Review article

Haoran Wang, Rainer Heintzmann and Benedict Diederich*

The power in your pocket – uncover smartphones for use as cutting-edge microscopic instruments in science and research

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Abstract: Since the development of the first light microscope over 400 years ago, the technology has continuously evolved and established itself as a powerful tool, especially in biology, diagnostics and point-of-care (PoC) applications. The miniaturization of mass-produced actuators and sensors enables the use of technically extremely complex functions in smartphones at a very low price. They can be used to implement modern microscopy methods for use in places where access to such techniques is often very limited. In this review, we show how easy it is to integrate a smartphone into the everyday microscopy-imaging routines of biology research. Such devices have also been used to identify diseases directly at the patient. Furthermore, we demonstrate how constantly increasing computing power in combination with the steadily improving imaging quality of cameras of handheld devices enables the realization of new biomedical imaging methods, which together with commercially available and 3D-printed components make current research available to a broad mass. Examples are smartphone-based super-resolution microscopy (SRM) or task-specific single-board computer-based devices, which can analyze plankton in sea water.

Keywords: diagnostics@home; low-cost; microscopy; open-source hardware; point-of-care; smartphone.

***Corresponding author: Benedict Diederich**, Leibniz Institute of Photonic Technology, Albert-Einstein-Straße 9, 07745 Jena, Germany; and Institute of Physical Chemistry, Abbe Center of Photonics, Helmholtzweg 4, 07745 Jena, Germany,
E-mail: benedictdied@gmail.com. https://orcid.org/0000-0003-0453-6286
Haoran Wang, Leibniz Institute of Photonic Technology, Albert-Einstein-Straße 9, 07745 Jena, Germany
Rainer Heintzmann, Leibniz Institute of Photonic Technology, Albert-Einstein-Straße 9, 07745 Jena, Germany; and Institute of Physical Chemistry, Abbe Center of Photonics, Helmholtzweg 4, 07745 Jena, Germany. https://orcid.org/0000-0002-4950-1936

1 Introduction to modern smartphones

Starting with the first handheld mobile phone in the 1980s the modern cellphone became one of the fastest developing innovations reaching approx. 3 billion users every day [1]. Recent devices are the result of a continuous development process to make cutting-edge technology available on a large scale and small footprint. A few large manufacturers share the market with global sales of $400 billion per year [2] currently relying on only two major software eco systems; the Android and iOS operating systems. To increase their respective market share, smartphone manufacturers are forced to attract the interest of customers with ever better technological refinements in the form of better hardware, better computing performance or user experience [3–5].

The rise of social media/networks and the ability to easily sharing photos with the community directly from the cellphone has led to a rapid evolution of cellphone cameras. Increased pixel number and sensor size, as well as the widespread use of back-illuminated (BI) CMOS sensors to increase the fill factor and the signal-to-noise (SNR) performance created highly integrated electronic assemblies. A dedicated image signal processors (ISP) realizes real-time image processing such as denoising [6], autofocus [7] and image stabilization [8]. Together with recent advances in highly optimized objective lenses realized using a concatenation of multiple injection molded aspheric lenses [9], cellphone cameras aim to compete with digital still cameras and even digital single-lens reflex cameras (DSLR) over the last decade [10]. The optical design of these lenses must meet a number of requirements identified by users as necessary for a good camera, while also being as compact as possible to make efficient use of the limited space available in the smartphone assembly. Features such as a large field of view, a flat camera module, the ability to refocus the image, a well-performing modular transfer function (MTF) across the entire field, a sharp image for close-by (i.e. macro photography, <100 mm) as well as far-away objects (infinity)

and reduced chromatic aberrations are very difficult to achieve in one device. Additionally, the available space, manufacturing capabilities, manufacturing tolerances and the available material for injection molding which is often thermoplastic offering a low Abbe number (i.e. large variation of refractive index as a function of the wavelength) govern the design of micro lenses for the use as cellphone camera objectives. Studying available patents of cell phone lenses [11–13], one finds that very often more than three highly parameterized aspherical lenses form the final objective. Each surface is the result of a computationally expensive optimization process to reduce aberrations (e.g. optimizing Seidel coefficients, reducing field curvature, and improving MTF). However, some of the errors can also often be compensated for by image processing running on the camera electronics. These include correction of distortions (e.g. barrel distortion) and lens shadowing correction due to the high tilt angle of contributions far off the optical axis [14].

Recent CMOS camera sensors not only offer a reduction in production costs, but also about 50% in energy consumption compared to older generation CMOS sensors, making them ideal for widespread use in devices, where energy is very limited [15, 16]. Since the iPhone 4 became available in 2010 [17], BI-CMOS sensors providing a higher quantum efficiency with less read noise, became the sensor of choice for modern smartphones [18]. Since 2012, one can observe a race towards gigapixel resolution, which does not always lead to better images, but is used as a marketing argument [19, 20]. The available space in smartphones is typically very limited, hence resulting in smaller pixels to keep up with the high pixel density. Xiaomi for example recently announced the “Mi 10T Pro” which offers a 108 megapixel (MP) sensor (Samsung, 1/1.33”) with a pixel pitch of 0.8 µm, that is not much larger than the detected wavelength [21, 22]. Cellphone cameras very often suffer from high noise contribution especially in low-light situations, where users want to capture a “selfie” at night. One solution to this problem is the use of multiple cameras, where information of different sensors and perspectives is correlated. Alternatively, the recently presented Huawei P40 Pro for example uses a very large 50 MP CMOS sensor (1/1.28”) in order to maintain a larger pixel pitch (1.22 µm) [23]. Denoising algorithms running on dedicated hardware, taking advantage of recent progress in signal processing on low-powered devices and artificial intelligence (AI) in particular, can also help to solve the problem of images being corrupted by noise [24].

As already mentioned, a growing number of cellphones offer multicamera sets each equipped with a different purpose-specific objective lens (e.g. wide angle and telezoom) [13, 25]. Some of them even provide periscope camera modules for a true optical zoom for far-away photography [23], optical image stabilization using integrated voice-coil motors [8] or monochromatic sensors to increase the photon budget [26–29].

Even though camera sensors are a unique selling point by the cellphone manufacturers, they are almost exclusively purchased as independent electronics, e.g. from Sony (IMX series) or OmniVision (OV series) [30, 31]. The CMOS sensors are very similar to those used in industrial or surveillance cameras and determine the physical acquisition parameters such as read noise, gain, sensitivity, and quantum efficiency of the image acquisition.

However, highly integrated and specialized system-on-chip electronics give manufacturers the opportunity to implement vendor-specific algorithms such as the aforementioned noise reduction, but also digital image stabilization, demosaicing [32], hot pixel removal, compression, or general “beautification” of the images to satisfy user expectations [33]. The ISP thus not only supports the smartphone in image processing but ultimately ensures that only the finished processed still image or compressed video stream is sent back to the cell phone’s central processing unit (CPU) through the mobile industry processor interface (MIPI). This is a huge drawback for the potential use of smartphones in any scientific context since access to RAW images is either very limited (e.g. due to bandwidth) or impossible at higher frame rates. The interaction between the low-level hardware interface MIPI and the operating systems (OS) is carried out by dedicated application protocol interfaces (API), where developers grant access to control parameters and data retrieval. In Google’s camera API 2 for example, the hardware abstraction layer (HAL [34]) represents a unified interface, where a developer can set parameters such as exposure time and gain vendor-independent. Additionally, it ensures high data rates by means of transferring data from the ISP to the cellphone by taking the computational capabilities of the cellphone (i.e. CPU and GPU) into account. Finally, in most cases, the cellphone’s internal hardware (RAM and CPU) very often limits the bandwidth at which image information can be transferred and processed on the phone’s mainboard.

In addition to cameras, smartphones host wireless communication technology to rapidly transmit data. They also accommodate powerful computing units and intelligent energy management to be independent of the existing infrastructure. The OS handles proper device control, while a graphical user interface (GUI) in the form of a mobile application/app (APP) ensures intuitive user

interaction. In addition, many smartphone manufacturers integrate dedicated neural processing units (NPUs), powerful system-on-a-chip-designs [35] or even graphic processing units (GPUs) [36] in their smartphones aiming to relieve the main CPU for real-time applications such as image enhancement [37], classification or speech recognition. These, as well as external artificial intelligence (AI) frameworks, can help to compensate for inexpensive lower quality production. Using open-source machine learning libraries for embedded vision applications such as OpenCV [38], TensorFlow (lite) [39], or pyTorch (mobile) [40], modern cellphones can profit from previously trained networks. Researchers make use of these libraries by developing real-time object recognition [41] and virus detection [42] for example. The training, which often requires high computational power, can be carried out by machines equipped with high computational power, whereas the exported models can be applied on a portable device with limited resources [43], hence allowing processing data without an Internet connection to external servers.

All this makes a smartphone an ideal instrument for use in scientific contexts [44] as successfully shown in spectroscopy [45, 46], astronomy [47], point-of-care [48, 49] (PoC) diagnostics, microscopy [50, 51], and neural network applications [37].

Light microscopy in turn is a powerful method, where many different disciplines work hand in hand, to create tools with high optical resolution to observe (sub-) cellular structures at the micro- or even nano-scale [52]. Typically, an inverse relationship between optical resolution and price or footprint is noted, making cutting-edge research tools not available to the vast majority of people who cannot afford it. In this review article, we will show how the scientific community surpassed this problem by exploiting the aforementioned developments in modern smartphones, to make cutting-edge microscopy not only available, but also portable.

First, we show how cellphones can be used as standalone brightfield and fluorescence microscopes, by only adding a small portion of external hardware. Then we show how smartphones enable image processing with sophisticated algorithms in order to realize super-resolution microscopy (SRM). Additionally, we emphasize how standalone cellphone camera sensors, as used by the Raspberry Pi or the NVIDIA Jetson Nano, can contribute to the idea of field-portable imaging devices. Finally, we introduce some reports for PoC applications and show that a well-chosen combination of biological assays and low-cost diagnostic devices can help identifying diseases such as the novel coronavirus SARS-CoV2.

2 Cutting-edge cellphone-based research microscopy

Depending on the illumination and detection scheme, light microscopy can roughly be divided into brightfield, phase contrast and (widefield) fluorescence microscopy. It has been shown that a single smartphone can replace multiple of the core components of a microscope. The inbuilt camera can act as the detector [53–59], the inbuilt LED or the screen as the illumination source [60–63]. Smartphone objective lenses can act as microscope objectives [64–67]. This significantly reduces the price for the whole assembly, often ranging from 15–100 k€ to less than 200–1000 € [68–70]. In general, integrating existing smartphones into microscopes can be achieved in three different ways:

(1) Using a smartphone as the camera with the help of optical adapters such as an eyepiece [71–73]
(2) Creating a self-sustainable device with a custom optical design adapting the inbuilt lens [27, 74]
(3) Using accessory lenses (e.g. a second cellphone lens in retro-fit [64–66], droplet lens [75–77], or customized lens [78]) to create a ~1:1 magnification, which produces a resolution pixel pitch of about two detector pixels.

Attaching a smartphone to a preexisting microscope becomes a relatively simple task. Customized adapters [71] ensure a mechanically stable mount of the entrance pupil of the cellphone lens relative to the exit pupil of the ocular. Correct imaging is achieved when the camera lens (more precisely: entrance pupil) is placed in the Ramsden disk of the eyepiece. Parameters of the smartphone, such as the size of the aperture (k_{eff}, see also Table 1) have a direct influence of optical efficiency and has to be taken into account when choosing the adapting lenses. Another important factor is the effective pixel size, which can be set using auxiliary lenses (e.g. eyepiece with different magnification) to match the Nyquist–Shannon sampling criteria for the individual application. The focal length of the lens of a cell phone camera is very often kept as a trade secret, but can be estimated from the pixel size and the f-number/aperture of the lens, since the sampling of the photographic image often follows the Nyquist–Shannon criteria as well.

Using this configuration on an inverted top-shelf microscope, Diederich et al. [26] demonstrated that single-molecule localization microscopy is possible using a monochromatic cellphone camera chip. The final resolution better than 80 nm was similar to the one achieved by the electron multiplied CCD camera (Andor iXon 897). The smartphone camera shows higher read noise and reduced

Table 1: List of smartphone microscope publications with some key features.

Imaging modality	Main feature	Author year	Smartphone sensor (Pixel pitch, k_{eff})	Lens NA Final optical resolution
BF	Retrofit iPhone lens packed on smartphone camera	Switz 2014 [64]	iPhone 4S IMX145(1.4 µm, f2.4)	NA 0.21 3.4 µm
BF/DF	Microscopy with smartphone on-board flashlight	Orth 2018 [65]	iPhone 6S IMX315(1.22 µm, f2.2)	NA 0.23 4.48 µm
BF/DF	Multimodal microscopy using two smartphones	Kheireddine 2019 [63]	Lumia 1020 CK26V1(1.12 µm, f2.2)	NA 0.23 2 µm
BF	Microscope using droplet oil as objective lens	Szydlowski 2020 [79]	Huawei Honor 7X IMX230(1.25 µm, f2.2)	NA 0.23 24.8 µm
BF	Machine learning distortion correction	Rivenson 2018 [80]	Lumia 1020 CK26V1(1.12 µm, f2.2)	NA 0.23 870 nm
BF	Open configurable imaging platform	Li 2019 [69]	Raspberry Pi Camera IMX219(1.12 µm, f2.35)	NA 0.65 460 nm
Fluo	In-chip TIRF fluorescence microscope	Sung 2017 [81]	Lumia 640 OV8856(1.12 µm, f2.0)	NA 0.15 2 µm
BF/Fluo	3D printed, autonomous microscope	Collins 2019 [82]	Raspberry Pi Camera IMX219(1.12 µm, f2.35)	NA 0.65 480 nm
SMLM	Replace an emCCD camera with a cellphone camera; on-device machine-learning based image processing	Diederich 2019 [26]	Huawei P9 IMX286(1.25 µm, f2.2)	NA 1.49 80 nm
SMLM	Cheap single molecule localization microscopy	Diederich 2020 [27]	Huawei P20 Pro IMX600(1.01 µm, f1.8)	NA 1.25 120 nm
SMLM	Single molecule detection of DNA Origami to quantify the sensitivity of smartphone-based microscope	Vietz 2019 [29]	LG V10 Huawei P10 Plus (f2.2)	- ~10 fluorophores
SMLM	Smartphone microscope with addressable nanoantennas	Trofymchuk 2021 [28]	Huawei P20/- (1.01 µm, f1.8)	NA 0.25 1.2 µm
Confocal	Handheld reflectance confocal microscope	Freeman 2018 [70]	Huawei P9 IMX286(1.25 µm, f2.2)	NA 0.8 lateral 2 µm, axial 5 µm
DIM	Smartphone camera adapted on a Jamin–Lebedeff microscope	Diederich 2017 [83]	LG Nexus 5 IMX179(1.4 µm, f2.0)	NA 0.22–1.2 µm

The lens NA and final optical resolution represents the optical properties from the final microscope setup. Abbreviations used in the table: BF-Brightfield, DF-Darkfield, Fluo-Fluoresence, SMLM-Single molecule localization microscopy, DIM-Differential interference microscopy; NA-Numerical Aperture.

quantum efficiency in the calibration experiments, but its performance is still in an acceptable range for single-molecule localization microscopy (SMLM) using bright fluorescent dyes such as AlexaFluor® 647. The side-by-side comparison between BI-CMOS cameras and an emCCD camera revealed a very good performance in terms of read noise and linearity as summarized in Table 1. One problem is the vendor-specific image processing step carried out on the camera module, which applies a non-linear relationship between the photons and the measured signal [84].

Since smartphones offer image acquisition, processing and sharing in one device, the creation of portable self sustainable microscopes for various applications is a unique feature which cannot be achieved with classical research-grade microscopes. In the following sections, we therefore discuss ways to realize classical brightfield and fluorescence microscopes with cellular and high-resolution imaging devices with a resolution close to the single molecular level (see Table 2).

2.1 Bright-field microscopy at cellular optical resolution

Based on the retro-fit mechanism, Switz et al. [64] reported a compact and cheap smartphone-based bright-field microscope by simply adding a second phone camera lens (iPhone 4S objective, $k_{\text{eff}} = 1/2.4$, NA = 0.21, ~3 $) in reverse orientation in front of the inbuilt camera lens. This configuration produces a magnification factor of one and a theoretical Rayleigh resolution on the sensor of about 2.44× pixels = 3.4 µm at the field of view (FOV) of ~10 mm^2 (Figure1a and b). Due to the use of Bayer color filters, which, compared to red- and blue- have twice as many green-sensitive pixels, the required sampling distance according to Nyquist further increases by a factor of $\sqrt{2}$ and 2 for green and red/blue, respectively, yielding 4.8 and 6.8 µm. Similarly, Orth et al. [65] extended this idea by also using the flashlight of an iPhone 6s with the onboard camera (Figure 1c–e). The smartphone's flashlight is

Table 2: Comparison of various parameters between scientific cameras and modern smartphone cameras.

Camera	Andor iXon 897	PCO.edge 4.2	Huawei P9	Huawei P20 Pro	Raspberry Pi v2
Sensor type	emCCD	sCMOS	BI-CMOS	BI-CMOS	BI-CMOS
Sensor	Not available	Not available	IMX286	IMX600	IMX219
Pixel number	512 × 512	2048 × 2048	3980 × 2460	7296 × 5472	3280 × 2464
Pixel pitch (µm)	11.6	6.5	1.25	1.01	1.12
Read noise (e^-)	<1 RMS with EM gain	0.9 RMS	1.23 RMS	1.88 RMS	2.12 RMS
Quantum efficiency (540 nm)	90%	80%	70–80% [26]	Not available	~70% [69]
Price	20 k	24 k	300	400	30

Considering the price, the smartphone camera shows acceptable quality. The analysis of the smartphone camera was tested with the monochrome sensor in the cell phone and the color CMOS sensor of the Raspberry Pi camera v2.1.

reflected by an additional mirror, such that the light can transmit the sample before the scattered light is captured by the camera in bright- or dark-field mode. Everything joined by a 3D printed clip (Figure 1e). The final resolution is 4.48 µm, allowing its use e.g. for cell culture imaging or video microscopy for on-site monitoring.

An alternative to proprietary objective lenses was demonstrated by Szydlowski et al. [79] who created customized auxiliary lenses using oil droplets, which can be applied in very low-resource settings (Figure 1f and g). The freeform lens is created by placing an immersion oil droplet on a coverslip close to the sample. Compared to spheroids formed by water hence acting as lenses, oil droplets show much slower evaporation and offer larger indices of refraction, which is in combination with the droplet's volume (e.g. 1–5 µL) responsible for the lenses' focal length. In case of the oil droplets, the focal length was typically between 4 and 9 mm. The resolution is specified as 24.8 µm by measuring a USAF resolution target using a Huawei Honor 7X placed at a defined distance in front the droplet in order to avert the change of magnification induced by the autofocusing mechanism. By using common off-the-shelf oils, virtually any smartphone can be quickly transformed into a microscope, but on a relatively small FOV.

An alternative approach to creating short focal length auxiliary lenses is using polymers such as PDMS [75–77]. Dyeing the PDMS enables the creation of low-cost fluorescence microscopes, where the integration of special emission filters can be omitted. Yet another approach to create customized lenses was shown by [85]. The authors report the development and fabrication of highly specialized metalenses, where subwavelength nanostructures shape the light in a way, that the nanostructures can be used as a lens. This enables the creation of customized lenses also for fluorescence microscopy with an extended large field of view (~8 mm) and a resolution comparable to that from a 20×/NA 0.75 microscope lens. Their application to cellphone microscopy is yet to be investigated.

2.2 Fluorescence microscopy at cellular optical resolution

Fluorescence microscopy, as an important tool for the study of fluorescent samples, is used whenever high resolution at the subcellular level or the functional organizations of organisms are of interest [86, 87]. This involves the analysis of specifically labeled or autofluorescence cells, cellular components and molecules with high degree of specificity. The creation of a uniform illumination pattern usually requires a sophisticated optical design and a well-chosen combination of excitation light sources as well as emission filters, usually resulting in a very high price. Sung et al. [81] demonstrate a different strategy, by providing a low-cost and open-source total internal reflection fluorescence (TIRF) microscope for investigative fluorescence microscopy (Figure 2a–c). A 3D-printed assembly weighing only 27 g is attached to a Lumia 640 and holds a set of light-emitting diodes (LEDs) directly coupled into the glass slide which acts as an optical waveguide. The resulting evanescent field close to the glass surface excites fluorophores in TIRF mode, hence producing an additional optical sectioning effect, where only fluorophores close to the coverslip are excited. An additional emission filter is placed between the sample and the camera to block the scattered signal and increase the contrast. With the help of multiple different LEDs with varying excitation spectra, different fluorescent samples can be imaged. The total cost is estimated to be $20, while the maximum resolution is given as 2 µm after an additional deconvolution post process.

Another approach is followed by Kheireddine et al. who demonstrated a dual-phone imaging system for multimodal microscopy [63, 88]. This includes bright- and dark-field, phase contrast, and fluorescence microscopy (Figure 2d and e). In their work, one smartphone is used for the imaging process while the other one is used for displaying different illumination patterns with its inbuilt LCD

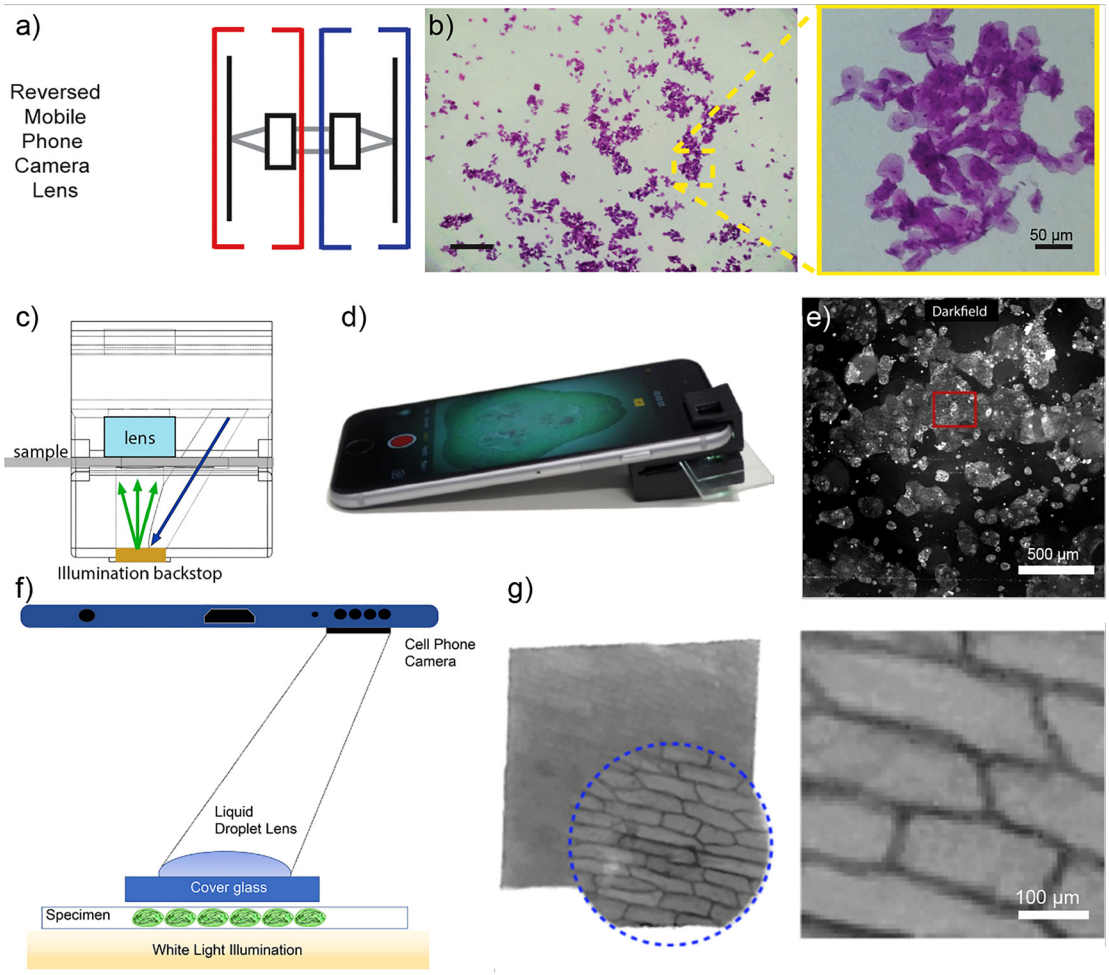

Figure 1: Bright-field microscopes using smartphone.
a) Schematic of a smartphone microscope based on a cell phone lens in reverse orientation with an exemplary micrograph in b). Adapted from Ref. [64] with permission from PLOS ONE, licensed under CC-BY-NC 4.0. c) In addition to a), the smartphone LED is used to illuminate the object utilizing a mirror. d) The 3D-printed clip adapter allows bright- and dark-field imaging e). Adapted from Ref. [65] with permission from Scientific Reports, licensed under CC-BY 4.0. f) Unlike in a), an oil drop on a cover glass is used as a microscope objective to realize a smartphone microscope. g) An exemplary image of an onion epidermis acquired with the microscope created using an oil droplet. All devices can be quickly replicated to turn virtually any smartphone into a microscope. Adapted with permission from [79] © The Optical Society.

screen. A customized illumination pattern created with a PowerPoint slide is displayed on the high-resolution LCD screen, where each pixel can block the red, green and blue part of the white background light before it passes through the sample directly placed on the digitizer. In order to achieve fluorescence imaging, an additional fluorescence emission filter was inserted between the phone's screen and the glass slide. Similar to Switz [64] they added a smartphone lens to the Lumia 1020 camera and achieved a resolution of 2 µm. Fluorescent imaging was achieved by displaying a blue circle, capable of exciting CellTracker Green labeled HEK 293 cells. However, due to the low power of the excitation signal, the system requires a very long exposure time of 4 s to get one frame.

A similar but yet more generic approach was introduced by Diederich et al., who provided a low-cost open-source modular microscopy toolbox, which realizes different microscopy methods by combining different optical modules [74]. Various electrical and optical components such as LEDs, lenses and mirrors are mounted in 3D printed cubes attached to magnetic grid. This way, modules can be combined to form arbitrary complex optical setups exemplary shown in Figure 3a. In addition to stand-alone cameras like the one from a Raspberry Pi, the smartphone can easily be integrated into any microscope exemplary demonstrated with high-resolution images of *Escherichia coli* bacteria in wide-field mode (Figure 3b) or human pulmonary microvascular endothelial cells (HPMECs) cells using a frugal

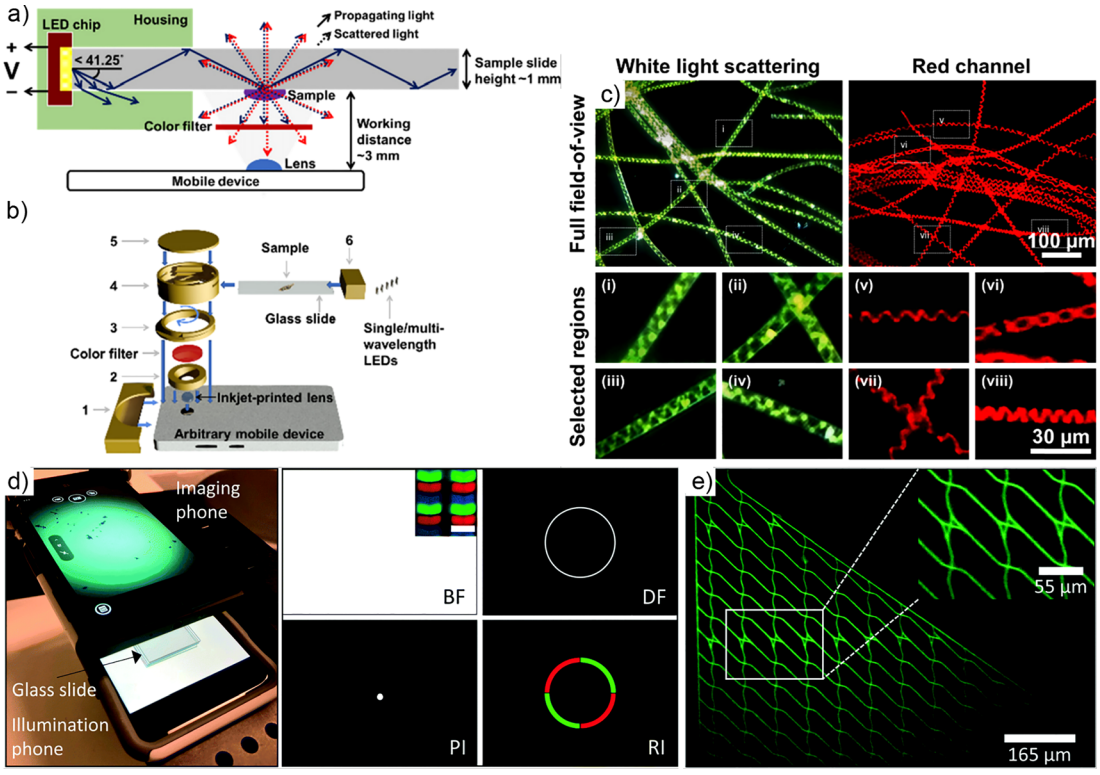

Figure 2: Smartphone-based fluorescence microscopes.
a) An LED coupled into a coverslip enables a highly cost-effective and compact total internal reflection fluorescence (TIRF) setup, with all components attached to a smartphone in a 3D-printed housing b). c) Autofluorescent *Spirogyra algae* can be imaged using different fluorescent excitation. Adapted with permission from [81] © The Optical Society. d) With the help of a second smartphone where the screen serves as an adaptive light source, different illumination patterns can easily be realized e.g. for e) fluorescence detection in a microfluidic device or also for quantitative phase imaging (QPI). Adapted from [63] – Published by The Royal Society of Chemistry.

image scanning microscopy module [89] (Figure 3c). The open-source nature of this project enables easy user interaction, by only adapting individual components into the open-standard electronic modules, such as the focusing stage, host ESP32 (Espressife, China) microcontrollers, that can communicate with the smartphone through a WiFi connection. Utilizing the internet-of-things-based communication protocol Message Queuing Telemetry Transport (MQTT), smartphones can control various hardware modules and acquire results simultaneously.

2.3 Super-resolution fluorescence microscopy at sub-cellular optical resolution

The need to circumvent the Abbe diffraction limit, which avoids resolving features smaller than about half the wavelength, created the field of super-resolution microscopy (SRM). The interplay between modern fluorescent or photo-switchable probes, cutting-edge optical microscopes, and highly specialized image postprocessing, has the potential to provide insights down to the molecular level [90]. However, an inverse relationship between resolution and price can be observed for such methods, where stimulated emission depletion (STED [91]), direct stochastic optical reconstruction microscopy (dSTORM [92]) and structured illumination microscopy (SIM [93]) are only a few of these techniques. Additionally, the associated setups often require a large footprint, exhibit a high system complexity and often have very limited access [26, 27].

The need for affordable and available tools has created a new research field called “frugal science”. Vietz et al. [29] first demonstrated that recent smartphone camera sensors are sensitive enough to detect DNA origami nanobeads. The setup works in darkfield mode, where the excitation laser beam illuminates the sample under an angle of 45° angle in order to block the scattered signal. The authors make use of two different smartphones, (LG V10 and Huawei P10 Plus), the latter featuring a monochrome camera sensor, offering a better quantum efficiency for monochromatic light detection (Figure 4a) as also visible

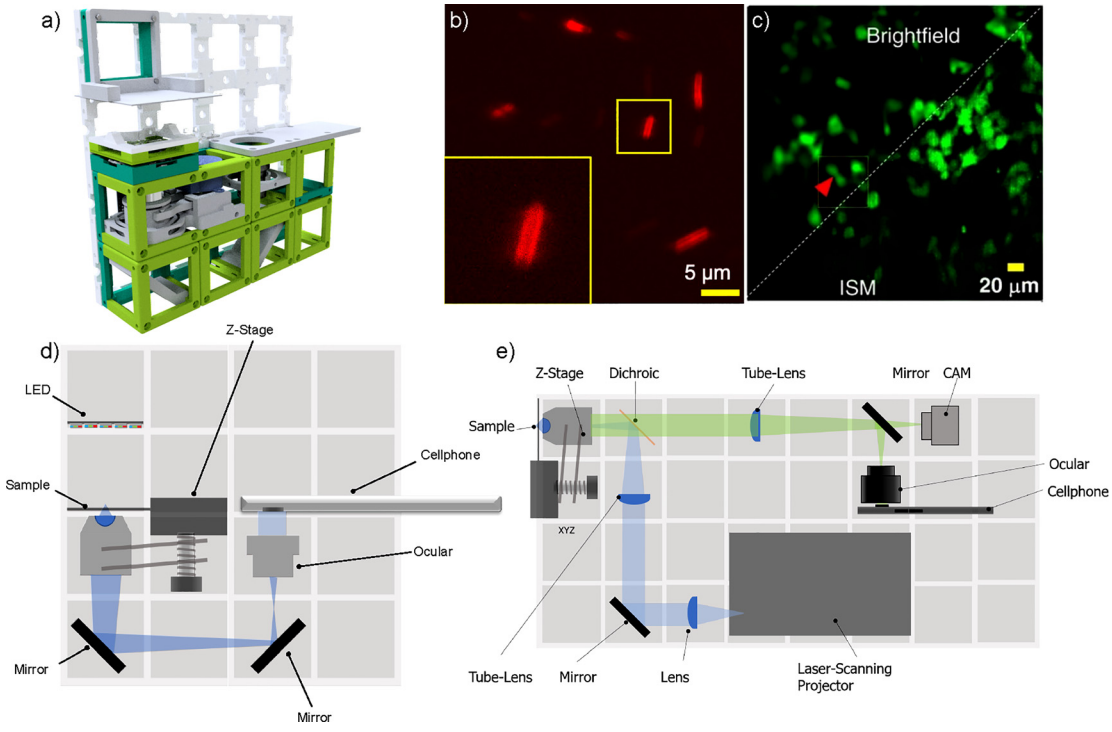

Figure 3: A versatile 3D-printed modular microscope toolbox realizes easy integration of the smartphone into different microscopy techniques.
a) A visualization assembly of bright-field microscope with the toolbox. A library of available low-cost electro-optical modules realizes e.g. brightfield d), standard fluorescence b), dark-field and image scanning microscopy (ISM) (c and e). Adapted from Ref. [74] with permission from Nature Communication, licensed under CC-BY 4.0.

from an increased contrast level in a direct comparison. The monochrome camera chip exhibits higher sensitivity over the RGB camera and can detect ~10 fluorophores per diffraction-limited spot whereas the color sensor is only sensitive to several hundreds of fluorophores per spot [59] (Figure 4b). Although the sensor cannot compete with scientific emCCD camera chips, often used for single-molecule fluorescence microscopy, the camera module is more than one order of magnitude lower in price compared to commercially available emCCD cameras, rendering it very attractive for low resource areas. A follow-up of this project is shown in [28], where a portable version of the aforementioned setup takes advantage of addressable nanoantennas suitable for the analyzation of portable bioassays. They report the analysis of antibiotic resistance such as *Klebsiella pneumonia* on the road.

However, the small form factor is accompanied by reduced image quality due to compromises in the selection of electronic and optical components for the available space. Machine learning has shown to overcome this bottleneck with the help of learning a relationship between bad and good data samples, with the goal to recover good from bad images [95, 96]. Rivenson et al. [80] unfolds its potential by applying deep learning in order to correct the distortion of the smartphone-based microscope image (Figure 4c and d). They used a Lumia mounted on a 3D-printed optomechanical assembly with an external lens (f' = 2.6 mm) to achieve a magnification of 2.77×, a FOV of around 1 mm^2 and an optical resolution of 0.87 µm. A previously trained convolutional neural network (CNN) running on a standard desktop computer rapidly processes the image (t = 0.42 s) in a feed-forward network.

Similar to [88], the "Beamerscope" uses a video projector as an adaptable Koehler-illumination in order to illuminate a phase-only sample the way that the phase-contrast is maximized. The standalone device computes the best illumination geometry, which maximizes contrast of an arbitrary sample with the help of a previously trained CNN [97]. A Nexus 5 is converted into a microscope with a secondary lens, acquires the images, calculates the illumination pattern and displays them on the low-cost LED video projector using the in-built HDMI interface. The authors also show the ability to use it for quantitive phase reconstructions.

The already presented "cellSTORM" [26] features a generative adversarial network (GAN) running on the

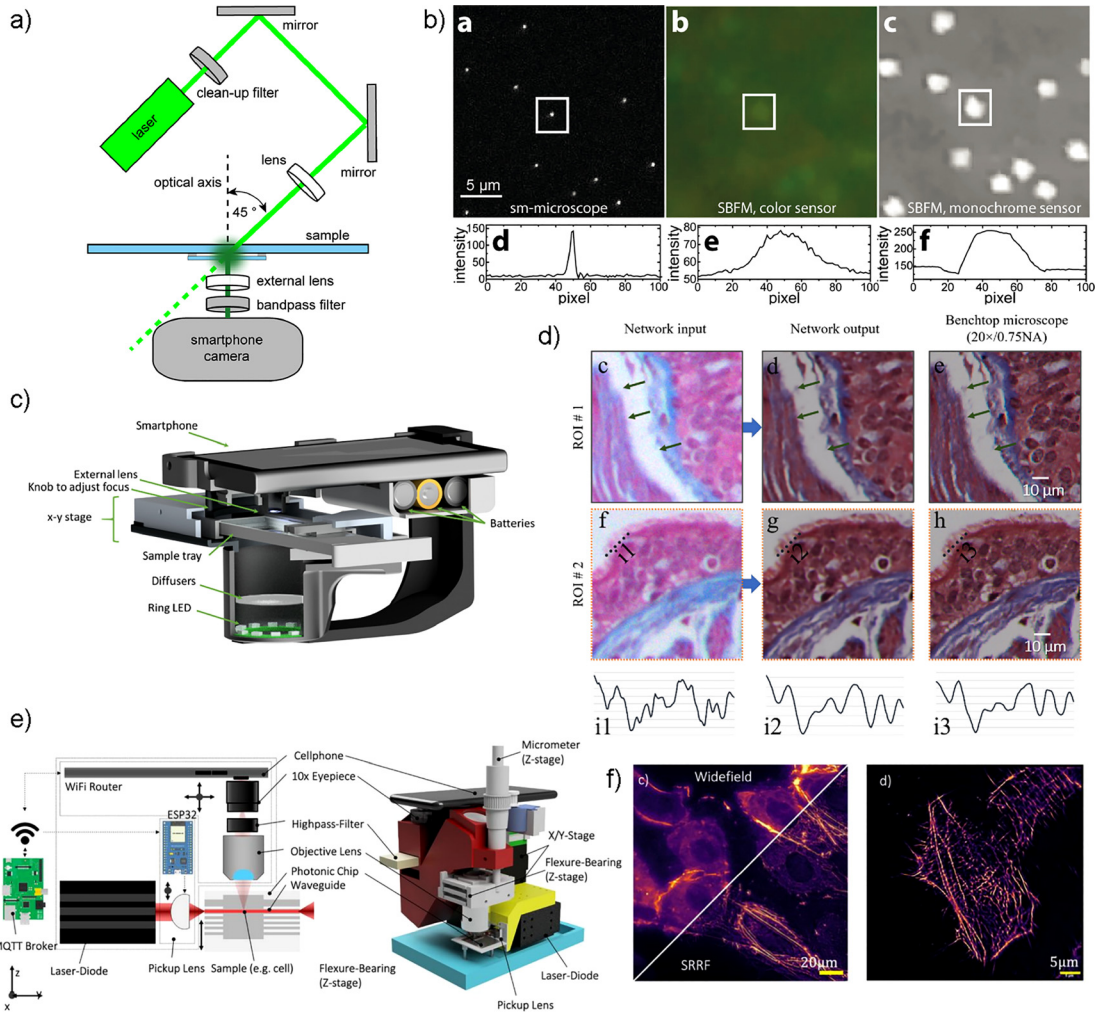

Figure 4: The smartphone as a super-resolution fluorescence microscope.
a) Using DNA origami nanobeads, the sensitivity of different smartphone cameras was quantified. b) The phone's monochrome camera shows an acceptable result and can detect down to 10 fluorophores per diffraction point signal. Adapted with permission from [29]. Copyright (2019) American Chemical Society. c) A schematic of a smartphone microscope and the image is processed by a deep learning neural network on a standard computer, the signal-to-noise ratio and color distortion of the smartphone images are improved by the algorithm as shown in d). Adapted with permission from [80]. Copyright (2018) American Chemical Society. e) The low-cost cellSTORM setup represents a compact super-resolution fluorescence microscope. The optomechanical parts are 3D printed and with the low-cost optical components, the setup can achieve a resolution of 100 nm at a cost of $1000 using photonic waveguide chips (Chipnano, Norway). f) Left figure shows the resolution comparison between widefield and after SRRF reconstruction [94] processing, right figure achieves ≤100 nm optical resolution with high NA objective lens (100×/NA 1.25). Adapted from Ref. [27] with permission from BioRxiv, licensed under CC-BY-NC-ND 4.0.

cellphones's NPU (Huawei P20 Pro) to directly localize single molecule blinking events with a network previously trained on a dataset which hosts simulated SMLM data corresponding to the cellphones imaging model. The model is derived from an extensive characterization of the cameras (see Table 1). This way, unknown sources of artifacts such as video-compression and noise which remain largely unknown, can successfully be compensated. The recently presented follow-up "cellSTORM II" combines the idea of democratizing SRM using recent progress in high quality cellphone cameras by providing an open-source nanoscopic imaging device for around 1 k$ [27]. A single-mode high refractive index photonic waveguide (WG) chip confines the excitation field to a 150 nm small TIRF region, where the intensity suffices to bring fluorescently labeled cells into a blinking state. Using SMLM reconstruction algorithms, a final resolution better than 120 nm was reported. An optical pick-up (OPU) from a scraped PlayStation 3 (PS3, Sony, Japan) directly controlled using the wireless MQTT protocol by an Android application

software, maintains stable coupling of a high intensity laser diode into the 150 nm high and >20 µm wide WG. This way, the *X*–*Z* scanning ability of the OPU is not a limitation, since the *y*-direction does not require precise adjustment. An additional autofocus and its small footprint enables its use for long-term experiments in incubators or laminal flow hoods (Figure 4e). A Huawei P20 Pro equipped with a monochromatic sensor detects and processes the fluorescent signal in real-time using a convolutional long-short term memory network (cLSTM) (Figure 4f). The work shows that the autonomously working device is capable of resolving the SARS-CoV-2 virus and aims to become a new tool for high biosafety laboratories, where access to such tools is often very limited. The authors raise yet another concern about the validity of preprocessed cellphone imaging data. To come by the issue of unknown processing, they show how raw imaging data can be acquired at reasonable framerates.

2.4 Specialized microscopy methods

Freeman et al. [70] announced a handheld smartphone-based reflectance confocal microscope (RCM) for imaging cellular structures in human skin (Figure 5a–d) and aims for better disease diagnosis in development countries. The setup involves a broadband white light LED first filtered with a slit aperture, before the collimated beam is diffracted into the back focal plane (BFP) using a diffraction grating. The light e.g. reflected by human skin again passes through the grating and is filtered by a detection slit aperture, before a lens system relays the image onto a cellphone camera of a Nexus 5X. Instead of mechanically scanning a beam across the surface, a diffraction grating encodes the spatial coordinates with wavelengths. A second grating decodes the reflected signal, where out-of-focus light is blocked by an adjacent slit aperture to increase optical sectioning in the acquired image [98]. The whole device is based on standard optical elements joined by a 3D-printed assembly. As an imaging lens it features a 40×/NA 0.8 water immersion objective exhibiting a lateral and axial resolution of 2 and 5 µm, respectively. This is comparable to the commercial devices (1 and 5 µm, respectively), while the imaging frame rate is limited to 4.3 fps being slower than the commercial device with 6–9 fps.

Even though monochrome cameras are beneficial for most applications in microscopy to have a superior SNR performance, [83] demonstrates how RGB cameras in cellphones can successfully upgrade hardware such as a Jamin–Lebedeff interference microscope to perform single-shot quantitative phase measurements. The authors used a

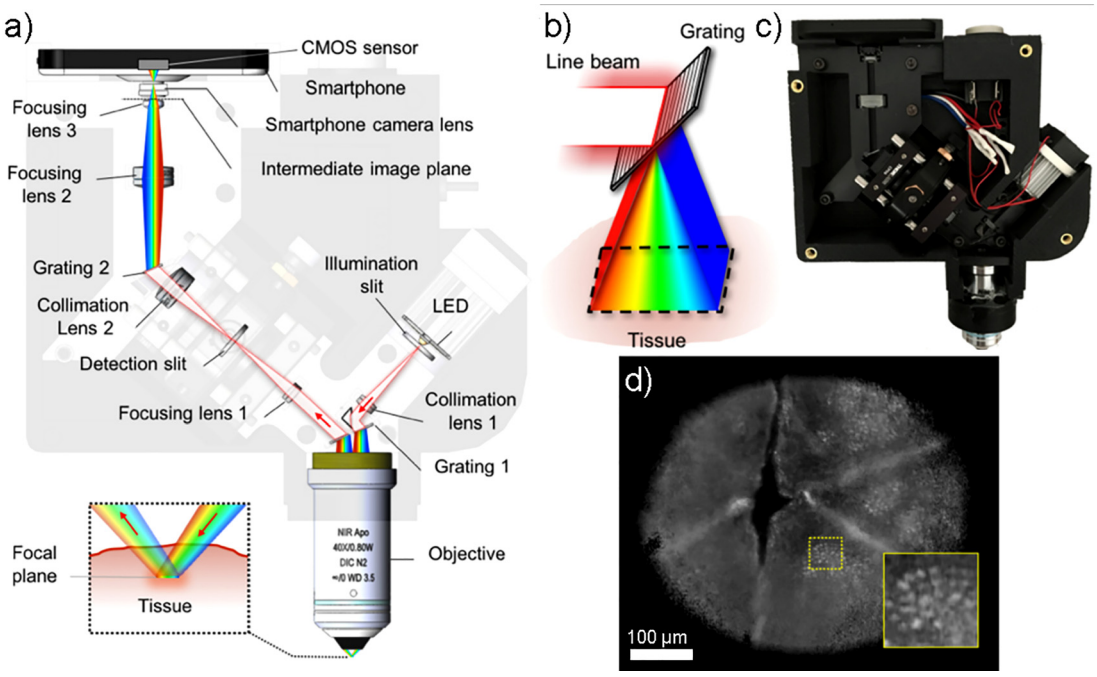

Figure 5: Confocal microscope with the smartphone.
a) Optical path of a confocal reflection microscope c) with a 3D-printed housing. b) The illumination light is diffracted by a grating and encodes an axial coordinate into a wavelength. The device provides enhanced imaging for deep tissue (>50 µm) such as is required for studying the epidermis d). Adapted with permission from [70] © The Optical Society.

LG Nexus 5 and a Huawei P9 as imaging devices (Figure 6a–d), directly attached to the eyepiece of the microcope body. The working principle of Jamin–Lebedeff microscopes is somewhat similar to that of differential interference contrast (DIC) microscopes but with a much larger distance between the two interfering sample images. Here, the optical path difference (OPD) or quantitative phase of the sample is converted into (interference) color by means of white-light interference. Typically, a Michel–Levy chart is used to map the visible colors back into the samples' phase of cells' dry mass. Here the authors report an inversion of this OPD-to-color relationship by using a previously captured fiber as a calibration sample and a consecutive inversion using image processing running on an external computer. This inverted look-up table can be used to reconstruct the quantitative phase of arbitrary samples in a single exposure, thus enabling real-time phase measurements (Figure 6d).

3 Raspberry Pi-based microscopy

The Raspberry Pi [99] is a well-known open-source single-board computer which is broadly used in different fields such as education, automatization and research. Even though this device is not a cellphone itself, it features a MIPI interface to connect to smartphone camera modules, like the Sony IMX219 featured in the Pi camera V2.1, which is also used in some older smartphones [30, 100]. The company "Arducam" [101] also offers different sensors to interface with these boards. One key advantage is that the objective lens can be easily removed to use the sensor directly as a photon detector. Based on this feature, the widespread availability, its low price and simple programmable environment, the Raspberry Pi has established itself in multiple different microscope projects [69, 102–105].

Collins et al. [82] developed an open-source robotic microscope called OpenFlexure microscope (OFM) which is solely based on 3D printed components and realizes bright-field, fluorescence, and polarization contrast microscopy in epiconfiguration as well as transmission configuration as shown in Figure 7a–c. The 3D printed flexure-based stage allows three-dimensional motion up to a resolution of 50 nm in z and 70 nm in x- y- direction, respectively. The spatial resolution using a 40×/NA 0.65 plan-corrected objective lens is determined as 480 nm by the full width at half maximum of the point spread function. A high-resolution version of the microscope cost less than 300 dollars, which makes it ideal

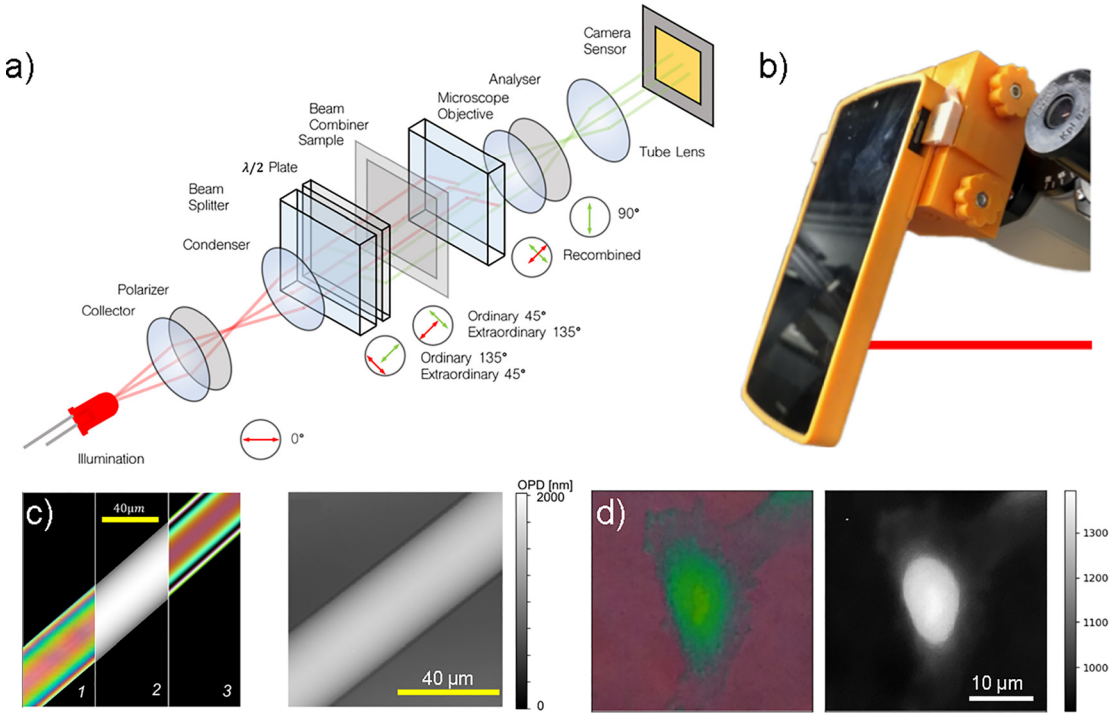

Figure 6: A smartphone-based Jamin–Lebedeff interference microscope.
a) Optical setup of a classic Jamin–Lebedeff interference microscope that closely resembles that of a differential intereference contrast (DIC) microscope. b) The smartphone connected by a 3D-printed adapter captures the color-coded interference images, which are later converted back to a quantitative phase map on the computer with the aid of a calibration object c). d) One-shot reconstructions of video sequences (example frame shown here) are possible with this method, whereby fine details such as the cell membrane are preserved. Adapted from Ref. [83] with permission from PLOS ONE Copyright, licensed under CC-BY 4.0.

for field research, as demonstrated in regions like Tanzania and Kenya, where more than 100 microscopes were set up. This work demonstrates how open-source scientific projects can be used as certified devices for the clinical context.

With FlyPi, Chagas et al. [68] presented yet another 3D printed microscope toolbox aiming for open neuroimaging as illustrated in Figure 7d–e. The Pi camera allows video acquisitions with a framerate up to 90 Hz or time-lapse series over many hours to study the dynamics in fluorescently labeled zebrafishes for example. With the price tag of 100 euro, the setup can do brightfield (Figure 5f left and g) and fluorescence imaging (Figure 5f right) with the resolution of 10 µm by using a CCTV camera lens. Similar to the OpenFlexure project, FlyPi aims to make neurogenetics research available for educational purposes also in development countries.

The PlanktonScope (Figure 8a) recently presented by Pollina et al. [106] represents yet another holistic microscope system, where the device control, image acquisition and processing is carried out on a single portable device. There are two different versions, one in which the various components, such as the Pi camera, lens, stage and fluid pump, are placed in different modules and then stacked together. The other version is a monolithic assembly which can also be purchased as a do-it-yourself (DIY) kit [107] for around 400 $. The all-in-one solution has the advantage to be used on a boat in the sea, where plankton observations (Figure 8c) in bright- and dark-field mode can be accomplished *in-situ*. The current version can image 1.7 ml solution per minute with a resolution of 1.5 µm.

Octopi represents another entirely open and configurable robotic microscopy platform which is based on metal machined parts [69]. The project divides in different tasks being imaging, slide scanning, *trans*- as well as oblique-angle laser illumination, control and computation as shown in Figure 8d. Different modules can be mixed into individual microscope configurations using a magnetic snap mechanism to, for example count red-blood cells (Figure 8e) or detect malaria parasites on site (Figure 8f and g). They used the fluorescent nucleic acid dye DAPI to stain the sample and reported a 10 nm emission spectral shifting between *Plasmodium falciparum* malaria parasite infected

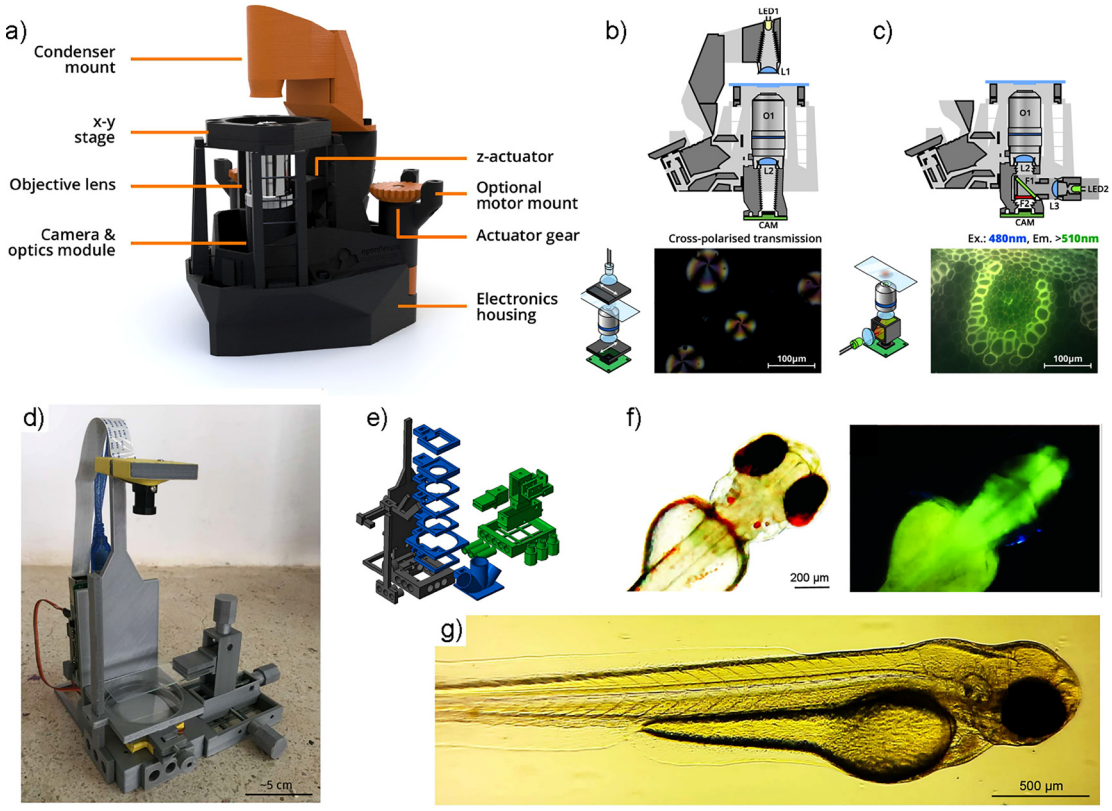

Figure 7: Single-board computer based microscopy using smartphone cameras.
a) A 3D-printed open-source robotic microscope where most components can be easily printed with off-the-shelf printers. The microscope can operate in different configurations, such as continuous polarization contrast (b) and epifluorescence (c). Adapted with permission from [82] © The Optical Society. d) Another low-cost 3D-printed imaging platform and can be used for e) brightfield f)-g) and fluorescence on macroscopic samples. Adapted from Ref. [68] with permission from PLoS Biology, licensed under CC-BY 4.0.

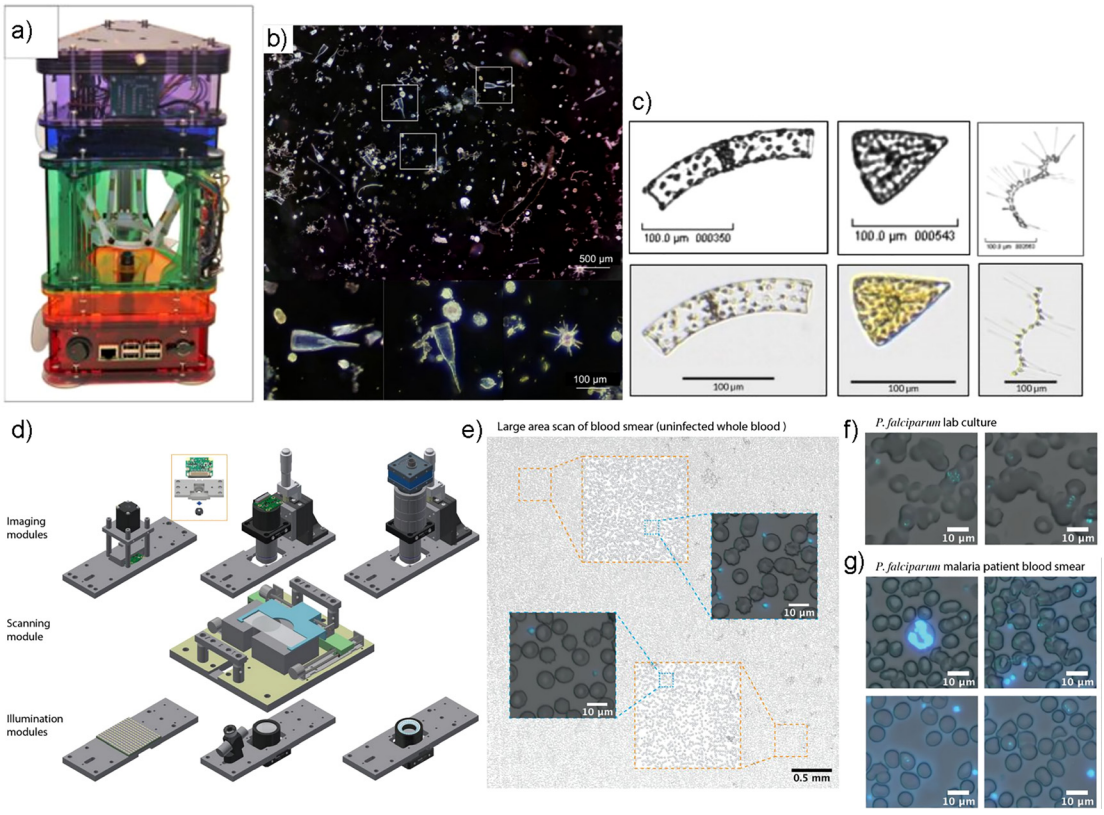

Figure 8: Single-board computer based microscopy using smartphone cameras.
a) A low-cost imaging system for oceanography in which each module is assembled and stacked together in the individual blocks. It can continuously image 1.7 ml of solution per minute for several hours. b) A dark field image taken with the PlanktonScope and c) Comparison of PlanktonScope and Flowcam Ultra data sets. Adapted from Ref. [106] with permission from BioRxiv, licensed under CC-BY 4.0. d) A reconfigurable modular imaging platform with different replaceable modules. e) Image of DAPI-stained healthy blood smear sample with high mag imaging module (40×/NA 0.65 objective). f) Fluorescent imaging of selected field of view with *P. falciparum* infection in lab culture. g) Blood smear from patient diagnosed with malaria. Adapted from Ref. [69] with permission from BioRxiv, licensed under CC-BY 4.0.

and healthy platelets. They achieved a robust separation of the two classes. For the camera they use industry-grade CMOS sensors and a Raspberry Pi camera (v2.1), which works well with edge computing devices and single board computer such as the Raspberry Pi, Nvidia Jetson or Google Coral. These microscopes find application in field research, where access to these tools is often very limited. Using battery packs, the imaging assemblies can perform automated imaging tasks outside the lab, where image processing algorithms running on the handheld computers can perform tasks such as denoising, segmentation, and cell counting. Compared to the rapid innovative iterations made by smartphone cameras every year, the relatively old Raspberry Pi camera shows poor imaging performance [68, 74, 108]. However, these cameras have the advantage of a reproducible flexible and cost-effective imaging solution, where the objective lens is not a limitation w.r.t. the optical adaption. Using open-source Python libraries such as "picamerax" [109] one has full access to all acquisition parameters such as exposure time, digital/analog gain, as well as access to the RAW sensor data, which is helpful for rapid-prototyping scientific-grade microscopy solutions.

4 Microscopy-based point-of-care

Today, healthcare is becoming a priority issue as a key to quality of life. In recent years a trend towards "Diagnostic@Home" [110] can be observed, where medical devices act as remote sensors and either diagnose directly or send data to physicians for further investigation. Equipped with a large number of different sensors, such as accelerometer, magnetometer, global-position system (GPS) and cameras, and cellphones have found their way into the field of PoC and telemedicine [111–113]. With the help of freely available APPs for Android and iOS, standard smartphones can already collect data for mobility, sleep and accident tracking, which can be evaluated

e.g. by means of neural networks. Providing customized hardware adapters to the camera, together with specialized biomedical assay such as the enzyme-linked immunosorbent assay (ELISA) or lateral flow immunoassay (LFIA), smartphones can act as portable and low-cost disease detectors [48, 114].

As a very recent use case Ning et al. [115] developed a smartphone-based saliva COVID-19 test platform using CRISPR-FDS assays (Figure 9a and b) to bring the SARS-CoV-2 pandemic in 2021 under control. The fluorescence probe in the sample is excited by a blue (488 nm) laser diode, while the emitted signal is collected by a lens with short focal length and passes through an additional fluorescence emission filter, before the smartphone camera captures and analyses the image using a customized APP. The instrument shows a robust, broad linear range of viral load. The limit of detection is reported as 0.38 copies/µl, which is lower than commercially available RT-PCR assays. With the on-device running image processing pipeline, the device enables a 15 min sample-to-answer time and doesn't require RNA isolation or laboratory equipment.

Similarly, Soares et al. [116] reported their smartphone-based centrifugal microfluidic platform to diagnose COVID-19 using the loop-mediated isothermal amplification assay (LAMP) (Figure 9c and d). The total time for analyzing a sample is about 1 h with the sensitivity of around 94%. The device only hosts a single heated centrifuge module, which makes more complex heating-cooling cycles as known from RT-PCR obsolete.

Song et al. [117] developed a handheld tunable lens smartphone-based fluorescence microscope. The tenable lens consists of an elastomeric membrane with a chamber filled with mixture (n = 1.412) of water and glycerine. The radius of the curvature can be adjusted by the applied pressure from a piston. The objective has a maximum resolution of 22.1 µm, which is limited by the membrane-formed

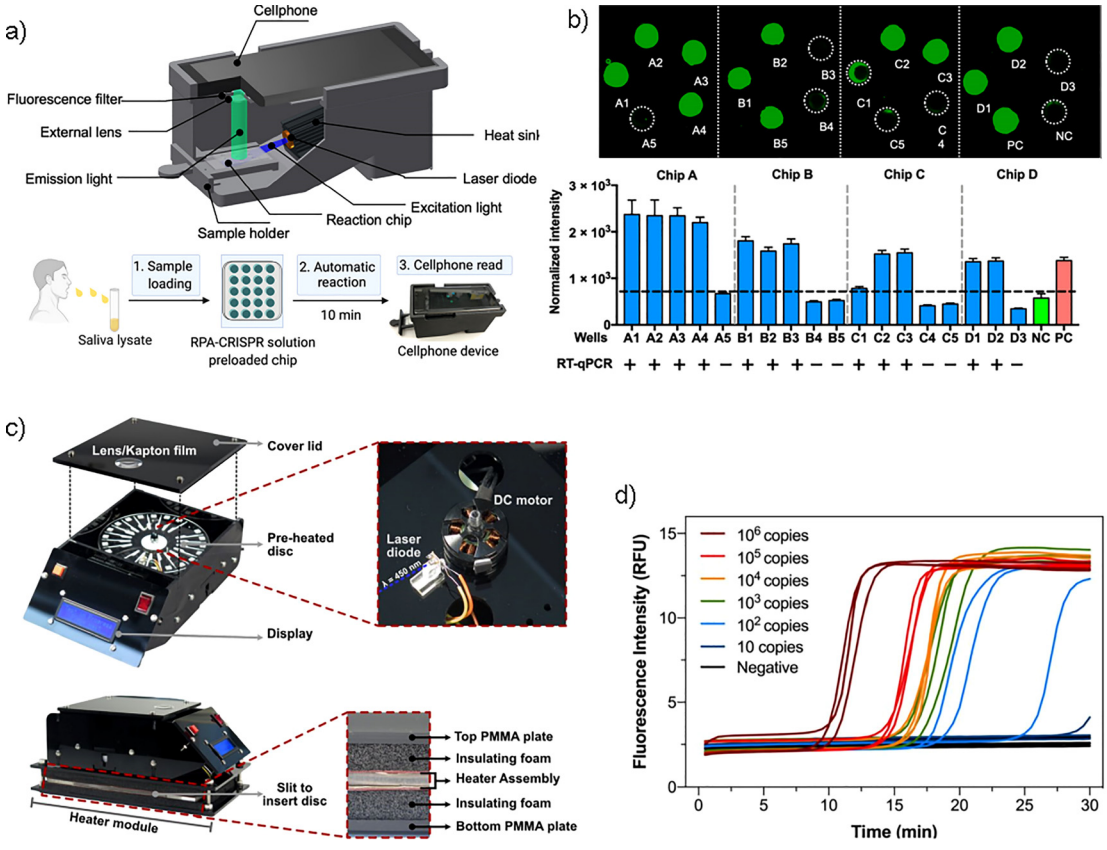

Figure 9: Applications of smartphone-based point-of-care devices.
a) A CRISPR-Cas12a COVID-19 diagnostic device that can complete the analysis of saliva samples within 1 h. b) The fluorescence response of 11 different patient samples compared to a gold-standard real-time quantitative polymerase chain reaction (RT-qPCR) measurement. Adapted from Ref. [115] with permission from Science Advances. c) Another LAMP assay-based COVID-19 assay device, where the device has a heatable centrifuge module. d) The rate of increase in fluorescence intensity of COVID-19 RNA dilution series pre incubated at 65 °C and with the LAMP assay shows a significant difference in the duration of the signal increase. Adapted from Ref. [116] with permission from medRxiv, licensed under CC-BY 4.0.

lens shape, as well as the refractive index and dispersion of the solution. Different concentration of glucose solution is excited with 489 nm LED and analyze the emission signal at 516 nm with the smartphone. The results show a good linear detection range of 0–6 mM glucose, which fit as an early diabetes diagnosis. All these prototypes make use of a highly specialized biochemical protocol and a simple optical assembly, where the cellphone only reads out a binary response, making it suitable for diagnostics in the field. At the same time, a new trend can be observed, where medical sensors or even microscopic imaging is integrated into cellphones directly. The cellphone-based Raman spectroscope "AIRaman" aims for drug screening, food control or material identification on the go. Raman spectroscopy can be used to unambiguously detect substance-specific properties optically, with a spectrogram resembling a fingerprint of a substance. Since there are usually no molecularly pure substances in the environment and the spectra are therefore always a superposition of different molecules, this system relies on a pretrained neural network to decipher the spectra. For this purpose, it uses cloud-based algorithms that decode the locally recorded spectra and assign them uniquely to individual substances. Inside the device a 785 nm/500 mW laser is used to excite the sample, an additional, but inbuilt spectrometer captures the spectrum [118, 119]. The recently presented Oppo X3 Find Pro offers a true microscopy camera module built-in. Even though it is ought to be used for lifestyle applications, it could be used for sophisticated PoC applications, where, based on a biological essay, an image-based response needs to be processed. An in-detail investigation of the resolution and quality of the images is still outstanding [120].

5 Discussion and outlook

With the quality of the photos, smartphone manufacturers have one of the few unique selling points with which they can increase their market share. This has led to a tremendous pace of smartphone development in recent years, with the effect that high-quality imaging equipment can fit into a remarkably small footprint. The price pressure associated with the competition and the high-volume production mean that the technology is available for a small fraction of the price of conventional laboratory instruments at a consistently high quality. The physical obstacles to capturing a low-noise image are reduced by using multiple or even monochromatic cameras and highly specialized signal processing algorithms to suggest the impression of a high-quality image. The resulting loss of raw information unfortunately turns out to be a disadvantage for scientific use of such devices. Additionally, the speed which new smartphone models are released also poses the risk that imaging results between different models, brands and even different firmware versions are difficult or even impossible to compare to each other. This is one reason why certifying the above-mentioned methods for the medical use is much more difficult, even though the low price and high availability makes their application very attractive.

However, as a multifunctional core element in biomedical devices, the smartphone can perform a variety of tasks and thus provide innovative approaches to diagnostics as well as to being used for scientific purposes. The possibility to acquire data, process them directly on-site and, if necessary, control external devices based on the results, allows the development of autonomous miniature labs or can make low-cost and portable rapid tests available – as shown with a growing number of test-kits for the COVID-19 virus. For widespread uses, it seems helpful to share the design files so that others can recreate and test them in their environments, as has been demonstrated by many research groups already.

With the Apple Watch 6's recently introduced ability to monitor blood oxygen levels [121], it can be seen that smartphone manufacturers see a business case in integrating sensors that provide health parameters directly into handheld devices. The increasing miniaturization of electronic and optical components together with highly adjusted production techniques, as previously shown in optical pickup units, it is very likely that some of the projects currently still in the laboratory context will find their way into the mass market. The fast-growing field of machine learning in combination with fast mobile Internet (e.g. 5G) can create powerful telemedical applications. Here a disease could be detected on-site with the help of previously trained neural networks. Another scenario is the ability to send real-time information from smartphone adapters that produce micrographs of skin tissue to medical professionals, who can then make better diagnoses based on the data collected. With new production techniques, such as 3D printing of optics, highly specialized micro-optics can be manufactured on demand, resulting in a wide variety of customized and compact imaging solutions in smaller and larger scales. The smartphone could then realize the role of the previously missing connection between optical adapters and Internet-based access of the data and results.

For the certification required for use in medical areas, calibration by means of suitable tools or the introduction of a manufacturer-independent standard in image output is conceivable, with which protocols for the detection of diseases can be quickly evaluated digitally and quantitatively.

In their current form, smartphones can serve as a versatile alternative to industry-grade CMOS cameras, enabling rapid prototyping in microscopy where costs and space are limited.

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Bionotes

Haoran Wang
Leibniz Institute of Photonic Technology, Albert-Einstein-Straße 9, 07745 Jena, Germany

Haoran Wang received the M. Sc. degree in the Leibniz University Hannover, Germany, in 2020, with the topic of fibre-based optical manipulation with a 3D-printed microfluidic chip. He is currently a PhD student in the Heintzmann Lab at the Leibniz-Institute of Photonic Technology, Jena, Germany. His research focus is structured illumination microscopy and frugal science using cellphones. After doing an apprenticeship as an electrician.

Rainer Heintzmann
Leibniz Institute of Photonic Technology, Albert-Einstein-Straße 9, 07745 Jena, Germany
Institute of Physical Chemistry, Abbe Center of Photonics, Helmholtzweg 4, 07745 Jena, Germany
https://orcid.org/0000-0002-4950-1936

Rainer Heintzmann studied physics (major) and computer science (minor) at the University of Osnabruuck, Germany, where he received his diploma in 1996 working on X-ray scattering at holographic structures written by visible light. He obtained his Dr. rer. nat. 1999 in Physics under the supervision of Prof. Dr. Christoph Cremer with work on high-resolution light microscopy using axial tomography and particle localizations. He then continued as a postdoctoral fellow (2000–2002) and junior group head (2002–2004) at the Max-Planck Institute for Biophysical Chemistry in Goottingen, Germany, in the department of Dr. Thomas Jovin. From 2004 to 2015 he headed the "Biological Nanoimaging" group at the Randall Division, King's College, London, U.K., and since 2010 he is a full professor of physical chemistry at the Friedrich Schiller University, Jena, and head of the Research Department "Microscopy" at the Leibniz-Institute of Photonic Technology, Jena, Germany. His research interests are various methods of super-resolution light microscopy (SIM, OPRA, and image inversion interferometry) and image processing

(deconvolution and inverse modeling). He has published more than 100 peer-reviewed journal articles and book chapters.

Benedict Diederich
Leibniz Institute of Photonic Technology, Albert-Einstein-Straße 9, 07745 Jena, Germany
Institute of Physical Chemistry, Abbe Center of Photonics, Helmholtzweg 4, 07745 Jena, Germany
benedictdied@gmail.com
https://orcid.org/0000-0003-0453-6286

Benedict Diederich started studying electrical engineering at the University for Applied Science, Cologne. A specialization in optics and an internship at Nikon Microscopy, Japan, pointed him to the interdisciplinary field of microscopy. After working for Zeiss, he started his PhD in the Heintzmann Lab at the Leibniz IPHT, Jena, where he focusses on bringing cutting edge research to everybody by relying on tailored image processing and low-cost optical setups. Part of his PhD program took place at the Photonics Center at the Boston University in the Tian Lab. A recent contribution was the open-source optical toolbox UC2 (You-See-Too, https://www.youseetoo.org), which attempts to democratize science by making cutting-edge affordable and available to everyone, everywhere.