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To cite this article: Christian Eggeling 2018 *J. Phys. D: Appl. Phys.* **51** 040201

OPEN ACCESS
IOP Publishing
Journal of Physics D: Applied Physics
J. Phys. D: Appl. Phys. **51** (2018) 040201 (3pp)
https://doi.org/10.1088/1361-6463/aaa259

Editorial

Advances in bioimaging—challenges and potentials

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Welcome to Advances in Bioimaging (see here)——it is with great pleasure I introduce this special collection of multidisciplinary research articles, reviews and opinion pieces published in *Journal of Physics D: Applied Physics* on the exciting and fast developing area of bioimaging. As its Topic Editor, I will be bringing together some of the leading voices as well as emerging developments in this diverse and multidisciplinary community to produce this collection.

Efficient functioning of the human body involves a multilevel synthesis emerging from collective brain activity to the immune system. Signalling, whether in immune, neuronal, or other cells, is usually controlled by the local redistribution and interactions of a relatively large set of proteins throughout one or different cells. Microscopy has allowed a detailed look into cellular structures. Yet, interdisciplinary efforts are still required to improve its full potential in biomedical research, especially when it comes to novel developments such as super-resolution or correlative microscopy approaches.

The spatial scale of organizational changes of molecules in cells and organelles ranges from micrometres to single molecular dimensions, i.e. nanometres. In addition, these changes may occur on multiple timescales from micro/milliseconds to minutes/hours, and many are driven or modulated by physical parameters such as forces or electrical currents [1]. For example, during neuronal communication, ion fluxes and cellular structures such as axons and synapses have been identified to play a crucial role. Key molecules are involved, whose re-organization is required to maintain and mediate the communication mechanisms. Similarly, triggering of immune cells such T-cells require close interactions between different cells, involving re-organization of proteins such as receptors on the cell surface and other structures such as the actin cytoskeleton in the cellular interior, alongside with forces acting in-between the cells.

Understanding the complex interactions of the molecular processes underlying these mechanisms is one of the main objectives of biomedical research. Disorders of these dynamic interplays can lead to disease, but their comprehension to the development of novel therapies. Considering the complexity of, for example, autoimmune diseases or cancer, to-date medical practice demands the most physiological conditions for their research—which can be best matched by directly studying cells and/or organisms, if possible in their living state. Covering a large range of spatial (nanometres to centimetres) and temporal (microseconds to minutes/hours) scales, this necessitates most sensitive observation techniques, optimally, following the theme ‘Seeing is Believing’, directly picturing structures in organisms and the spatial organization of cells and proteins.

Consequently, there is a vast number of bioimaging approaches such as electron, optical or x-ray microscopy, magnetic-resonance imaging (MRI), or imaging involving physical parameters such as forces, electrical currents or molecular masses, each of which are characterized by unique features [2]. For example, electron microscopy allows disclosing cellular and molecular structures with a resolution of down to the molecular and atomic level, optical microscopy molecular structures in living cells, x-ray microscopy those of unstained samples, and MRI those in whole organisms. Scientifically, it is important that the observation reveals the true state of the system, i.e. that the experimental conditions required for observation do not bias the biological system. Unfortunately, most of the above techniques are still prone to such artefacts or feature inherent limitations, such as the need for accurate fixation in electron microscopy (potentially changing molecular structures and impeding direct live-cell investigations and thus studies of molecular dynamics), a

limited spatial resolution and the need for labelling in optical microscopy (thus lacking the disclosure of cellular structures on the often relevant molecular scales and potentially interfering with the functionality of molecules), or the potentially harming radiation in x-ray microscopy (damaging the cellular sample).

Over the years, many advancements have been introduced, trying to optimize the sensitivity of the microscopy approaches and to minimize possible artefacts. Examples are improvement in sample preparations (e.g. fixation protocols), irradiation (e.g. x-ray and laser sources), microscope design (e.g. optics) and detection technology (e.g. quantum yields and frame rates of cameras), to name only a few. A seminal progression is for example the establishment of optical super-resolution microscopy, nowadays allowing the monitoring of structural details with down to macromolecular resolution in living cells, and awarded the 2014 Nobel Prize in Chemistry, or the development of electron tomography, revealing molecular structures with unprecedented resolution, and rewarded the 2017 Nobel Prize in Chemistry. On the other hand, studies on model systems such as model membranes or synthetic biology approaches for reconstructing cell-like systems help reducing experimental complexity and building up bottom-up know-how of cellular functions or enabling the use of cellular (or cell-like) systems as (bio)engineered tools (e.g. for drug delivery or nanotechnology). Finally, the combination of different read-outs such as correlative recordings of electron- and optical microscopy images or of optical microscopy and forces or electrical currents has shown to additionally enhance the acquired information content and thus sensitivity of bioimaging [2].

Unfortunately, an improved accuracy usually comes at a price of enhanced sensitivity towards other artefacts, requiring improved control of the experimental design, for example improved sample preparation or data acquisition protocols. Thus the potentials but also challenges in bioimaging grow steadily, and any further optimization requires input from different disciplines, (bio)chemistry, engineering, physics and mathematics. Taking optical microscopy as an example, new labels provide higher photostability and signals as well as improved ways of tagging the molecules of interest (chemistry); more efficient light sources such as improved lasers realise optimised ways of exciting and manipulating signals (engineering/physics); improved optics such as adaptive optics or light-sheet and multi-spot illumination deliver the light to the sample in a more efficient way and thus minimise aberrations and phototoxicity and maximise acquisition speed (engineering/physics); and intelligent data analysis algorithms enhance the content one can extract from an image (mathematics/informatics).

In general, the demands of biomedical research are large with applications requiring different aspects of spatial and/or temporal resolution, 3D imaging deep inside the sample or even living organism, and/or long acquisition times with low toxicity. The fact that all bioimaging approaches are complementary promotes research environments with access to various kinds of microscopes, depending on their suitability for the case in hand. On the other hand, research environments should be strongly interdisciplinary, allowing (bio) chemists, physicists, engineers and biomedical researchers to tightly work together to optimise technology for its use in biomedical research.

An ultimate goal would be a microscope that can combine all of the demands set by the users. Unfortunately, much advanced technology developed by engineers, physicists, mathematician or chemists has not made its way into applications, simply because of missing tight links with biomedical users. The question arises whether we have missed opportunities. Therefore, funding and dissemination possibilities have to be created, promoting interdisciplinary research environments with access to a broad range of complementary state-of-the-art technology as well as with the chance to test out new approaches.

The Advances in Bioimaging programme aims at disseminating the potentials and challenges in bioimaging, linking different disciplines, describing remaining limitations and disclosing remedies, hopefully opening new chances for understanding cells, and curing diseases. We have already published multiple articles on bioimaging such as the 2015 super-resolution microscopy roadmap [1], and will now continue with publishing the 2018 correlative microscopy techniques roadmap [2], which will outline some of the exciting developments here (as I have outlined above). Following this, we will be publishing a series of special issues relating to the excellent developments in super-resolution microscopy.

We also have a special issue on neurophotonics which will highlight some of the technical challenges in brain imaging. We have much more planned, which we will announce at regular intervals.

I hope you will enjoy reading the work we publish here and find it useful.

Acknowledgment

CE acknowledges general funding support by the Medical Research Council (grant number MC_UU_12010/unit programs G0902418 and MC_UU_12025, grant MR/K01577X/1), the Wellcome Trust (Micron Advanced Imaging Unit Strategic Award 091911), Deutsche Forschungsgemeinschaft (Research unit 1905), Oxford internal funding (EPA Cephalosporin Fund and John Fell Fund), and the Wolfson Foundation (initial funding of the Wolfson Imaging Centre Oxford).

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