A versatile and customizable low-cost 3D-printed open standard for microscopic imaging

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Modern microscopes used for biological imaging often present themselves as black boxes whose precise operating principle remains unknown, and whose optical resolution and price seem to be in inverse proportion to each other. With UC2 (You. See. Too.) we present a low-cost, 3D-printed, open-source, modular microscopy toolbox and demonstrate its versatility by realizing a complete microscope development cycle from concept to experimental phase. The self-contained incubator-enclosed brightfield microscope monitors monocyte to macrophage cell differentiation for seven days at cellular resolution level (e.g. 2 μm). Furthermore, by including very few additional components, the geometry is transferred into a 400 Euro light sheet fluorescence microscope for volumetric observations of a transgenic Zebrafish expressing green fluorescent protein (GFP). With this, we aim to establish an open standard in optics to facilitate interfacing with various complementary platforms. By making the content and comprehensive documentation publicly available, the systems presented here lend themselves to easy and straightforward replications, modifications, and extensions.

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Growing demand in biological research for spatial and temporal resolution, imaging volume, molecular specificity, and high throughput leads to ever more complex and expensive microscopes\textsuperscript{12}. Alongside numerous imaging modalities, long-term observations of living organisms, which have minimal impact on their natural behavior, became an important aspect in light microscopy. The need to keep the cells in a well-controlled environment poses additional constraints being addressed by imaging inside an incubator\textsuperscript{3–8} or exploiting on-microscope incubator units\textsuperscript{5–8}. Assembling, maintaining and improving microscopes, as well as analyzing and verifying the produced data very often requires a consulting specialists dedicated to the respective instrument, thus further separating microscope engineers from their users\textsuperscript{9,10}. For a large variety of imaging tasks, such as those mentioned above, tailored solutions are indeed commercially available, yet they are often costly, hard to extend or modify and rarely documented sufficiently to enable users adapting them for “out-of-the-box tasks”, outside the range of their primary purposes.

Separately, in light of the growing pressure to publish as soon as possible, science is approaching a reproducibility and quality crisis\textsuperscript{11}. Open research, in which every step is recorded transparently and made fully accessible to the general public, can help to restore the confidence in scientific literature, which has been visibly compromised in recent years\textsuperscript{12}.

Modern optical setups are reaching immense complexity, combining a growing number of optical and photomechanical components. They typically originate from different manufacturers adhering to various industry standards such as the International Organization for Standardization (ISO) or Royal Microscopy Society (RMS), whose intra-compatibility is often not guaranteed. This makes it particularly hard to tailor or even reconfigure optical systems, requiring handcrafted adapters or unnecessarily long attachments compromising the systems' integrity and stability.

What we see as a substantial space for improvement, is an open standard\textsuperscript{13} permitting straightforward interfacing between constituents of modern microscopes including sources, optics, optomechanics, and detector components. Such platform would facilitate simple constructions of versatile imaging instruments, easy to adapt to almost any imaging task at hand. The change from one imaging system to another could thus be reduced to a mere reconfiguration rather than a new design. Such a tool would be useful not only for research, but also immensely helpful in optics education. It would substantially reduce the effort required to build a setup and allow students to actively perform system reconfigurations within minutes. Such hands-on experience would lead to understanding and enabling everyone to perceive optics as a playground, where many ideas can easily be explored. In order to realize such a system, an open standard is paramount, as only in this way an effortless reconfiguration can be permitted without being overly restrictive to the possibilities. Luckily many great steps in this direction have already been made.

Recent approaches like the Flamingo\textsuperscript{9,10} set out to establish light sheet microscopy-as-a-service to everyone, thereby addressing the issue of accessibility. A number of very well documented open-source projects such as the lattice light sheet\textsuperscript{14} or open-SPIM\textsuperscript{15} nowadays spawn educational workshops and thereby attract users to contribute to its development. In terms of hardware design, projects like the “open-flexure stage”\textsuperscript{16}, the “100 € lab”\textsuperscript{17}, the smartphone-based “Foldscope”\textsuperscript{18} and open-source single-molecule localization microscopy (SMLM) systems\textsuperscript{19,20} demonstrate flexible and low-cost microscopy solutions capable of great performance. More generic approaches have been realized in the form of an opto-mechanical toolbox\textsuperscript{21} and in form of a functional unit box-like approach called μ Cube\textsuperscript{22}. With the widespread availability of and easy access to rapid prototyping tools such as 3D printing, programmable electronics (e.g. Arduino\textsuperscript{23}), high-quality cameras in smartphones or mini-computers (Raspberry Pi\textsuperscript{24}), it is now indeed possible to develop an open standard that is accessible to everyone, thus ensuring wide dissemination, adaptation and expansion. Impairments to image quality due to less corrected inexpensive optical components or less stable mechanical arrangements, can often be real-time compensated by smart electronics and software algorithms. Methods like autofocus-routines, deconvolution\textsuperscript{25}, or the recovery of hidden information like the quantitative phase using simple LED arrays\textsuperscript{26} are recent examples of such possibilities.

With our UC2 (You. See. Too) approach, we strive to create such open standards. Relying on the concepts of matching focal planes (Fig. 1a) makes UC2 particularly easy to use, flexible to reconfigure and versatile for a large range of applications. It is equipped with open-source software, open design-files, and blueprints for a large variety of setups and openly accessible documentation. UC2 facilitates a cost- and time-efficient opportunity for pupils and students at all levels to experience designing and applying a variety of complex optical setups. It further enables access to modern light microscopy for a wide-spread group of users and developers by exploiting purely off-the-shelf consumer-available components (Supplementary Notes 1 and 8 for the bill of material) and thereby creating inexpensive microscopic imaging devices for around 100–400 Euro.

The manuscript details the entire development cycle of an incubator-enclosed bright-field microscope from its assembly to the successful application, where four identical systems are exploited to a parallel 168 h long imaging session of monocyte to macrophages in-vitro. The device is further transformed into a light sheet microscope, which exploits the original bright-field microscope assembly and only a few additional components. In order to demonstrate UC2’s applicability to biomedical research, we provide imaging results from a variety of biological samples including fluorescing transgenic human pulmonary microvascular endothelial cells, Drosophila melanogaster, zebrafish, E. coli bacteria, which have been obtained using a range of UC2 based microscope modes, particularly the bright-field, wide-field fluorescence, image scanning microscopy, intensity diffraction tomography, and structured illumination.

Results

Open-Standard: The Basic Cube. Modern microscopes with infinity-corrected objective lenses often follow the so-called 4f-configuration (Fig. 1a), where lenses are aligned in a way that focal-planes (f) of adjacent elements coincide to limit the amount of optical aberrations, to realize tele-centricity, and to predict the system behavior using Fourier-optics\textsuperscript{27}. The name 4f results from the sum of the focal-distances of a simple imaging system with two adjacent lenses stacked with coinciding focal planes, leading to 2f per lens, hence 4f in total. We adapt this inherently modular design with a generic 3D-printable framework, in which individual modules (i.e. optical building blocks) in the form of cubes Fig. 1b and Supplementary Notes 2 are arranged in such a way that the focal planes of optics in successive cubes often coincide.

By analyzing many available optical components, imaging systems, and frameworks, we found that a design pitch of \( a_{\text{block}} = 50 \) mm seems to optimally balance compatibility, handling, and flexibility for enabling Fourier-Optical (4f) setups. Separating the cube into a base and a lid simplifies printing using standard fused deposition modeling (FDM) 3D-printers and allows to easily insert components as plug-ins.

Having neodymium ball magnets (\( \mathcal{O}_{\text{magnet}} = 5 \) mm) positioned in a grid pattern on an extendable baseplate and ferro-
magnetic cylindrical bolt screws (DIN 912) sitting in the cube’s edges allows a stable and precise magnetic mount. Multiple orientations of baseplates allow to built in three dimensions. We found a four-point fixation as a good compromise between the common rectangular arrangement of optical setups and mechanical stability.

External electro and optical components (e.g. lenses, mirrors, LEDs; see Fig. 1b) and already existing equipment (e.g. rail-systems from Thorlabs, Quioptics, Edmund Optics) can be easily adapted by plug- and modifiable inserts (see Supplementary Notes 4). A module developer kit (MDK, Supplementary Notes 1) with a generic reference design for customized inserts provides a simple interface to work or add designs to the toolbox, even for users lacking technical training.

Scaling complexity of optical systems starting from a simple magnifying glass up to a fully working light sheet fluorescence microscope (Fig. 2) is ensured by relying on the previously introduced library of modules that are combined and put in the appropriate order (Supplementary Notes 5). Adding more advanced consumer electronics (cameras, motors, video-projects, etc.) allows the use as smart microscopes and enables remote control. Micro-controllers ensure wired (i.e. I2C) or wireless (i.e. WiFi, IoT-based protocol using Message Queuing Telemetry Transport (MQTT)) communication interface to trigger light-settings or focusing mechanisms (Supplementary Notes 6.1). Power is supplied through the conducting magnets or wires with rectifiers in the cubes.

**Versatile: a bright-field microscope for long-term incubator-enclosed in-vitro imaging.** The development cycle of creating a microscope visualized in Fig. 2 starts by identifying a problem which requires optical imaging. Here it is the minimization of...
external influences causing problems such as bacterial infections in in-vitro-experiments (Fig. 2a) of eukaryotic cells. We found that a small inverted microscope (Fig. 2b) in transmission bright-field-mode (BF) with an optical resolution on the subcellular level (i.e. $<2.2 \mu m$) for $\approx 300$ Euro fulfills the quality requirements for long-term monitoring of human primary cell cultures. After combining the UC2-basic cubes, base-plates, inserts, and necessary components digitally to test for spatial limitations (Fig. 2c) we 3D-printed and assembled the system (Fig. 2d). For cross-verification, stability measurements and to increase the throughput, we placed four BF-sets $(2 \times PC_{1}, 2 \times MQTT$-interface; two of them shown in Fig. 2e) into a single incubator. We designed a graphical user interface (GUI) on the Raspberry Pi, to preview the region-of-interest, set the imaging parameters (focus, illumination) and ensure autonomous image acquisition (Supplementary Notes 6.1).

We performed multiple long-term measurements under conditions of high humidity ($\approx 100\%$) and at $\approx 37^\circ C$, $CO_2 = 5\%$ over 7 days taking images at a rate of 1 frame per minute. This way we are continuously monitoring the morphological changes and plasticity during monocyte to macrophage differentiation (see Fig. 3a and b). As part of the innate immune system, macrophages notably reside within the tissue, where they act as phagocytosing cells involved in the clearance of pathogens and dead cells. Monocytes can be isolated and differentiated in-vitro within 7 days in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) to macrophages. During the differentiation process, these cells increase in size and are able to change their morphology depending on their polarization.

We cultured monocytes in 3 ml X-Vivo medium within 35 mm dishes. The shape of adhesive monocytes appears round and elongates during cell movement (not further quantified). The graph in Fig. 3d shows the increase in the area of individual macrophages over time. We observed a significant increase of size within 5000 min observation (Analysis Of Variance, NOVA with post-hoc Turkey’s) in agreement with published reports. Macrophage locomotion and phagocytosis is mediated by the concerted formation of pseudopodia. We were able to monitor pseudopod formation and to follow macrophage movement and associated morphological alterations in cell shape. This enables us to relate the elongated form of the macrophage to its movement (see Supplementary Fig. 1), which is increased upon detection of pathogens, damage associated molecular pattern, or cytokines. We also observed phagocytosis (Supportive Notes 1) of dying and dead cells (Fig. 2).

During imaging, the magnetically-mechanically fixed in-vitro sample (e.g. $\varnothing = 35 \text{ mm}$ petri-dish, organ-on-a-chip, or standard microfluidic chips, e.g. Ibidi $\mu$-chip) experienced a significant focus drift due to temperature-dependent deformation (see Supplementary Video 1), especially using Poly-Lactic Acid (PLA, Supplementary Notes 7.2). We found that Acrylnitril Butadien Styrol (ABS) outperformed PLA in terms of stability at higher temperatures. Even though a working autofocus routine (see Supplementary Notes 7.3) was developed, our ABS-printed stages proved sufficiently stable after a thermal equilibration period and so we decided to conduct our long-term incubator-enclosed experiments without the use of autofocus (see Support Videos 1/2). A temporal drift analysis of the PLA printed stage is presented in Supplementary Notes 7.2.
Enabling: light sheet microscope for educational areas. In this section, we demonstrate versatility by transforming the BF-system of the previous chapter into a light sheet microscope (Fig. 2g) by exchanging the LED array in favor of a laser-pointer, adding a second microscope-objective, beam-expander, cylindrical lens, and the sample stage using a larger base plate. A video explaining the conversion together with a detailed conversion recipe and a detailed scheme of the open SPIM-inspired\(^\text{15}\) setup is given in Supplementary Video 4) and Supplementary Notes 7.7 respectively. We acquired a 3D data-stack of zebrafish

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**Fig. 3 UC2 imaging modalities.** a, b Variation in macrophage’s morphology, where elongated cells are clearly visible after 42 h (red arrow) imaged in transmission mode. c The bright-field channel superposed with a fluorescent signal of fixed macrophages labeled with CellTracker green captured with the incubator-enclosed microscope. d The growth of a differentiating cell is plotted as the average area of cells across multiple time-steps and different experiments (n = 4). Whisker plots: 10\(^{\text{th}}\) – 90\(^{\text{th}}\) percentile, the box represents the 25\(^{\text{th}}\) and 75\(^{\text{th}}\) percentile with the line in the box marking the median. Statistical testing with one-way ANOVA and Tukey’s correction with GraphPad Prism (GraphPad, CA, USA), p = 0.034 (F = 10.76, DF = 11). Data of four independent experiments is shown. e Wide-field fluorescence (top-left) and the computed “superconfocal” result (bottom-right) of GFP-labeled Human Pulmonary Microvascular Endothelial Cells (HPMCs) illuminated with a laser-scanning projector, recorded with a cellphone camera. The zoomed-in images show the improvement of the optical sectioning in the case of structured illumination (g) compared to wide-field (f), where smaller cell-structures are lost. h A comparison of the same sample acquired with a commercial laser-scanning confocal microscope. A benchmark from the infinity-corrected fluorescence microscope using the Raspberry Pi (i) and cellphone camera (j) and a research-grade microscope (k) of mCLING-ATTO 647N labeled fixed E. coli bacteria, where the cellphone clearly resolved the bacterial membrane. l A Z-stack of a GFP-expressing zebrafish acquired with the UC2-light sheet. m LED matrices can rapidly switch between bright- and dark-field imaging as shown in (n).
larva expressing GFP in the blood vessels which was further drift-corrected and deconvolved using the “GenericDeconvolution” program by Heintzmann et al. (available upon request) (Fig. 3l, Supplementary Fig. 3). At the moment the results show merely a proof of concept that it is possible to build a light sheet system at such a low price (400 Euro). Better optical components and better adaptation to applications would be necessary for better performance. However, our light sheet microscope proved its usefulness in the educational area, giving the users a valuable insight into a method they frequently work with but know it only as a black box. We analyzed the minimum required number of printed and off-the-shelf components to build the formerly mentioned setups as well as telescopes, projectors, Abbe diffraction experiments, or holographic (e.g. lens-less) imaging devices in a cost- and resource-effective way to compile a ready-to-print collection of open-sourced parts and documentation—named “TheBOX” (see Supplementary Notes 7.11) and a version optimized for microscopy training courses “CourseBOX”. It is supported by continuously improving documentation with step-by-step guides and tutorials. We tested the system at various conferences, workshops, and educational environments (see Supplementary Notes 9) and obtained plenty of constructive feedback to further improve the system. We noted a declining usage- and understanding barrier of new workshop-participants during these iterations due to improvements in documentation and steadily increased robustness of the cubes.

Multimodal: fluorescence and label-free imaging. Although we were able to show that fluorescence imaging is possible using the UC2 incubator-enclosed and light sheet configuration (e.g. fluorescence overlay in Fig. 3c), the sensitivity of the Raspberry Pi camera suffered from high noise contribution as quantified in Supplementary Notes 7.5 and the reduced sensitivity due to the Bayer pattern. Replacing the RGB Raspberry Pi camera with a cellphone featuring a back-illuminated monochromatic camera (P20 Pro, Huawei, China), capturing up to 4× more photons improved the imaging performance significantly. A quantitative comparison was obtained by acquiring mCLING-ATTO 647N (SYSY, Germany) labeled E. coli using a UC2 laser-based infinity optics fluorescence microscope (×100, NA = 1.25 oil, λex = 635/637 nm, see Supplementary Notes 7.4) equipped with a Raspberry Pi or cellphone camera with a standard research-grade microscope (Zeiss Axiosvert TV, ×100, NA = 1.46) in Fig. 3i–k. The cellphone camera clearly resolved the plasma membrane of the bacteria (see Fig. 3i–k, small sub ROI). We determined the practical resolution to be a cellphone = 0.6 μm compared to dBAUSSI = 1.13 μm and dZEISS = 0.27 μm, at similar experimental conditions (e.g. exposure time, gain, laser intensity) using Fourier ring correlation (FRC)38 (further quantified in Supplementary Notes 7.4). Using the GUI on the Raspberry Pi, we were further able to schedule a time-lapse series of moving fixed but mobile (e.g. in aqueous suspension) E. coli bacteria at 1 fps using the previously mentioned infinity-corrected setup (see Supplementary Video 7).

UC2 also enables the creation of more sophisticated systems. As an example, we present the creation of an image scanning microscope (ISM)39, where we replaced the excitation laser in the previous infinity-corrected setup with a customized module hosting a laser-scanning video-projector (Sony MP.CL1A, Japan; Supplementary Notes 7.9). We compare images of GFP-labeled Human Pulmonary Microvascular Endothelial Cells (HPMEC) acquired with the UC2-ISM (Optika, ×20, NA = 0.4, N-plan, further information Supplementary Notes 7.9) to a state-of-the-art laser-scanning confocal microscope (Leica TCS SP5, Fluotar ×20, NA = 0.5, Germany) in Fig. 3e–h. The computationally reconstructed “superconfocal” image40 Fig. 3g shows optical sectioning compared to the wide-field equivalent Fig. 3f.

Further, when using an LED matrix (Adafruit #1487, NY, USA) as a light-source in transmission mode, the selection of the illumination wavelength, particular patterns for contrast-maximization41 using the openKoehler module (Supplementary Notes 7.10), dark-field illumination (Fig. 3n) or quantitative phase-methods like “(quantitative) differential phase contrast” (qDPC26, see Supplementary Notes 7.6) and “Fourier Ptycho-Graphy Microscopy” (FPM42) are straightforward. We replaced the matrix with an LED ring (Adafruit#1463) to demonstrate computational refocusing of a recovered phase map of cheek cells (Fig. 3m) to apply “Annular Intensity Diffraction Tomography” (aIDT43, see also Supplementary Notes 7.6 and the reconstructed Z-stack in Supplementary Video 3).

Discussion

We here introduce a modular toolbox with the potential to serve as the truly open standard. This standard is defined by the dimensions and shape of the basic cube based on a variety of parameters and experiences to be as generic as possible. Our aim to not only create new parts, but define a common interface for the ever-growing variety of different components, was achieved. By interfacing UC2 also with existing railings or cage systems from Thorlabs, Newport, Edmund Scientific, and the like as well as with existing lab equipment, we facilitate users to start interfacing and reusing existing components and setups, therefore reinforcing the idea as an open standard.

We demonstrated the inherent versatility of the UC2 toolbox by first realizing a whole microscope life-cycle in a few steps for an incubator-enclosed bright-field configuration and then presented examples of how exchanging a few components can implement different modern microscopic techniques.

Yet there are of course also limits with respect to the long-term stability of 3D-printed setups, which are attributed to the PLA and ABS materials which deform in dependence of temperature. The iterative design-process resulted in a replaceable mechanical module with minimal bending which can be actively supported by an autofocus-routine or manual refocus. This allowed us to achieve long-term stability in multiple experiments imaging with 4 incubator-enclosed microscopes over 7 days without notable focus-drift, where in-vitro macrophage differentiation was continuously observed. Access to long-term measurements allowed the replication of data published by Xia et al.37, where the elongated shape of macrophages is correlated to their movement. The incubator-enclosed microscope proved the benefits of its inherent small footprint and high throughput capability by parallelizing experiments on a very low budget while providing customized imaging tools for e.g. microfluidic chips or inside high-safety biological environments (BSL3 +) at the same time.

Another major limiting factor in fluorescence imaging (e.g. light sheet setup) is the performance of the Raspberry Pi camera used (v2.1), which can be improved with more sensitive camera sensors, e.g. from mobile phones or industrial cameras. Therefore, the light sheet system is more of a low-cost (~400 Euro) proof-of-concept, which provides valuable insight into the method for educational users, rather than being a productive imaging tool.

With “TheBox” we introduced a sophisticated toolset for educational purposes. Together with a series of ready-to-use documentations, optical concepts (interference, image formation, etc.), and a variety of light microscopy methods we provided an openly accessible microscopic platform for a price between 100 and 600 Euro. This gives students and end-users the possibility to experience how advanced optical methods work and promote interdisciplinary approaches where several educational...
Several concepts are interacted to make UC2: an embedded computing platform that provides a low-cost solution for scalable optical microscopy. A 7-inch touchscreen display is used to collect images, and a 14-bit, 2400×1800 resolution camera is employed for high-quality image capture. The system is designed such that the camera controller and the computer can be separately replaced if needed.

The UC2 system is designed with a focus on optical microscopy and automation, allowing for easy integration into existing setups. The system includes a custom-made motorized stage with a resolution of 0.15 mm, providing high resolution and stability for all optical setups. The stage allows for precise control over the sample position, making it ideal for time-lapse imaging experiments.

In addition to the hardware components, software tools are provided to enhance the user experience. Fiji is used for image processing, and various libraries are included for data analysis and visualization. The system is designed to be open-source, allowing for customization and adaptation to specific research needs.

The UC2 toolbox is designed to be scalable and can be easily integrated into existing microscope setups. It is particularly suited for applications where high resolution and precision are required, such as in cellular biology and neuroscience. The system is designed to be user-friendly, with an intuitive interface and comprehensive documentation to aid in its use.

In conclusion, UC2 is a versatile and cost-effective solution for optical microscopy, providing a powerful platform for researchers to conduct experiments with high precision and resolution. Its open-source nature and modular design make it an ideal tool for both academic and industrial applications, enabling a wide range of scientific discoveries.
Data availability
All the data responsible for producing the figures in this article are available in the Zenodo repository https://doi.org/10.5281/zenodo.4018965. All the data supporting the findings of this study are available from the corresponding authors upon reasonable request.

Code availability
All files such as 3D printing STL and design files, Python code and a GUI for data acquisition as well as a bill of material and user guide for printing/assembling and acquisition can be found in publicly available github repositories. We host all hardware-related components in https://github.com/bionanoimaging/UC2-GIT, assigned with the https://doi.org/10.5281/zenodo.4041339 and all software-related components in https://github.com/bionanoimaging/UC2-Software-GIT, assigned with the https://doi.org/10.5281/zenodo.4014134. The GenericDeconv program for deconvolution is available upon request.
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Author contributions
B.D., R.L., and S.C. conceptualized the UC2 idea, B.D., R.L., S.C., B.M., R.H. and H.W. performed data curation, B.D., R.L., and S.C. contributed to formal analysis, B.D., B.M., and H.W. developed hardware components, B.D., R.L. and X.U. developed acquisition software, B.D., R.L., and R.H. organized funding acquisition, B.D., R.H. and R.L. supervised, conceived, and planned the project, designed the instrument, interpreted the data, and wrote the manuscript. All authors read and approved the final manuscript.

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