferometric lattice *light-sheet*), **MT-SPIM** (Multiview Tiling SPIM), **ldSPIM** (local-delivery SPIM), **M-SPIM** (Multi-view SPIM), **2022 – Flexi-SPIM** (So good!), **OPSIM** (OPM with SIM), **IDDR-SPIM** (Isotropic Divide stages-to-process [IDSP] double-ring [DR] modulation-SPIM), **NIR-II-ASLM** (Near-InfraRed II-ASLM), **LLSDM** (Lattice Light-Sheet by fluorescence Differential Detection), **ctASLM** (cleared-tissue ASLM), **SOLEIL** (Single Objective Lens Inclined Light sheet localization microscopy), **AO-LLSM** (Adaptive Optics-LLSM), **VFC-iLIFE** (Volume Flow Cytometry-integrated Light-Sheet Flow based Enquiry). **And Companies – SPOT** (Single Plane Optical Tomography), **Leica DLS** (Digital Light Sheet), **MuviSPIM-LS** (Live Sample), **MuviSPIM-CS** (Cleared Sample), **MuviSPIM-PM** (PhotoManipulation), **MegaSPIM**, **LCS-SPIM** (Large Cleared Sample), **LightSheet 7**, **QLS scope** (Quantitative Light Sheet), **Smart-SPIM**…

1.4 The Building of a Community

The diversity of available light sheet set-ups led to the broadening of the portfolio of applications of light sheet microscopy in biological research. Developmental biology remains the main driver of light sheet technology development [21]. Animal embryos are large, typically spherical objects rather impenetrable to light. The multi-view imaging implemented by light sheet microscopes gives biologists an equivalent of the access to the dark side of the moon – the part of the embryo away from the detection lens of the microscope. Imaging embryos more or less completely allows biologists to ask questions about long-range interaction between tissues that are difficult to realize with other imaging modalities. Next came applications in neurobiology [22]. Here the speed of light sheet set-ups gives not only access to imaging neuronal reporters in freely behaving animals [23], but has also become the method of choice for volumetric imaging of large, fixed brains [24]. Although resolution is typically not mentioned as the strength of light sheet microscopes, thinner light sheets and higher numerical aperture (NA) objectives have brought the benefits of speed and low phototoxicity also to cell biological investigations of subcellular structures [25]. Light sheet microscopes were always geared toward imaging biological objects in 3D and thus became natural choice for the booming field of organoid research [26]. Affordability of the imaging systems made them also an attractive

choice for researchers in evolutionary biology where light sheets are now routinely used to capture the biodiversity of embryonic and adult forms [27]. In fact, one would have a hard time to find a research field that was not impacted by light sheet microscopy. From plants to beating hearts [28, 29], from single molecule biophysics to histology [30, 31], everywhere, the speed, versatility, and low photodamage of light sheet has opened new avenues. Another purpose of this book is to give the glimpse of the impact that light sheet technology has had on biological research.

Light sheet microscopy is an imaging technique developed to help answer biological questions, yet its impact goes beyond biology. Light sheet microscopes are notorious for producing vast amounts of image data. Regardless, whether a biological object is imaged fast, for a very long time or a single vast object is scanned at high-resolution, the results are Terabytes of imagery. Engineering challenges associated with storing such data, moving them around and opening them for inspection required definition of new ways for representing image data in computers [32]. Moreover, the light sheet data are not only big, but they are also often not directly usable in their raw form. Microscopy image post-processing kept researchers in applied computer science busy long before introduction of light sheets, but with their arrival the challenges multiplied due to the sheer scale of the image data [33]. Finally, the diversity of microscopes combined with diversity of biological applications inevitably resulted in a tremendous diversity of image analysis tasks that need to be solved for the big image data. Together, these challenges have led to a much closer collaboration between biology and computer science communities on light sheet datasets. The beneficial side effect of this interdisciplinary collaboration has been the development of powerful open-source platforms designed to deal with image analysis at scale [34]. Several chapters in this book highlight how light sheet fueled new concepts in biological image data analysis, making the algorithms resilient to whatever volume of data microscopists ultimately reach.

Over the past two decades, an active interdisciplinary research community formed around light sheet microscopy. It unites physicist, engineers, biologists, and computer scientists in a quest to build, disseminate, and apply ever more sophisticated light sheet microscopes to frontier biological questions. This community was initially small and met for intense invitation-only workshops [35]. As it grew, light sheet microscopy became increasingly featured at major microscopy conference venues and the light sheet dedicated workshops grew to full scale conferences. The experimental light sheet systems developed in academic labs, typically for specific research purposes, have become increasingly complemented by general purpose microscopy products developed at companies. An important role in the growth of the light sheet community was played by the EMBO practical courses where the academic labs interacted with the commercial sector [36]. The level of trust and information exchange among the two worlds are rather unprecedented in the light sheet field and supports sustainable development of the technology. It is well documented by the productive co-existence of several open-access light sheet microscopy projects alongside similar but more advanced commercial products [37]. This book reflects the partnership between academia and industry through several chapters dedicated to the open access and commercially available systems.

In 2008 a typical light sheet microscope was a complex-looking arrangement of Thorlabs components on an optical table curiously distinguished by the absence of an eye piece. Nowadays, it is more likely to be a shiny box with a company logo and still no eye piece. Decade ago, light sheet microscopists could be seen running around with a bouquet of capillaries loaded with samples embedded in agarose. These days, light sheet microscopes have been adapted to almost all possible sample-mounting paradigms including the dreaded coverslips. While early on light sheet image processing and analysis was a dark magic accessible only to computer geeks, now it is a matter of clicking a button (almost). Fifteen years ago, we would be impressed with volumetric imaging that lasted for a day or with capturing a slice through a beating heart. Today, organoids are happily growing for weeks under constant surveillance of light sheet microscopes, and light sheets are slicing through tissues expanded to almost macroscopic dimensions. The progress has been spectacular, and it is difficult to predict what will come next. It took ten years to put together this book. Let us hope that in another ten years we and/or our AI assistants will look with nostalgia at the simple light sheet microscopes described in this book, dealing with such ridiculously small data, and achieving only supra-atomic resolution in imaging of natural as opposed to synthetic biological systems.

References

1 Cahan, D. (1996). The Zeiss Werke and the ultramicroscope: the creation of a scientific instrument in context. In: *Scientific Credibility and Technical Standards in 19th and early 20th century Germany and Britain*. Archimedes, vol. 1 (ed. J.Z. Buchwald). Dordrecht: Springer https://doi.org/10.1007/978-94-009-1784-2_3.

2 Siedentopf, H. and Zsigmondy, R. (1903). Über Sichtbarmachung und Groessenbestimmung ultra mikroskopischer Teilchen, mit besonderer Anwendung auf Goldrubinglaesern. *Annals of Physics* 10: 1–39.

3 Thirkill, H. (1909). Ultramicroscopy and ultramicroscopic particles. *Science Progress in the Twentieth Century (1906–1916)* 4 (13): 55–89.

4 Zsigmondy, R. (1916). Nobel Lecture. NobelPrize.org. Nobel Prize Outreach AB 2023. https://www.nobelprize.org/prizes/chemistry/1925/zsigmondy/lecture/ (accessed 13 February 2023).

5 Mappes, T., Jahr, N., Csaki, A. et al. (2012). The invention of immersion ultramicroscopy in 1912-The Birth of Nanotechnology? *Angewandte Chemie International Edition* 51 (45): 11208–11212.

6 Jeffreys S. T. and Petty H. J. (1939). Photosculpture. US patent No. 2163124A. https://patents.google.com/patent/US2163124A/en (accessed 13 February 2023).

7 Huber, D., Keller, M., and Robert, D. (2001). 3D light scanning macrography. *Journal of Microscopy* 203: 208–213. https://doi.org/10.1046/j.1365-2818.2001.00892.x.

8 Barker, D.B. and Fourney, M.E. (1977). Measuring fluid velocities with speckle patterns. *Optics Letters* 1: 135–137.

9 Dudderar, T.D. and Simpkins, P.G. (1977). Laser speckle photography in a fluid medium. *Nature* 270: 45–47.

10 Grousson, R. and Mallick, S. (1977). Study of flow pattern in a fluid by scattered laser light. *Applied Optics* 16: 2334–2336.

11 Karaköylü, E.M., Franks, P.J.S., Tanaka, Y. et al. (2009). Copepod feeding quantified by planar laser imaging of gut fluorescence. *Limnology and Oceanography: Methods* 7: https://doi.org/10.4319/lom.2009.7.33.

12 Voie, A.H., Burns, D.H., and Spelman, F.A. (1993). Orthogonal-plane fluorescence optical sectioning: three-dimensional imaging of macroscopic biological specimens. *Journal of Microscopy* 170 (3): 229–236.

13 Lindek, S., Pick, R., and Stelzer, E.H.K. (1994). Confocal theta microscope with three objective lenses. *The Review of Scientific Instruments* 65: 3367–3372.

14 Stelzer, E.H.K., Lindek, S., Albrecht, S. et al. (1995). A new tool for the observation of embryos and other large specimens: confocal theta fluorescence microscopy. *Journal of Microscopy* 179: 1–10.

15 Fuchs, E., Jaffe, J., Long, R., and Azam, F. (2002). Thin laser light sheet microscope for microbial oceanography. *Optics Express* 10 (2): 145–154.

16 Huisken, J., Swoger, J., Del Bene, F. et al. (2004). Optical sectioning deep inside live embryos by selective plane illumination microscopy. *Science* 305 (5686): 1007–1009. https://doi.org/10.1126/science.1100035. PMID: 15310904.

17 Keller, P.J., Schmidt, A.D., Wittbrodt, J., and Stelzer, E.H.K. (2008). Reconstruction of zebrafish early embryonic development by scanned light sheet microscopy. *Science* 322 (5904): 1065–1069.

18 Power, R.M. and Huisken, J. (2017). A guide to light-sheet fluorescence microscopy for multiscale imaging. *Nature Methods* 14 (4): 360–373.

19 Bouchard, M.B., Voleti, V., Mendes, C.S. et al. (2015). Swept confocally-aligned planar excitation (SCAPE) microscopy for high-speed volumetric imaging of behaving organisms. *Nature Photonics* 9 (2): 113–119.

20 Dunsby, C. (2008). Optically sectioned imaging by oblique plane microscopy. *Optics Express* 16 (25): 20306–20316.

21 Weber, M. and Huisken, J. (2011). Light sheet microscopy for real-time developmental biology. *Current Opinion in Genetics & Development* 21 (5): 566–572.

22 Keller, P.J., Ahrens, M.B., and Freeman, J. (2014). Light-sheet imaging for systems neuroscience. *Nature Methods* 12 (1): 27–29.

23 Ahrens, M.B., Orger, M.B., Robson, D.N. et al. (2013). Whole-brain functional imaging at cellular resolution using light-sheet microscopy. *Nature Methods* 10 (5): 413–420.

24 Ueda, H.R., Ertürk, A., Chung, K. et al. (2020). Tissue clearing and its applications in neuroscience. *Nature Reviews Neuroscience* 21 (2): 61–79.

25 Chen, B., Legant, W.R., Wang, K. et al. (2014). Lattice light-sheet microscopy: imaging molecules to embryos at high spatiotemporal resolution. *Science* 346 (6208): 1257998.

26 Serra, D., Mayr, U., Boni, A. et al. (2019). Self-organization and symmetry breaking in intestinal organoid development. *Nature* 569 (7754): 66–72.

27 Wolff, C., Tinevez, J., Pietzsch, T. et al. (2018). Multi-view light-sheet imaging and tracking with the MaMuT software reveals the cell lineage of a direct developing arthropod limb. *eLife* 7: e34410.

28 Mickoleit, M., Schmid, B., Weber, M. et al. (2014). High-resolution reconstruction of the beating zebrafish heart. *Nature Methods* 11 (9): 919–922.

29 Valuchova, S., Mikulkova, P., Pecinkova, J. et al. (2020). Imaging plant germline differentiation within Arabidopsis flowers by light sheet microscopy. *eLife* 9: e52546.

30 Ritter, J.G., Veith, R., Veenendaal, A. et al. (2010). Light sheet microscopy for single molecule tracking in living tissue. *PLoS One* 5 (7): e11639.

31 Patel, K.B., Liang, W., Casper, M.J. et al. (2022). High-speed light-sheet microscopy for the in-situ acquisition of volumetric histological images of living tissue. *Nature Biomedical Engineering* 6 (5): 569–583.

32 Pietzsch, T., Saalfeld, S., Preibisch, S., and Tomancak, P. (2015). BigDataViewer: visualization and processing for large image data sets. *Nature Methods* 12 (6): 481–483.

33 Preibisch, S., Saalfeld, S., Schindelin, J., and Tomancak, P. (2010). Software for bead-based registration of selective plane illumination microscopy data. *Nature Methods* 7 (6): 418–419.

34 Eliceiri, K.W., Berthold, M.R., Goldberg, I.G. et al. (2012). Biological imaging software tools. *Nature Methods* 9 (7): 697–710.

35 Reynaud, E.G. and Tomancak, P. (2010). Meeting report: first light sheet based fluorescence microscopy workshop. *Biotechnology Journal* 5 (8): 798–804.

36 Reynaud, E.G., Peychl, J., Huisken, J., and Tomancak, P. (2015). Guide to light-sheet microscopy for adventurous biologists. *Nature Methods* 12 (1): 30–34.

37 Pitrone, P.G., Schindelin, J., Stuyvenberg, L. et al. (2013). OpenSPIM: an open-access light-sheet microscopy platform. *Nature Methods* 10 (7): 598–599.