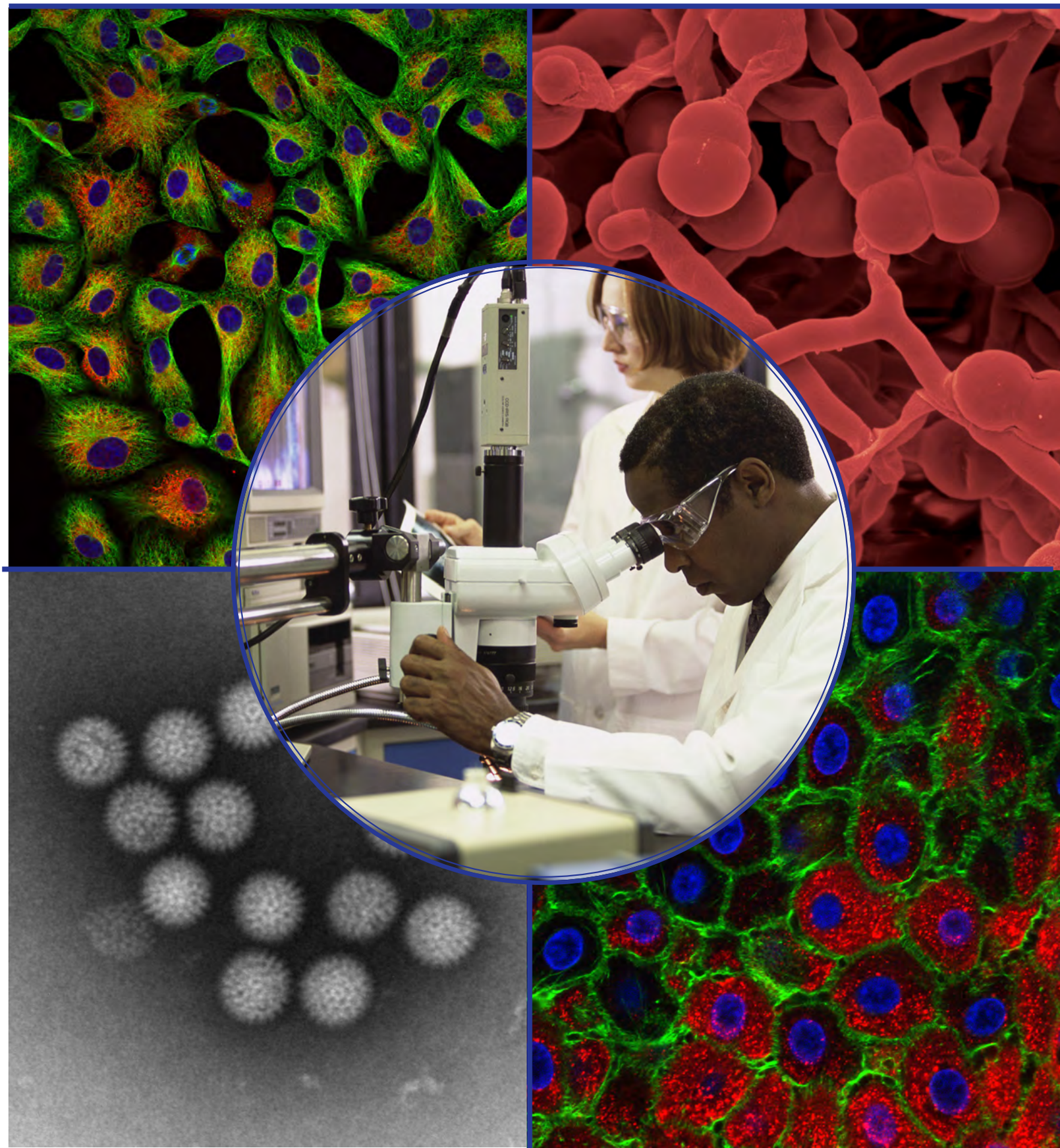
BBSRC
bioscience for the future

Strategic Review of Bioimaging



Cover images, from top (left to right):

Confocal laser scanning microscope image of an uninfected monolayer of Vero cells, labelled with antibodies against tubulin (green) and the endoplasmic reticulum (red). The nuclei are stained blue.
Credit: Pippa Hawes, The Pirbright Institute.

Research carried out at the John Innes Centre on the Norwich Research Park has revealed how the actinomycete M. corallina produces a very potent antibiotic, microbisporicin, which is active against a wide range of bacterial pathogens. This scanning electron micrograph image shows branching aerial filaments (hyphae) with pairs of spores (blobs) on the ends which give the bacterium part of its name – bispora. Credit: Lucy Foulston, Kim Findlay and Mervyn Bibb, John Innes Centre, NRP Image Library, Norwich Research Park.

Negative stain image of bluetongue virus core particles. The sample was stained with uranyl acetate and imaged at 100kV using a transmission electron microscope. Credit: Pippa Hawes, The Pirbright Institute.

Confocal laser scanning microscope image of food-and-mouth disease virus (FMDV) infected porcine tongue epithelium. The tissue section was cut using a vibrating microtome and labelled with an anti-FMDV antibody (red), and stained for actin (green) and DNA (blue). Credit: Pippa Hawes, The Pirbright Institute.

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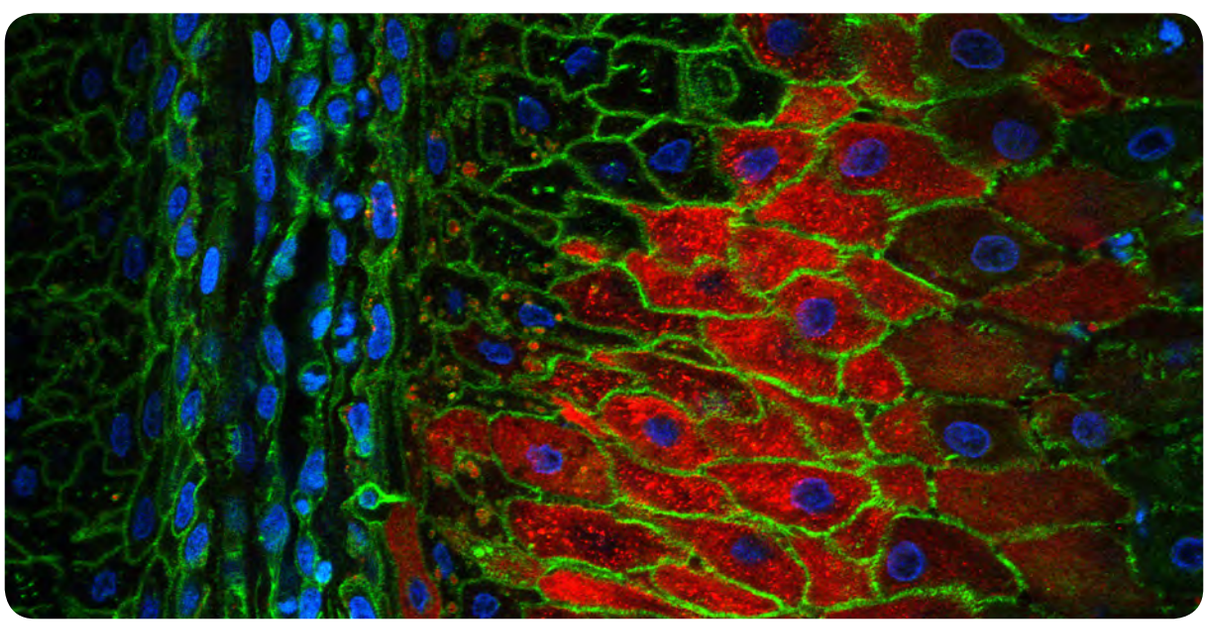
Executive Summary

Imaging is now the dominant form of analysis of molecules, cells, and tissues across the Life Sciences. Imaging of biological samples, or bioimaging, is an area of significant interest for BBSRC as bioimaging technologies cut across all areas of BBSRC's remit, from plant and animal phenomics to drug delivery. Bioimaging operates at all scales from high-voltage cryo-electron microscopes as used in structural biology, to enormously powerful super-resolution microscopes, through to whole plant or animal imaging.

Technology development has been rapid; with advances in sensitivity, resolution, speed and signal processing; allowing researchers to visualise and measure samples in ways not before possible. Advances in quantitative methods for imaging, and additionally image analysis, have also widened the scope of what imaging as a technology can enable in terms of scientific discovery. Further breakthroughs will follow by being able to integrate image data with other data types, for instance genomic and transcriptomic data with phenotypic data.



Confocal laser scanning microscope image of food-and-mouth disease virus (FMDV) infected porcine tongue epithelium. The tissue section was cut using a vibrating microtome and labelled with an anti-FMDV antibody (red), and stained for actin (green) and DNA (blue).
Credit: Pippa Hawes, The Pirbright Institute

Over the last few years, the UK bioimaging landscape has undergone dramatic changes. Further to the technological breakthroughs, there have been significant investments in imaging over the last 3-5 years, in addition to a coming together and coalescence of imaging researchers, resulting in the establishment of an identified and mobilised imaging community.

Taking into account the scientific drivers, technological breakthroughs, substantial investments made and recent community mobilisation, as well as the changing European context, it was agreed that this Strategic Review of Bioimaging should serve as an evaluation of BBSRC's current and future approaches to support for bioimaging in the UK.

It is recognised that this strategic review would potentially be of interest to a wide range of stakeholders including funders (research councils and charities), government policymakers, scientific researchers, facility managers, industry and learned societies. Accordingly, we have endeavoured to engage key informants across the biosciences research community.

The review was informed by BBSRC's expert advisory panels (Exploiting New Ways of Working, ENWW, and the Research Advisory Panel, RAP), but of critical importance has been the input of the dedicated Expert Review Group, comprising representatives from academia and industry; spanning a broad range of disciplinary expertise and career stages. Substantial evidence was gathered through an analysis of BBSRC's funded portfolio, followed by the publication of an open community survey, which generated significant interest and captured a broad range of valuable input. Additional targeted engagement was undertaken with key industry stakeholders and the perspective of other funders, primarily research councils, was actively sought.

This report of the review presents topics in different sections for the purpose of clarity; however none of these topics can be viewed in isolation as each impacts upon, and in turn is impacted by several, if not all, of the others. Throughout the report we have highlighted the main conclusions drawn **(in blue)** and the recommendations that flow from these **(in green)**. These are summarised at the end of the report, but can be grouped under a number of themes:

UK Bioimaging: Current Status

It is widely recognised that the UK produces world-class bioimaging-related research which underpins all of the biosciences. Bioimaging is a cross-disciplinary field; in addition to engaging the whole spectrum of biological sciences, it requires interaction with the physical and engineering sciences (particularly with computer scientists, mathematicians, engineers, physicists, chemists and material scientists) for technology development, but also with the medical and environmental sciences, where bioimaging underpins many important applications. To date the UK has been effective at facilitating these multidisciplinary collaborations, but there is an increasing need to enhance working across conventional discipline boundaries if greater impacts are to be realised in a rapidly changing landscape.

To this end, mechanisms for flexible and innovative funding directed towards research, training and equipment are essential, specifically BBSRC should consider regular bioimaging technology and resource funding initiatives, helping to renew existing facilities, invest in emerging instrumentation and encourage wider access to the UK's bioimaging capability.

In addition to enabling world-class discovery science, UK developments in bioimaging have led to notable technologies that have been commercialised and are now used worldwide, demonstrating the important contribution that UK bioimaging expertise can make to the bioeconomy. To ensure that the adoption of new and emerging technologies is timely and efficient, the UK bioimaging technology landscape, community and supporting structures, must all be appropriately sustained; failure to do so would lead to a detrimental effect on all UK bioscience. This support must include the 'enabling technologies', such as detectors, lasers and probes, which are an essential part of the bioimaging ecosystem. Therefore working in partnership with others, BBSRC should continue to support community-driven organisations to bring people together from different sectors and encourage activities for new and emerging technologies that would allow interaction between developers, industry, facility managers and users.

Infrastructure and Access

The UK bioimaging landscape encompasses a breadth of technologies and combines standard widely used technologies with state-of-the-art facilities. The UK has worked hard to develop this strong bioimaging technology capability and for continued excellence of the science, support and funding must enable the procurement and maintenance of both standard ('workhorse') and state-of-the-art equipment.

Access for UK researchers to bioimaging resources occurs at a variety of scales: from in-lab equipment, through to local core facilities, right up to high-end equipment in national (or international) centres. Each mechanism of shared access has its benefits, and a distributed network of diverse resources is

essential to provide access for UK researchers to the full range of available technologies, requiring BBSRC to facilitate a broad range of shared access mechanisms across all BBSRC funded bioimaging equipment and facilities.

Training and Skills

The future of UK bioimaging is reliant not just on advanced technologies, but on a well-trained and highly-skilled community of developers, users and technical staff. Training across disciplines and at all career stages is essential to ensure that there is sufficient bioimaging capability in the UK. One area identified as being in particular need of attention, is that of training in data skills, which are required across the biosciences community to enable high-quality quantitative bioimaging.

In addition to training opportunities at all levels, there need to be recognised and sustainable career pathways for bioimaging and other technical specialists. BBSRC should work with other funders, the learned societies, community groups, HEIs and industry to ensure support is available for high-quality training, and that appropriate career structures are recognised and established.

Data Management and Analysis

Image analysis is an essential part of the quantitative bioimaging pathway. The bioimaging community must work with computer scientists, engineers, physicists and mathematicians to exchange analysis techniques with other disciplines, and to develop new techniques that solve problems unique to bioimaging. In addition, the integration of data from different imaging modalities, and from imaging and non-imaging experiments, is an important emerging trend across the biosciences. Continued support of algorithm and software development is vital, and targeted calls such as TRDF are a key component, as is support via responsive mode grants. Cross-council funding, particularly with EPSRC and MRC, is likely to be particularly important due to the interdisciplinary nature of the work.

The integration and sharing of data will be enabled by open standards and improved data infrastructure technologies; however, the UK's data infrastructure is not currently suitable for the increasingly large amount of data produced by bioimaging technologies. This is a broader problem not limited to bioimaging; therefore BBSRC will need to work with other research councils, relevant government departments (e.g. BEIS, HMT), HEFCE, UK HEIs and other key stakeholders to develop a coherent approach for the replacement, upgrade and renewal of the UK's data infrastructure as required for bioimaging.

Working in Partnership with Industry

Successful imaging technology and methods development requires a true multidisciplinary approach. Support and training are required to maintain effective links not only across traditional discipline boundaries but importantly between academia and industry. Strong bioimaging facilities across the UK are valued by the bioimaging technology industry as hubs of technologies, training and expertise. Support for networking and pilot projects between UK bioimaging facilities and UK and global bioimaging technology companies will help to strengthen technology development for bioimaging in the UK. Furthermore, BBSRC should promote discussion between academics and industrialists, working with regulators and the British Standards Institute, to increase the use and validity of bioimaging tools and technologies across the breadth of UK industry and bioeconomy sectors.

Many areas have been identified where complementary and synergistic working already occurs between academia and industry, however, these could be further built upon and there are still many untapped opportunities providing scope for much greater impact and benefit to the UK bioeconomy.

International Engagement

The benefits of international engagement are clear in that international collaboration and participation in large-scale programmes and networks provide extremely useful mechanisms to access high-quality facilities and technology across the world, and to network and collaborate with highly-skilled researchers from other countries, sharing research methods, equipment and best practice. Accordingly, BBSRC should continue to provide flexible mechanisms for UK researchers (within BBSRC's remit) to visit and collaborate with a diversity of international imaging centres of excellence.

As many of the European and wider international programmes are still in the relatively early stages of development and are evolving rapidly, the UK has an opportunity to influence these efforts. A flexible approach to interactions is required which can accommodate the diversity and speed of evolution of these programmes. BBSRC should consider the future level of UK engagement in European (particularly post-Brexit) and International networks, such as Euro-BioImaging, CTLS and COST.

Furthermore, given the current constraints on resources and changing European landscape, BBSRC needs to consider its role as a national funder to ensure that our inputs to these programmes are driven by our scientific goals, and UK resources are deployed most effectively for the benefit of the UK research community.

Enabling Future World-Class Bioscience

The opportunities for new scientific discovery which will be enabled by advances in bioimaging are truly exciting. These range from foundational discovery science through to translation and application in industry. Indeed future bioimaging will underpin many aspects of the bioeconomy and is an essential component of the impact of bioscience on industry. To realise this ambition a combination of key technologies, interactions and infrastructure, as well as highly-skilled people are all essential.

BBSRC will need to work with other funding bodies to ensure that cross-disciplinary projects and networks focussed on the development of new bioimaging technologies, methods and analyses can be facilitated, and to encourage the exchange of knowledge and expertise across disciplinary boundaries. This will be vital to the continued success of UK bioimaging.

Whilst the current UK bioimaging backdrop and infrastructure is strong, this has arisen through huge effort and large investment by the community and funding bodies. Without maintenance, the strength of UK bioimaging will diminish in a matter of years due to the rapid rate of change in both enabling and imaging technologies.

In summary, it is essential that BBSRC works with the UK bioimaging community, including learned societies, other funding bodies, HEIs and HEFCE to ensure that UK bioimaging is receiving the support and funding necessary to maintain a world-class environment that will, in turn, enable world-class bioscience in the UK.

Background to the Review

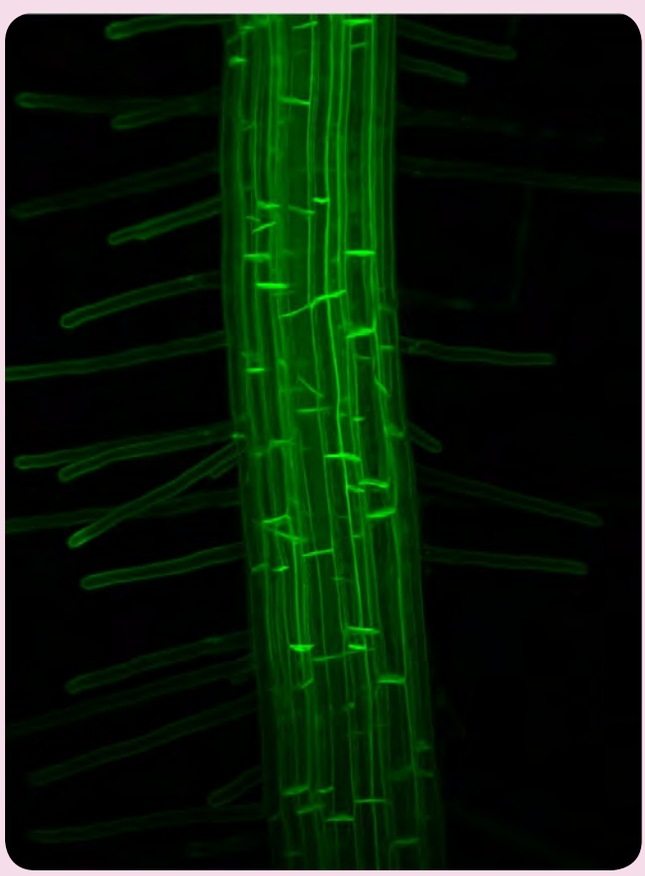
Imaging within a Bioscience Context

Imaging is now the dominant form of analysis of molecules, cells, and tissues across the Life Sciences. Imaging of biological samples, or bioimaging, is an area of significant interest for BBSRC as bioimaging technologies cut across all areas of BBSRC's remit, from plant and animal phenomics to drug delivery. Bioimaging technologies are being explicitly used in a minimum of 38% of BBSRC's funded portfolio of responsive mode grants, initiative grants, fellowships and strategic institute projects for the years 2010 to 2014. This corresponds to approximately one billion pounds of research funding between 2010 and 2014 that explicitly relies on bioimaging.

Bioimaging operates at all scales from high-voltage cryo-electron microscopes as used in structural biology, to enormously powerful super-resolution microscopes, which can break the light diffraction barrier at the 10-20nm level, through to whole plant or animal imaging used to improve agricultural sciences, well-being and the bioeconomy. See Box B.1 for some examples of bioscience enabled by bioimaging.

Box B.1 Examples of biological research utilising a wide range of imaging techniques

- Researchers at Durham University & the National Institute of Agricultural Botany used advanced light microscopy to analyse how plants respond to pathogenic fungi at the sub-cellular level (BB/H017569/1)
- Researchers at the University of Bristol have developed image analysis tools that help to measure the welfare and stress levels of pigs on farms (BB/I005641/1)
- Researchers at the University of Oxford have used imaging techniques to study pharmaceutical proteins; this understanding has led to improved shelf life of such products (**http://www.bbsrc.ac.uk/documents/improving-therapeutic-proteins-pdf/**)
- Researchers at the University of Edinburgh have used multiple super-resolution techniques to investigate the subcellular events of plant virus-host interactions leading to increased understanding of virus infection (BH/H018719/1)
- Researchers at the University of Dundee have used advanced imaging and image analysis tools to study the physical interactions of cells during animal development (BB/G015082/1) and the genes that govern the formation of bacterial biofilms (BB/H002340/1)



Maximum projection image of the root of an Arabidopsis seedling. Cell membranes are stained with GFP. The image was taken on a light sheet fluorescent microscope. Light sheet microscopy allows plants to be imaged in 3D, as they grow, at the cell scale. It can be used to study anatomical changes in plants over time, such as in response to nutrient stress.
Credit: Andrew French, The University of Nottingham

- Researchers at the University of Nottingham have used light sheet microscopy (BB/M012212/1) and X-ray microCT imaging (ERC Advanced Grant FUTUREROOTS) combined with advanced image analysis software to study root adaptive responses to water and nutrient availability in their soil environment.

Being able to generate biological images, analyse and then interpret them is extremely important and of great value in its own right. Technology development is rapid; with advances in sensitivity, resolution, speed and signal processing; allowing researchers to visualise and measure samples in ways not before possible, including in three and four dimensions, using continuous real-time measurements. Advances in quantitative methods for imaging, and additionally image analysis, have also widened the scope of what imaging as a technology can enable in terms of scientific discovery.

Recognition of the Importance of Imaging and Image Analysis

The importance of imaging across all areas of science and industry has been recognised in a number of high-level strategic documents recently published in the UK.

Cutting-edge biological imaging technologies were highlighted as an area of strategic importance in the Research Councils UK Large Facilities Roadmap 2010[1]. Imaging is also highlighted as a key enabling technology for biological and medical research in the Research Councils UK Framework for Capital Investment 2012[2], in particular as an area of investment for new and transformative equipment for world-leading research. More recently, an imaging Centre of Excellence and medical imaging are referenced in the UK government response to the 2014 Consultation on Proposals for Long-term Capital Investment in Science & Research[3].

Development of technology from inception to application was considered broadly by the Maxwell Report, published by EPSRC in 2014[4]. This report considered the importance of engineering and physical sciences research to the life and health sciences, and imaging was a strong theme in the report.

Imaging was a clear focus of the cross-council Technology Touching Life (TTL) consultation in 2015[5]. The TTL programme and subsequent consultation is a collaborative programme between BBSRC, EPSRC, and MRC. Throughout the consultation, imaging and related technologies were both identified as needs and opportunities at the Technology Touching Life interface. An early strategic framework has been produced, outlining the objectives and scope of TTL.[6]

Recent Developments within Bioimaging

Over recent years, the UK bioimaging landscape has undergone dramatic changes. Technological breakthroughs have enabled a wide range of scientific endeavours that were not possible beforehand. These include the discovery and development of new fluorescent proteins, which won the 2008 Nobel Prize in Chemistry, super-resolution microscopy techniques, which won the 2014 Nobel Prize in Chemistry, light sheet microscopy, particularly SPIM, SBF-SEM and FIB-SEM, and multi- and hyper-spectral imaging, including near-infrared optical tomography, a technology once used for space missions by NASA and now used to collect measurement of soft tissues. Most recently, the technique of cryo-EM won the 2017 Nobel Prize in Chemistry, with Professor Richard Henderson from the MRC Laboratory of Molecular Biology in Cambridge, UK, as one of the laureates. Many of these technologies have received large-scale funding and are now accessible to a significant number of UK researchers.

Further to these technological breakthroughs there have been significant investments in imaging over the last 3-5 years. These have included investment in: research utilising current state-of-the-art methodologies; development of bioimaging tools and technologies; provision of the latest cutting-edge equipment; and the development of new tools for data analysis and management. This

[1] **http://www.rcuk.ac.uk/documents/research/rcuklargefacilitiesroadmap2010-pdf/**; p26

[2] **http://www.rcuk.ac.uk/documents/publications/rcukframeworkforcapitalinvestment2012-pdf/**; p19

[3] **https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/383439/14-1248-science-capital-consultation-response.pdf**; p13, p16

[4] **https://www.epsrc.ac.uk/newsevents/pubs/the-importance-of-engineering-and-physical-sciences-research-to-health-and-life-sciences/**

[5] **http://www.bbsrc.ac.uk/documents/1509-tech-touching-life-consultation**

[6] **http://www.rcuk.ac.uk/research/xrcprogrammes/technology-touching-life/strategy/**

investment (some examples included in Table C.1 in the Annex) has been made across a number of funders whose remits cut across the breadth of research using imaging and development of imaging technology across the UK.

In addition to the development in technologies, and recent investments in imaging research and technology in the UK, a renewed mobility of UK researchers has resulted in the establishment of a clear, self-identified bioimaging community. BioImagingUK was formed as a grassroots network in August 2009, galvanised by the advent of the ESFRI project Euro-BioImaging which had an initial meeting held in Frankfurt in June 2009. Since the first meeting of the BioImagingUK group, this informal network has met on an annual basis to discuss future strategy and areas of common concern in the imaging community, along with training requirements and career development opportunities for imaging specialists.

Following development of grassroots networking activity, the BioImagingUK network was funded in June 2014, with an award of £100k made over three years, and co-funded by BBSRC, EPSRC, MRC and the Wellcome Trust. The network grant includes investigators from across the biological and biomedical imaging community, and aims to develop links within the imaging community across different facets, define strategic priorities for imaging, extend training resources for the imaging community through development of a catalogue of training opportunities, and develop a greater evidence base of investment into personnel who are developing or delivering imaging technology or resources.

As already noted, the development of the BioimagingUK network was initially prompted, in part, by developments in the Euro-BioImaging project. Euro-BioImaging (EuBI) is a large-scale pan-European research infrastructure project on the European Strategy Forum on Research Infrastructures (ESFRI) Roadmap. It was included on the Roadmap in 2008. The EuBI mission is to build a distributed imaging infrastructure across Europe that will provide open access to innovative biological and medical imaging technologies for European researchers.

More detail on the background and status of Euro-BioImaging and other relevant international projects is included later in this report; however the EuBI project is now coming towards the end of an interim phase, where decisions will need to be made as to the level of UK engagement in this project as it enters the construction phase. In this context, having the outputs of this review will guide BBSRC's national strategy, and in turn, help to define the optimal positioning for UK bioimaging in relation to European and International activities such as Euro-BioImaging.

Initiation of a Review of Bioimaging

Taking into account the aforementioned scientific drivers, technological breakthroughs, substantial investments made and recent community mobilisation, as well as the changing European context, an evaluation of the UK's and in particular BBSRC's current and future positioning in imaging is timely and even necessary. Therefore it was proposed to conduct a strategic review of bioimaging in the UK.

Following this proposal, input was sought from BBSRC's Research Advisory Panel (RAP) and Exploiting New Ways of Working Strategy Advisory Panel (ENWW SAP). Both panels expressed enthusiasm and endorsed the need for a review, and offered initial thoughts as to the scope and content.

Purpose of the Review

The purpose of this review of bioimaging in the UK is to provide advice on how best BBSRC can support and develop the UK bioimaging capability, in order to underpin and maximise the potential of UK bioscience. Specifically to:

- Consider the key science-led bioimaging needs (of the BBSRC research community) in the medium term.

- Informed by the scientific need, identify potential future infrastructural requirements and consider whether they can be fulfilled by current provision and available mechanisms.
- Guide BBSRC's national strategy for the coming years (2016-2020).
- Identify the optimal positioning for UK bioimaging in the context of European and International activities.

Scope of the Review

When formulating the scope of the review it was essential to keep in mind what BBSRC is seeking to learn from the review alongside the needs of the UK community. It is important for BBSRC to be able to develop a medium-term strategic overview that encompasses an appraisal of what cutting edge research will be enabled by underpinning state-of-the-art imaging capabilities and the practical infrastructural requirements associated with this.

The review had the potential to be very broad-ranging in terms of remit, topic inclusion, physical scale and time-frame. The following considerations were used to assist with framing the review from the outset:

- The review should focus on the UK biosciences community but will need to consider the interfaces with related sectors in the physical and material sciences, computing and (bio)medical sciences.
- Imaging applications span spatial scales from sub-atomic levels up to field-scale imaging.
- The review should aim to capture emerging scientific areas and technology developments, including those where there are likely to be changes in the equipment/infrastructure requirements.

There were a number of topics which utilise imaging methods that could have been included in the scope of this review, but in the interest of keeping the scope manageable, it was decided that the review would exclude some of these. For example, the review includes imaging up to whole organism level, but not beyond (hence excluding larger scale/field phenotyping and observation studies). We have also excluded electron microscopy when applied to non-biological samples, and medical imaging technologies applied to humans rather than animals. The decisions as to whether these topics would be included took into account a number of considerations including the breadth of the review and whether including other topics would be feasible in the scope of this review, whether specific topics were within BBSRC remit, and whether the overall spectrum of imaging being considered by the review is representative of the BBSRC imaging community.

Field-scale phenotyping was one area considered for inclusion, however guidance from several advisory functions led to the conclusion that this area was wider in scope than imaging alone, and therefore it would be hard to fully reflect under the stated scope of this review. Similarly areas such as electron microscopy when applied to non-biological samples and medical imaging technologies for use with humans are recognised as important and were considered, but for the purposes of this review were deemed out of scope.

While it was essential to define a specific scope for the review, it has been acknowledged throughout the review process that the conclusions and recommendations from this review are likely to be more broadly applicable to some of the areas of imaging, or areas using imaging technologies and techniques, that are not within the review scope. This may not be the case for all conclusions however, as they may have considerable specificity to bioimaging in a BBSRC context.

As part of the review process, other research councils and funders with an interest in imaging were consulted in order to understand their interests and priorities in relation to funding and support for imaging research. This was important in ensuring that the review was reflective of bioimaging as applied to the BBSRC remit, and to identify any complementarities in remit or funding priorities.

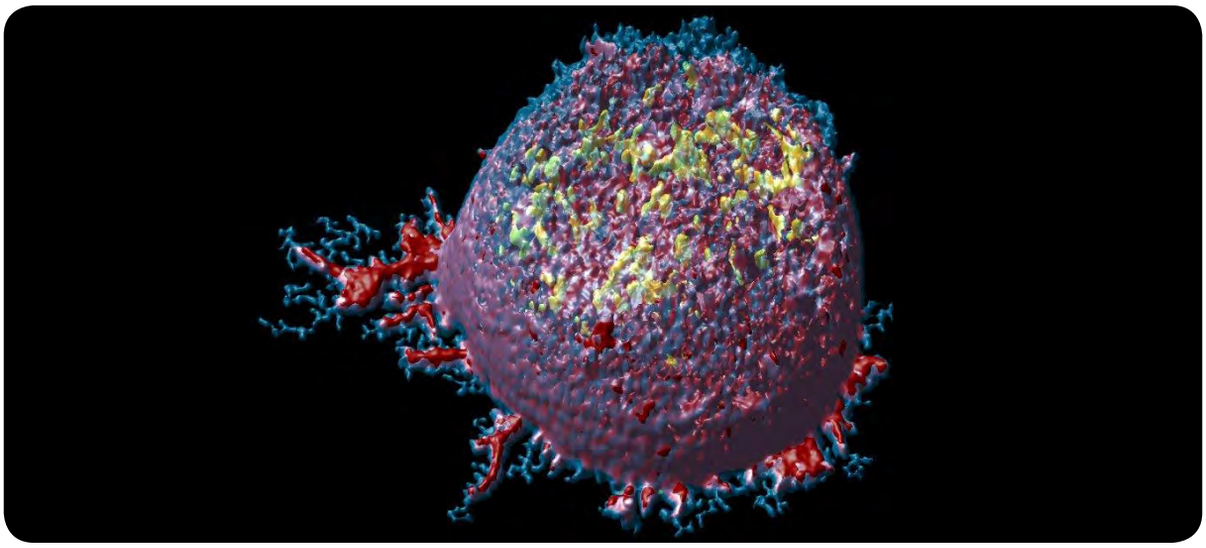


Image of a crawling T lymphocyte using g-STED. The image has been deconvolved and the final visual effect obtained by surface rendering. Blue-colour shows labelled plasma membrane with a specific lipophilic dye, red- the actin filaments, and yellow- the internal cytosolic vesicles. Credit: Laura Zanetti-Domingues, Science and Technology Facilities Council

Stakeholders

At the outset of this process it was recognised that a BBSRC review of bioimaging would potentially be of interest to a wide range of stakeholders including funders (research councils and charities), government policymakers, scientific researchers, facility managers, industry and learned societies. Accordingly, we have endeavoured to engage key informants across the biosciences research community. In terms of researchers this has included both individuals and the wider community in the form of appropriate community groups and the learned societies.

Methods of Working

The review process included the following elements:

- An expert review group was convened, which included active early, mid and senior-career researchers from across the UK, representatives from Europe, plus industry (membership at Annex A). The group met three times in person and participated in several teleconferences to gather the key science challenges and provide valuable input throughout the process. The group was instrumental in shaping the community survey and drawing the main conclusions from all of the inputs received.
- In addition a cross-office/research council group was established to gather input from relevant members of staff, reflecting different functions within BBSRC, and the perspective of different research councils.
- A detailed analysis was undertaken of BBSRC's funded portfolio to provide an evidence-base for what is/has already been supported through a variety of BBSRC's funding mechanisms.
- A community survey was conducted, with the questions informed by input from the above groups. The survey launched on 20 November 2015, and closed on 18 December 2015, and aimed to gather the views of researchers and other stakeholders with an interest in bioimaging. A full list of the questions and accompanying text are included at Annex E. The survey encouraged responses from larger groupings of people, as well as individual responses. It was publicised on the BBSRC website, through social media, and was also distributed to relevant imaging contacts, the Exploiting New Ways of Working Strategy Advisory Panel (ENWW SAP), BBSRC industry contacts, strategic partner universities and BBSRC-funded institutes.
- The survey received 182 responses of which 104 were full responses and 78 were partial responses. High level themes for the survey included science-led priorities, skills and training, support for image analysis and equipment provision, and access to facilities.

- Further to the survey, additional engagement with key industry stakeholders was undertaken to ensure that we had a more complete understanding of the requirements of industry with respect to bioimaging.
- Discussion points and opinions were also gathered from other relevant BBSRC Advisory Panels (Exploiting New Ways of Working and Research Advisory Panel).

Objectives

The objectives for the review reflect the scope and the deliverables, and have formed the basis of the structure of the review report:

- Review the UK bioimaging landscape in a science-led fashion and identify the current ability/ future potential of bioimaging to impact on world leading bioscience in the UK.
- Have an understanding of the current bioimaging technologies and infrastructure of the UK, including data management, considering whether or not it can fulfil future scientific requirements.
- Identify future requirements and emerging trends with regards to technologies used, the support needed and the technical limitations experienced by the UK bioimaging community in order to guide future science and technology strategy.
- Alongside the future technology requirements, identify the needs associated with having a cohort of people with the required skills and expertise, and the training that needs to be accessible to enable this.
- Understand the future data requirements, uses and potentials within the UK bioimaging community.
- Understand technology development in the UK for new bioimaging technologies with particular emphasis on the UK's bioimaging industry and the wider bioeconomy that benefits from this.
- Consider the future UK bioscience that will be enabled by bioimaging, outlining the key technologies and infrastructure that will be required to facilitate world-class bioscience.
- Identify how best to position UK bioimaging in an international context such that future needs may be met.

Outputs from the Review

This report presents the findings and conclusions covering the specific topics identified and which:

- Describe the future science-led bioimaging opportunities identified.
- Identify any accompanying infrastructural requirements, whether equipment, software, data management needs or training.
- Highlights roles for BBSRC in support for, or development of, the provision of any identified resources.
- Provides comment on mechanisms for fulfilment of these requirements.
- Considers who BBSRC should be partnering with to deliver the requirements.
- Provides some consideration of models of support e.g. investment at research group, departmental, regional or national facilities level.
- Considers the rationale for, and extent of, engagement in international activities such as Euro-BioImaging.

Following publication of the review report, the conclusions and recommendations from it will be used to shape future BBSRC strategy related to bioimaging.

1. Bioimaging in the UK

The UK is a world leader in bioscience research. Reaching these heights has required the prompt uptake and continued use of core technologies and techniques. One such technology is bioimaging, which encompasses many techniques and technologies for discovery.

Bioimaging technologies are being explicitly used in a minimum of 38 %[7] of the BBSRC's funded portfolio of responsive mode grants, initiative grants, fellowships and strategic institute projects for the years 2010 to 2014.

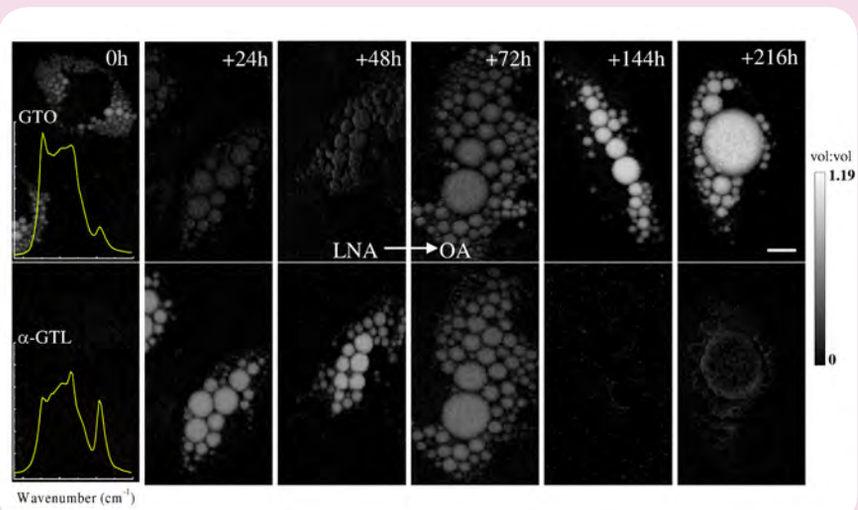
Bioimaging Enabling Bioscience

Bioimaging is a group of technologies and a research area that underpins all of the biological sciences. From single molecules to whole organisms, bioimaging technologies operate across a wide range of scales and bioimaging enables studies at the molecular level through to whole plants, animals and humans. Research projects utilising different types of bioimaging are seen throughout the BBSRC funded portfolio: from ageing through to systems biology (see Box 1.1 & 1.2 for examples; see Figure B.1 & B.2 (Annex) for a plot of the community survey data).

Box 1.1 Bioimaging in Bioscience for Health

There is increasing evidence showing that cytosolic lipid droplets (LDs) play a key role in many cellular functions, for example, obesity and type II diabetes have been directly related to malfunction of LD synthesis, lipid storage, and degradation. Yet the chemical composition of LDs at the individual droplet level is essentially unknown due to the lack of suitable quantitative measurement techniques. In this research project we have developed and built a new generation optical microscope able to image single LDs and quantify their composition label-free in living cells, as well as simultaneously detect specific associated fluorescently-labelled proteins. With this novel imaging technology we quantified for the first time the lipid type and content of individual LDs in living human adipose-derived stem cells during differentiation over several days. These are unprecedented findings, exemplifying that the quantitative imaging method demonstrated here could open a radically new way of studying and understanding cytosolic LDs in living cells, with wide-ranging impacts to improve the diagnosis and treatment of lipid-related health problems.

Professor Paola Borri, Cardiff University

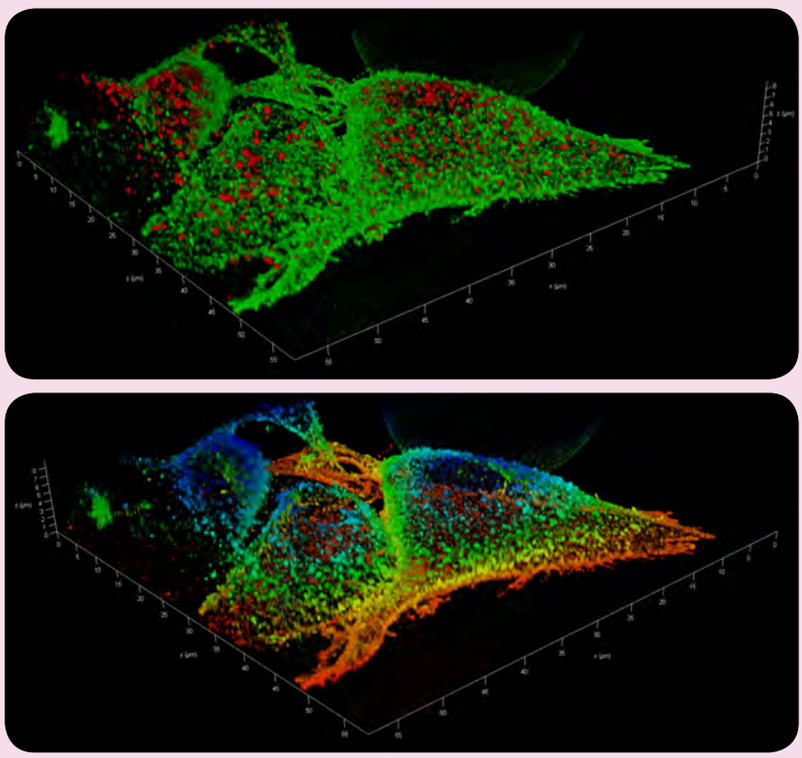


Comparative quantitative analysis over a temporal dataset of CARS hyperspectral images acquired in living human adipose-derived stem cells. The spatial distributions of the volume concentration are shown at different time points for the lipid components (glyceryl trioleate (GTO) and α-glyceryl trilinolenate (α-GTL)), on a greyscale as indicated. Scale bar is 10μm. Retrieved Raman-like spectra are shown (in yellow) for the lipid components. Credit: Paola Borri, Cardiff University. Adapted from Di Napoli et al. Anal. Chem. 88 (7), pp 3677–3685 (2016).

[7] It is likely that this figure is actually higher, but mention of bioimaging was not explicit.

Box 1.2 Bioimaging in Systems Biology

The aim of this project was to unravel the complex function of a receptor family cell signalling network through the use of novel imaging techniques. A key to the project has been the development of single molecule imaging methods for the investigation of molecular structure in cells. Specifically, a new single molecule localization method has been implemented that allows the structural characterization of macromolecular complexes in cells, at 5 nm resolution. This method has required the development of not only specialized microscopy technology but also new data analysis algorithms based on Bayesian methods, allowing the extraction of quantitative data from the challenging environment of mammalian cells. Methods applicable to tissue imaging of these same parameters have also been established. Other techniques developed and used as part of the grant programme include single particle tracking (again using Bayesian analysis techniques) and new FRET methodologies to determine the conformation of receptor molecules in the plasma membrane. The imaging methods have been combined with molecular dynamics simulations to develop a detailed picture of the structure and dynamics of the EGFR receptor family in the plasma membrane.



In order to investigate the mechanisms of EGFR endocytosis, CHO cells were labelled with EGF-CF640R and endocytosis was allowed to proceed for 10 minutes before cells were fixed and counterstained with a membrane dye. Cells were imaged on a Leica gSP8 system in deconvolution mode to quantify the amount, size and shape of the endocytic carriers and their position relative to the volume of the cell. A) 3D render of labelled cells (EGF=red, membrane = green); B) False-colour render of the same cells, colour coded by depth within the image stack (blue= highest, red=lowest). Credit: Peter Parker, The Francis Crick Institute.

Professor Peter Parker, The Francis Crick Institute

The UK produces excellent bioimaging-related research: both the development of new bioimaging technologies or methods and the enabling of world-class bioscience research across the UK's research landscape. The UK's historical and current investment in bioimaging is essential as a basis for present and continued world-class bioscience. Bioimaging will enable a broad spectrum of future bioscience including detailing the behaviour of individual cells within the larger context of developing tissues, host-pathogen interactions, the analysis of molecule-level dynamics within cells and breakthroughs in agriculture and food security research.

Bioimaging technologies are at varying levels of development and deployment, from those which are well-established, such as confocal microscopy, to recent developments, including lattice light sheet microscopy, volume EM and cryo-EM. The community considered that new technologies are becoming more widespread and having a 'deep' impact, whilst established technologies will continue to have 'broad' impact. For both types of technology, their eventual impact is heavily reliant of the development of 'bioimage informatics' tools, i.e. image analysis and cross-modality data integration tools along with data storage, sharing and management tools.

Through intense community effort and recent, large investment, the UK produces world-class bioimaging-related research, underpinning all of the biosciences.

Bioimaging across the Disciplines

Bioimaging is not exclusive to the biosciences: the development of new bioimaging technologies requires interaction with the physical and engineering sciences and many imaging methods developed in the biosciences can be applied in, for example, the environmental sciences and, likewise, imaging methods from other disciplines, such as astronomy, can be applied to bioimaging. Strong relationships with chemists are also needed for the development of new labelling technologies.

Bioimaging has already been highlighted by other reports, such as the cross-council Technology Touching Life consultation[8], which identified imaging in the life sciences as one of several key areas where research councils working together could lead to major impact.

This included the development of new labelling and label-free approaches, multimodal and correlative studies, enhanced sensitivity and detectors, new non-invasive or *in vivo* methods, among other areas.

Responses to the community survey and wider consultation indicate that the UK is strong at building collaborations to develop new bioimaging methods and that these occur across disciplines with computer scientists, mathematicians, engineers, physicists, chemists and/or material scientists and largely focus on the development of new or bespoke equipment and data analysis (see Figure B.2, Annex). The access to technical expertise, support and novel technologies is seen as a further benefit of collaborations to develop new bioimaging methods.

Bioimaging is a cross-disciplinary field with interactions across the sciences. The UK is effective at developing the necessary collaborations and cross-disciplinary communication needed for bioimaging.

Bioimaging and Industry

The UK is a strong centre of bioimaging technology development and research in the UK has led to new commercial ventures and impacted the global bioimaging industry. Several technologies, now used worldwide, have been pioneered through UK research, for example fluorescence lifetime imaging microscopy, M-Scan mass spectrometry and the Ionscope scanning ion conductance microscope (see Box 1.3).

BOX 1.3 Examples of Bioimaging Technologies Developed in the UK

- *M-Scan*: Mass spectrometry services for new drug characterisation based on over 40 years of research at Imperial College London (**now part of SGS; http://www.sgs.co.uk/**).
- *Technologica*: A University of Essex spin-out company focussing on chlorophyll fluorescence imaging for rapid plant screening (**http://www.technologica.co.uk/**).
- Ionscope (now a brand of openbiolabs Ltd): A new microscope developed at Imperial College London and Cambridge University allowing protein-level resolution imaging on the surface of living cells (**http://www.openiolabs.co.uk/**).

The UK has a small but strong bioimaging technologies industry. The UK bioimaging industry is a mixture of custom instrument design, available from companies such as Cairn Research; microscopy components, available from companies such as Andor and Oxford Instruments; and novel technologies, often from university spin-out companies such as PhaseFocus. The strength of UK bioimaging research is essential to the continuation of this strong industrial sector and further UK research will, no doubt, lead to the establishment of further companies.

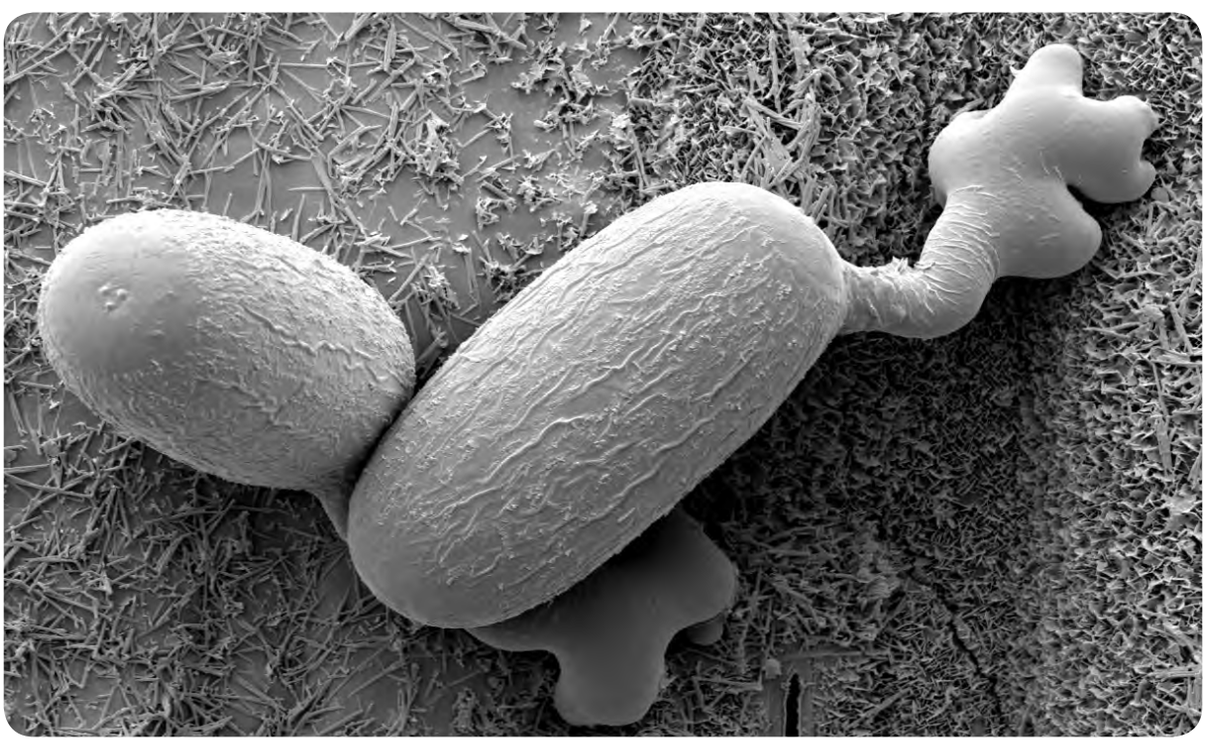
[8] **http://www.bbsrc.ac.uk/documents/1509-tech-touching-life-consultation**

Within the UK, much of industrial research and development requires imaging; some examples from our conversations with representatives from industry include seed production and commercial plant sciences, and food production. In our consultations with industry members the strength of UK bioimaging with regards to industrial-academic collaborations was regularly mentioned. These collaborations allow industry researchers to use the strength of expertise in the UK bioimaging community to solve problems essential to their product lines (see Objective 6 for further details).

UK bioimaging development has led to notable technologies that have been commercialised and are now used worldwide. Further, UK bioimaging expertise is regularly accessed by the private sector to solve core industrial problems to the benefit of the wider bioeconomy.

Technologies Backdrop

Collectively, our consultations during this review convey a strong sense of the breadth of technologies employed by the UK bioimaging community. Further, the worldwide bioimaging technologies are extremely well represented in the UK backdrop (Figure 1.1).



This scanning electron microscopy (SEM) image shows two fungal spores germinating on a wheat leaf. Scientists from the John Innes Centre on the Norwich Research Park collected leaves of several wheat (Triticum aestivum) varieties from the field to investigate the structure and types of surface waxes; these spores were observed on wheat variety 'Shango'. Credit: Nikolai Adamski, John Innes Centre, NRP Image Library, Norwich Research Park.

There are a high number of users of established technologies, such as confocal fluorescence microscopy. These technologies have, over recent years, become essential to the biosciences and represent an indispensable resource for the bioimaging backdrop of the UK. In order for bioimaging to enable future UK biosciences it is essential that this standard equipment, and staff trained to operate it, must be maintained such that established microscopy techniques are still available to all researchers who require access.

Further, fluorescence techniques such as FRAP, FRET and FLIM are in common use making (conventional) fluorescence microscopy the most used family of techniques across all of our sources of evidence. These techniques can be developed as part of larger fluorescence microscopy systems or as standalone tools, expanding the repertoire available to the bioscience research community.

Like fluorescence microscopy, core electron microscopy techniques, e.g. SEM and TEM, are in heavy use across both the portfolio and survey respondents. Indeed the portfolio analysis would suggest that EM is under-represented in the survey responses, which could be because EM is a highly specialised skill, performed in specialist centres housing expensive equipment maintained and run by expert users. Yet many forms of light microscopy can be performed on instruments installed in researchers' own laboratories, as well as centralised facilities, leading to a higher number of light microscope users compared to EM users.

Recent developments in electron tomography and volume EM have made these techniques more accessible, so FIB-SEM and SBF-SEM are well represented. However, there is still scope to increase usage of these techniques, along with correlative light and electron microscopy (CLEM), within the UK by increasing accessibility further and providing excellent technical support for these advanced instruments.

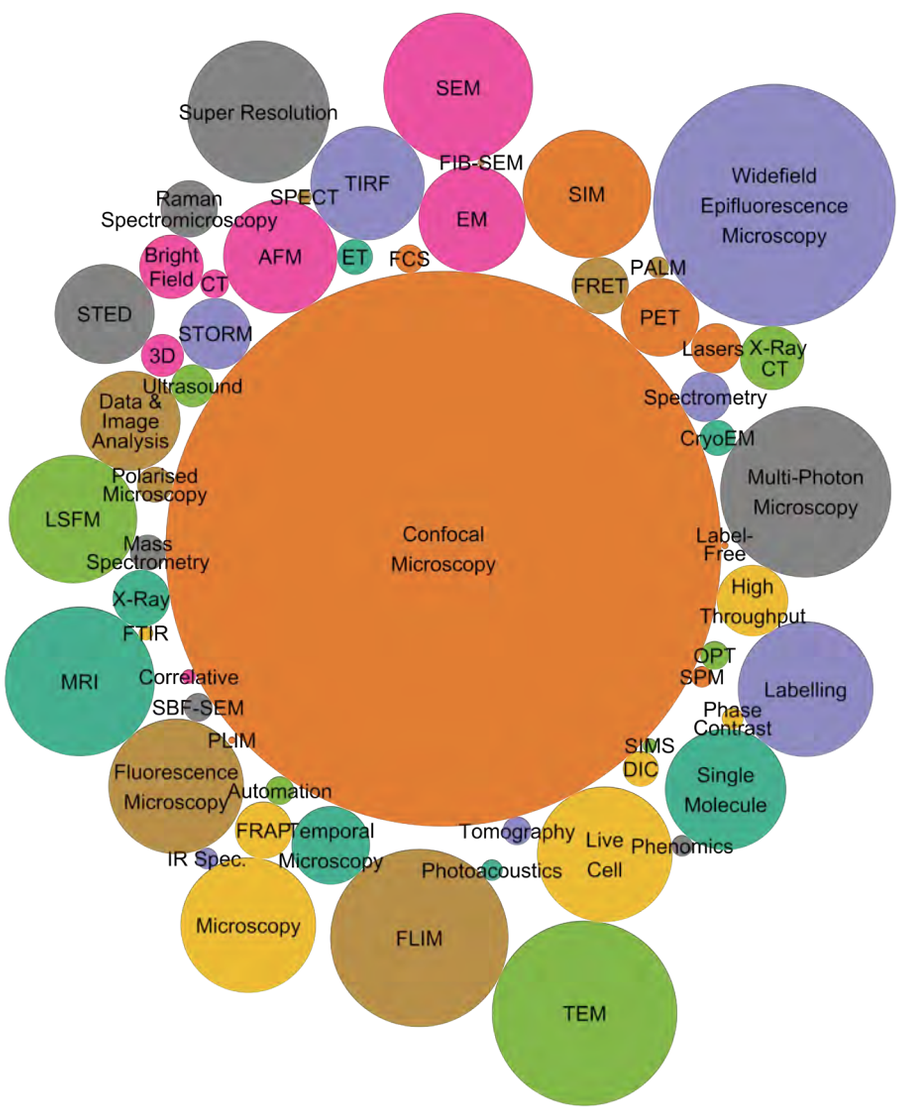


Figure 1.1 - Responses to the community survey question 'What imaging technologies do you use?' Respondents were able to give up to ten techniques, the results of which have been binned into major technologies. Each disc represents one technology and the size of the disc is representative of the number of respondents using that technology. Colour and position of discs is random.

Building upon this central core of microscopy technologies are other important recent developments in super-resolution and light sheet microscopy, soft X-ray tomography, and direct electron detectors used in structural cryo-EM studies.

Alongside microscopy techniques there are a broad range of technologies that contribute to the bioimaging backdrop of the UK. These include various spectroscopy and spectrometry techniques, especially mass spectrometry and Raman spectroscopy-based microscopy techniques; scanning probe microscopy, e.g. AFM; other tomography technologies, such as electron and X-ray tomography; and (bio)medical imaging technologies such as MRI, PET and ultrasound imaging.

As the breadth of technologies available to the UK's bioimaging community is essential to the future development of new technologies, approaches and knowledge, and is key to the underpinning of future bioscience, those core technologies used by the whole biosciences community must be maintained. Additionally, where there are developments in enabling technologies, such as lasers, detectors and cameras, these need to be embraced and adopted to preserve the UK's strong backdrop upon which the broad bioimaging technology framework can rest.

The UK bioimaging landscape encompasses a breadth of technologies and combines broadly impacting standard tools, such as confocal microscopes, and state-of-the-art technologies such as cryo-EM.

2. The UK Bioimaging Infrastructure

The UK has a strong bioimaging infrastructure: a wide range of technologies; high availability of core technologies; substantial expertise in methods and techniques; and strong research in enabling technologies allow UK bioimaging to be world class and to enable UK bioscience.

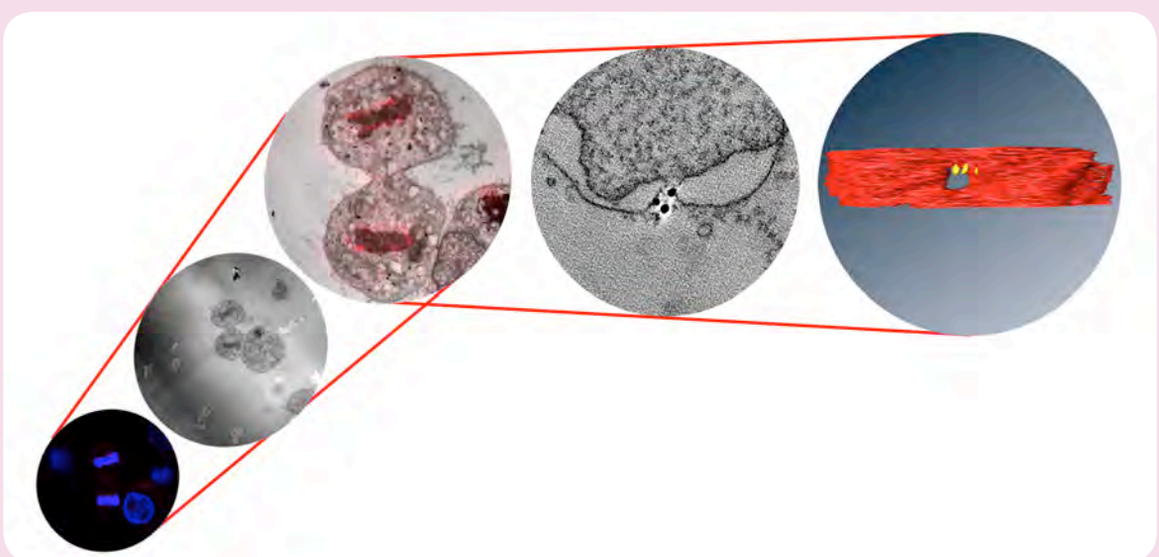
Bioimaging Technology Backdrop

The UK biosciences community has excellent access to a broad range of bioimaging equipment including light and electron microscopes; tomography devices; spectroscopy and spectrometry technologies; MRI, X-ray and ultrasound; and many other specialist imaging tools (Figure 1.1). This places the UK in a strong position for adopting new technologies, capitalising on new techniques and enabling world-class bioscience in the UK.

The strength of the UK's bioimaging backdrop has allowed a quick uptake of new, state-of-the-art technologies, such as super-resolution light microscopy, volume EM and cryo-EM (see Box 2.1 for further examples). One in five respondents to the community survey that use fluorescence microscopy already has access to a super-resolution modality.

Box 2.1 Examples of Recently Funded High-End Bioimaging in the UK through the BBSRC ALERT Initiative

- Elucidating cell structure in 3D by automated electron microscopy (Newcastle University)
- A facility for 3D cellular imaging that bridges light and electron microscopy (University of Warwick)
- A super-resolution multiphoton and dynamic STORM imaging facility (University of Leicester)
- Mass spectrometry imaging for biology and biotechnology (University of Liverpool)
- Fluorescence Light Sheet Microscopy for Live 3D and 4D imaging (University of Liverpool)
- Photo-oxidation and cryofluorescence for Correlative Light Electron Microscopy (University of Bristol)



During the cell cycle, which in HeLa cells takes approx. 22 hours, cells undergo division of both the cellular and nuclear content into the daughter cells. At the late stages of cell division the nuclear membrane has to reform around the condensing DNA to form the new nucleus. The ESCRT-III complex is present for only 90 second on this reforming nuclear membrane but its exact role is unknown. Correlative Light Electron Microscopy (CLEM) provided the perfect method to capture this snap-shot localisation over the whole cell cycle length. Chmp2a (part of the ESCRT-III complex) was labelled with a red fluorophore and gold particles. Whereas the red fluorescence allowed to pinpoint the very few cells late in the cell division cycle (left), the gold particles (right) showed that the ESCRT-III complex is present and involved in closing the very last gaps in the nuclear membrane. Credit: Paul Verkade, University of Bristol. Image adapted from Olmos et al., 2015, Nature, 522: 236-239.

Further, recent large investments from various funding bodies (see Table C.1, Annex) have enabled increased access to high-end bioimaging. Some of these funding initiatives included a focus on equipment sharing and widening access across institutes, encouraging collaborative bids with multiple institutions thus strengthening the UK's bioimaging access.

The current strength of the UK bioimaging technology landscape is heavily dependent on these and other sources of funding as well as the community effort through, for example, the Facility Managers Meetings. Maintaining the UK's high-quality bioimaging backdrop will require further dedicated support. This is even more important given the increased and continually increasing rate of change of bioimaging technology including detectors, lasers and other enabling technologies. As equipment becomes more advanced the need for specialist technical posts to run specific instruments grows. Dedicated expert staff members increase the efficiency of these highly complex instruments by helping researchers collect the best quality data in the time available, and by ensuring instruments are optimally maintained.

In a review of the previous BBSRC Research Equipment Initiative[9] it was identified that insufficient investment in mid-range equipment becomes apparent within three years and has a serious effect on UK researchers. The evaluation suggested that it would take only five years to lead to a UK-wide crisis in terms of equipment and technologies, leading to a loss of international competitiveness and weakening world-class bioscience research across the UK. Given the vital role of bioimaging in underpinning bioscience across the BBSRC's remit, these concerns should be heeded as still being valid and which align with similar concerns identified throughout the consultation process of this review.

Whilst investment in the purchase and development of new technologies is key to keeping UK bioscience at the global cutting edge, our consultations show that the community has concerns not just about new equipment but about the maintenance and turnover of older equipment, some of which is becoming obsolete, which supports the majority of the microscopy performed by UK scientists (Fig. 1.1).

At least 38% of all BBSRC funded research explicitly states the use of bioimaging technologies, with many more expected to also be using bioimaging in some capacity, many of which are using fluorescence and confocal microscopes. Technology driven research programmes and those using the very latest tools, such as super-resolution microscopy, volume EM and cryo-EM, still require the basics of confocal microscopy for screening and ground work experiments. It is these standard systems that underpin almost all of the additional microscopes funded over the last 10 years, and yet there have been little or no initiatives to fund the replacement of this ageing stock of essential microscopes.

With most equipment being bought through bioimaging technology companies, rather than built in-house, the user community is reliant on support by the manufacturer for new parts and upgrades to both hardware and software; however, companies will understandably support equipment for only a limited time. This leaves a proportion of essential bioimaging equipment ageing and potentially unsupported, an understandable concern of the bioimaging community.

Whilst the UK's ability to quickly adopt emerging technologies has and will provide essential 'deep' impact to particular areas of the biosciences, the sturdy backdrop of existing technologies provides a constant 'broad' impact across all the UK's bioscience research. The UK's world-class bioimaging backdrop will only be sustained if funding and support for essential maintenance and turnover of existing technologies is balanced with investment and uptake of cutting-edge, emerging technologies.

[9] **http://www.bbsrc.ac.uk/documents/research-equipment-initiative-evaluation-pdf/**

The UK has worked hard to develop a strong bioimaging technologies backdrop; however, without continued support and funding this could quickly weaken. Support and funding must enable the procurement of both commonplace and state-of-the-art technologies.

Recommendation 1: BBSRC should consider regular bioimaging technology and resource funding initiatives, helping to renew existing facilities, invest in emerging instrumentation and encourage wider access to the UK's bioimaging capability within a rapidly changing landscape.

The Bioimaging Community

Community mobilisation through BioimagingUK, the Facility Managers Meetings and learned societies, amongst other societies, networks and events, is invaluable to the UK bioimaging community. Such cohesion has led to the sharing of best practice, training guides, technical expertise and the establishment of a central database of microscopy facilities, hosted by the Royal Microscopical Society (see Box 2.2 for key bioimaging community organisations).

Box 2.2 Bioimaging Community Organisations in the UK

- BioImagingUK is a community-led organisation of UK bioimaging scientists (**http://www.bioimaginguk.org/**)
- UK Facility Managers Meetings are a series of informal meetings for UK bioimaging/microscopy facility managers
- The Royal Microscopical Society (RMS) is an international learned society providing a community for microscope users, including training, handbooks, industrial connections and outreach **http://www.rms.org.uk/**)
- The RMS Facilities Database is a database of microscopy and bioimaging facilities across the UK and was developed with RMS and BioimagingUK (**http://www.rms.org.uk/network-collaborate/facilities-database.html**); this was initially held by the University of York (**http://www.york.ac.uk/biology/technology-facility/imaging-cytometry/uk-lm-facilities/**)

Researcher-led community efforts in the UK allow for exchange of expertise, best practice and standards. The agreement of standards in particular, will enable the UK bioscience community to capitalise on emerging integrative and correlative approaches, combining data from multiple imaging modalities or with non-imaging data. Take up of community-led, research-driven standards and best practise will enhance the already strong UK bioimaging community and keep the UK as a major global competitor in terms of bioimaging development and enabling bioscience research.

Community cohesion and strong communication between different bioimaging stakeholders, such as different disciplines, will be essential to future UK technology development and bioimaging infrastructure. The UK is already strong in this area with many researchers working across disciplines to develop new bioimaging technologies and methods. The importance of working across traditional discipline boundaries is recognised through the community survey, where cross-disciplinarity was a recurring theme, particularly in answers where respondents were asked to consider limitations, technology development, future opportunities and future requirements.

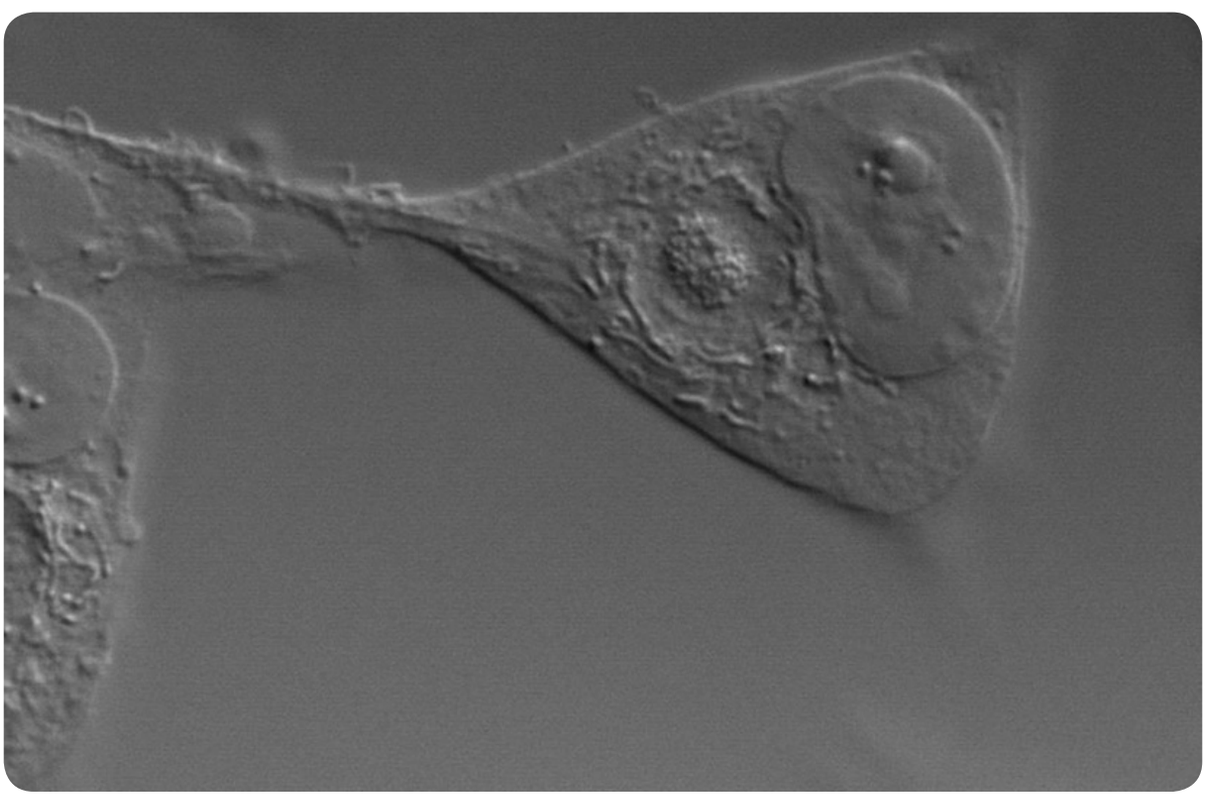
The idea of a strengthened community and increased cross-disciplinary approaches to problems was echoed in conversation with key industry members. Industry members noted that integrated, multi-disciplinary approaches led to quicker and/or better solutions to industrial problems. Furthermore, users of bioimaging technology within industry build networks and partnerships with academia through attending conferences and meetings across the UK and internationally. Having a cohesive bioimaging community establishes a good basis for industry members to identify appropriate research partners and institutions.

UK bioimaging has recently coalesced forming community-driven, researcher-led organisations such as BioimagingUK and the Facility Managers Meetings. Strong support of these community bodies already comes from the research councils, Wellcome Trust and learned societies but must be maintained in years to come.

Recommendation 2: BBSRC, working in partnership with others, should continue to support community-driven organisations and encourage their leadership in terms of training and skills, community resources and meetings.

Access to Bioimaging

The UK has an excellent backdrop of bioimaging technologies; advanced bioimaging facilities; cross-discipline support for enabling technologies; strong data services and image analysis expertise; and notable examples of access to and community sharing of imaging resources. The strength of the UK bioimaging technology backdrop is well demonstrated by those UK institutions that took part in the Euro-BioImaging (EuBI) infrastructure proof-of-concept study, opening access to researchers from across the EU[10].



Vero cell infected with African swine fever virus at 18 hours post infection. This differential interference contrast image shows a well-defined peri-nuclear virus factory (replication site). Credit: Pippa Hawes, The Pirbright Institute.

The UK's bioimaging technologies and access to them operate in a distributed fashion: results of our community survey suggest that access is mostly from within institutions, with bioimaging technologies most often being held within core bioimaging facilities. However, more recent technologies or those that require highly specialist support, such as those found at the Diamond Light Source and the Central Laser Facility, are accessed through national centres such as the Harwell Science and Innovation Campus.

[10] **http://www.eurobioimaging.eu/content-page/euro-bioimaging-proof-concept-studies**

Equipment-focussed funding initiatives, such as the BBSRC ALERT calls (see Table D.1 for other BBSRC mechanisms) and the MRC Next-Generation Optical Microscopy Initiative have enabled many fine examples of local and regional access and community sharing of advanced bioimaging technologies (see Box 2.3). Further funding along these lines will be required to maintain the strength of UK bioimaging.

Although the UK has plenty of examples of excellent access to imaging resources and equipment, approximately 15 % of community survey respondents cited access as a significant technical limiting factor for bioimaging-based research. It is clear that access to technologies is and will continue to be an important factor in enabling bioimaging to operate as an underpinning tool for bioscience in the UK.

Box 2.3 Examples of Successful UK Regional Access Enabled by BBSRC ALERT Funding

- A Facility for Advanced Imaging and Analysis under Hypoxic Conditions for Bath Scientists and GW4 partners (University of Bath; University of Bristol; Cardiff University; University of Exeter)
- A Super-Resolution Microscope for use by Plant Cell Biologists, N8 partners, Durham Scientists and Collaborators (Newcastle University; Durham University; University of Leeds; University of York; Lancaster University; University of Liverpool; The University of Manchester; The University of Sheffield)
- Liverpool 3View: a national hub for 3D-EM bioscience research (National)
- The Oxford Consortium for Three Dimensional Electron Microscopy (Oxford Brookes University; University of Oxford; Sir William Dunn School of Pathology)

Whilst the community recognises that some technologies, particularly cutting-edge or high cost technologies, may need to be shared through regional or national centres and that these centres offer a place for technical expertise and training, it is also important that many bioimaging technologies are available at a local level. This is particularly true of technologies that are used day-in-day-out, such as confocal microscopes, but also true of other technologies where transport of samples can be a limiting factor, for example live animal MRI where animals cannot be easily transported, if at all.

Mirroring this, there was strong support for locally or regionally shared facilities, such as Micron (Oxford), York Bioscience Technology Facility and ESRIC (Edinburgh Super-Resolution Imaging Consortium), that were considered to enable coordinated equipment management, collaborative cross-disciplinary research networks and technical support and training for those institutions and researchers involved (see Table B.1 for further examples of access).

The community also recognised the access and support available through the UK's exceptional national centres, such as the facilities at the Harwell Science and Innovation Campus, which enable access to state-of-the-art specialist technologies and knowledge. One key limitation identified with national centres was that they are often oversubscribed due to a high demand from users, although peer review of proposals for usage was seen as a positive way of enabling access. Such facilities are also viewed very favourably throughout our consultation with industry; although, the issues of limited or difficult access for industry were raised.

UK access to bioimaging resources occurs through various scales of access: from in-lab equipment, through to local core facilities, right up to high-end equipment in national centres. Each mechanism of access has its benefits and a distributed network of varying resources is essential to continued access in the UK.

Recommendation 3: BBSRC should facilitate a broad range of shared access mechanisms across all BBSRC-funded bioimaging equipment and facilities.

3. UK Bioimaging Training & Skills

Despite the world-class nature of UK bioimaging, researchers still experience challenges and limitations with regards to expertise, support and training. The UK has a number of well-developed training courses and strong communities and networks, which will be essential if future UK bioimaging is to remain world-class.

UK Bioimaging Training & Skills

Training of students, researchers and technical staff is an essential aspect of preserving the UK's world-class bioimaging. Bioimaging training is a broad area and training may be general or impart expertise on one particular technology e.g. on the background optics of developing new technologies; on methods for sample preparation; imaging techniques for specific biological problems; data handling and management of the imaging outputs; and/or bioimage analysis techniques and approaches. Not only does well-rounded training develop researchers in their own disciplines but it also builds tools for cross-disciplinary communication and research. A combination of training in these various topics and throughout a researcher's career is necessary to continue the UK's tradition of global excellence within bioimaging.

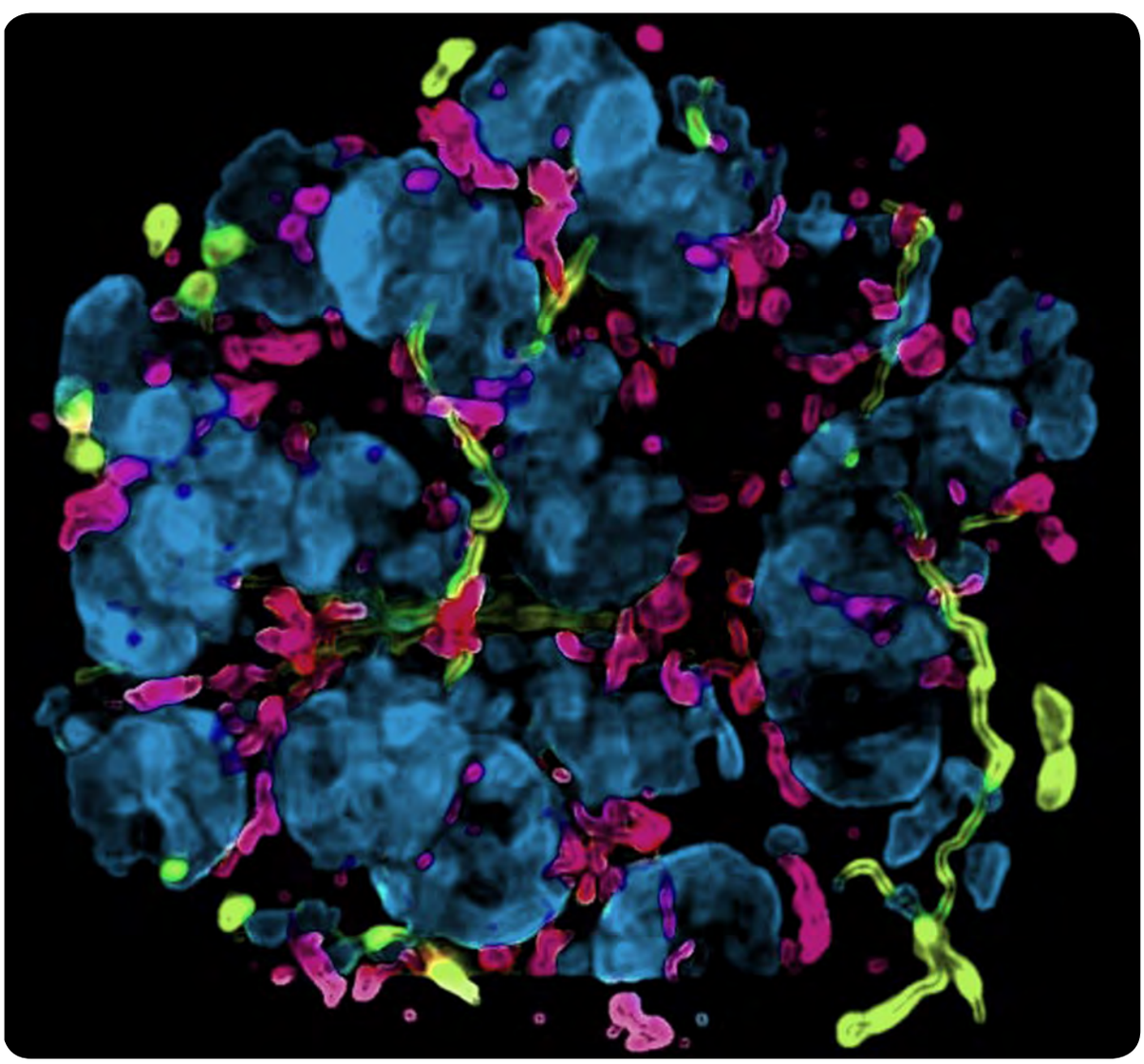


Image of a 3D cyst of human colon adenocarcinoma cells (Caco-2) in which the DNA has been labelled (blue) along with the Golgi apparatus (magenta) and primary cilia (yellow). The image is a rendering of a stack of confocal microscope images showing the 3D organization of the cyst and has been pseudocoloured and processed using Adobe Photoshop. Credit: David Stephens, University of Bristol.

Through consultation for this review, various methods of training are supported by the bioimaging community. These occur at different levels, from beginner to expert, at different scales, different career stages, and with different access routes. Each provides different aspects of a complete training scheme (see Table 3.1 for a summary of these training approaches). These training mechanisms are required at all career stages and necessary further training needs should be supported by funding bodies and learned societies.

Importantly, given the fast-paced nature of bioimaging, courses should be developed and updated to maintain an effective, high-quality training infrastructure across the bioimaging community. Driven by the community, with support from learned societies and funding bodies, this training infrastructure should aim to train new researchers, in core and advanced technologies, as well as increasing the skills of existing researchers. The UK already holds well recognised courses on the use of equipment and sample preparation put on by, for example, the RMS and institutions such as the Universities of York and Oxford. The increased availability of instruments capable of cryo-EM using direct electron detectors, for example those at the National Cryo-EM Centre at Harwell, has sparked a need for specialist training for structural biologists.

Training and skills should be driven and taken forward by the bioimaging community, with support where necessary from the learned societies, research councils and other funders. This could include the production of 'Best Practice' guides by the community, learned societies and research councils. Such guides could suggest best practice for facilities and facility-led training, 'train the trainer' activities, as well as general training for all career stages. BBSRC already provides a number of vehicles for training through the various Doctoral and Fellowship programmes, as well as through Advanced and Modular Training Partnerships, and the relatively new Strategic Training Awards for Research Skills[11] (STARS). STARS exists to support the development of strategically important and vulnerable research skills and capabilities in the biosciences. Of particular relevance to bioimaging is the inclusion of maths, statistics and computational biology, as well as interdisciplinary research.

Furthermore, membership of learned societies can give people access to Continued Professional Development schemes that recognise both role-specific training (i.e. specifically related to bioimaging) and more general training activities. Formally taking part in such schemes can be particularly beneficial for the career development of PDRAs and technical staff. Accredited training can be particularly beneficial due to the assurance this gives that training will meet stated minimum standards and be of high value. Moreover, evidence of taking part in accredited training courses as part of continued professional development is particularly useful in demonstrating to non-academic employers that the training undertaken is widely recognised and means those who have completed it will have relevant skills, knowledge, and experience.

The future of UK bioimaging is reliant not just on technologies but on a well-trained and highly skilled community of developers, users and technical staff. As such, high-quality training must be well supported by all those with a vested interest in UK bioimaging. Our goal should be to ensure there is sufficient bioimaging capability in the UK with opportunities for training at all levels, and sustainable career pathways.

Training across Disciplines

Cutting-edge bioimaging technologies and methods often cross the boundaries of traditional disciplines: the technology a bioscientist needs for an experiment may be so novel that it only exists in the lab of a physicist, or the image analysis tools needed might still be unrefined code developed by a computer scientist.

[11] **http://www.bbsrc.ac.uk/funding/filter/stars/**

Further development of such technology requires both users and developers of bioimaging technologies and methods to communicate skilfully within a multidisciplinary field. Such communication must overcome both the cultural and technical differences between the scientific disciplines in order to best allow new and developing bioimaging technologies and methods to enable bioscience. Such training is not limited to biology PhD students but spans across disciplines and all career stages. The solution is likely to be a combination of recruiting more physical scientists into this field as well as re-training bioscientists.

Training biologists to, for example, understand and develop code is just one side of training across disciplines; computer scientists, mathematicians, engineers, chemists and physicists must also be trained in understanding bioscience.

Bioimaging Training Directories & Resources

Similarly, community-driven, central directories of bioimaging related courses and resources, such as available MOOCs or on-line tutorials, would help to enable access and fully utilise the bioimaging training currently available. Such a directory would need to be curated and well publicised so that new courses and resources were added in a timely manner, and also removed once no longer relevant. Information on the level of prior knowledge required for participation in the course and the expected level of knowledge once completed, plus the amount of time that needs to be invested would also be useful. Some directories exist for training courses, society meetings and conferences, such as the RMS event calendar[12], and a directory of online resources has begun to develop on the BioimagingUK wiki site[13]. Although directories of such resources should be relatively easy to keep, maintenance of the individual courses kept or referenced from these will require continued support from institutions, other learned societies, community groups or networks and funding bodies.

Bioimaging is a skills heavy research area: the technology, methods development and the use of bioimaging require different levels of cross-disciplinary knowledge and expertise, including, for example, image analysis experience. Training and skills development is essential at all career stages and across the disciplines. Training can be supported through various mechanisms but available training and skills resources must be well advertised and accessible to the whole community.

Funding for Bioimaging Training

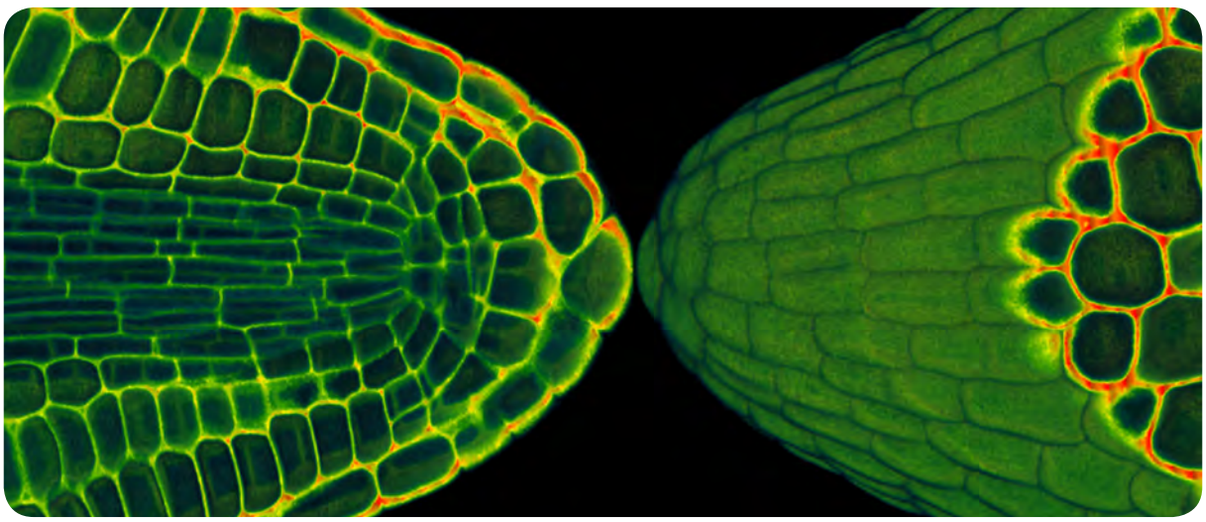
It was noted by the community that the emphasis of skills and training is towards PhD students, often through Doctoral Training Partnerships/Centres and skills schools, but training for PDRAs and researchers at more advanced career stages is also very important, especially in a field such as bioimaging where researchers may move between disciplines at any stage of their career. Funding for skills and training may come from different sources depending on the training mechanism and researcher career stage, for example, funding for PhD students may come through Doctoral Training Partnerships and Centres[14], whilst for PIs, PDRAs and technical staff, funding for training may be requested via normal grant funding mechanisms such as responsive mode grant proposals, or through institution funds. If individuals wish to request support to run training courses they can apply to the STARS scheme[15] (mentioned above) which will provide funding for small scale training, residential skills schools or development of on-line training materials.

[12] **http://www.rms.org.uk/discover-engage/event-calendar.html**

[13] **http://www.bioimaginguk.org/index.php/Training_%26_Documents**

[14] **http://www.onbicdt.ox.ac.uk/research/research-themes.html, http://medicalimaging-cdt.ucl.ac.uk/programmes, http://www.optima-cdt.ac.uk/**

[15] **http://www.bbsrc.ac.uk/funding/filter/stars/**



A mature Arabidopsis thaliana embryo was dissected from a seed. The image on the left shows a cut away revealing cell files and the image on right shows the reconstructed root surface. Optical sections were collected using a confocal laser scanning microscope. The image on the left shows a cut away revealing cell files and the image on right shows the reconstructed root surface. Credit: Peter O'Toole, The University of York.

Concerns from the community about the availability of important training schools and longer courses focussed on the fact that funding is often one-off and may have no 'future proofing'. As such, teachers and students may be uncertain about the future of a course, no matter the quality or impact the course has. Community consultation suggests that research councils and other funding bodies could focus on medium-term funding of courses, e.g. 3 year funding blocks, perhaps with preferential treatment to courses that are accredited (as discussed above).

Most mechanisms of training require some level of monetary support, especially in bioimaging where time on equipment and consumables are required for practical training. Funding is currently available from multiple sources and for multiple purposes. The UK bioimaging community must be supported in accessing the funds and resources available to the community.

UK Bioimaging Facilities and Technical Staff

Both local and national centralised facilities are important for access to highly specialised, advanced techniques. Essential to many of the training mechanisms is the role of the managers and technical staff at these facilities. Not only are these groups essential to the day-to-day running of facilities and shared equipment, but they also provide a clear source of in-house expertise and training.

It is vital for progress in the bioimaging field that these staff have access to advanced training for new and existing technologies, are able to train others in these technologies (train the trainer) and have a clear career path, including recognition, reward and retention within the field. This vocational training could be provided with support from research councils, learned societies and other funders through a mix of specific MSc courses, apprenticeships, sabbaticals or short courses.

Training and expertise can be effectively disseminated through the UK's bioimaging facilities. In order to maintain a high quality of training, facility managers should be constantly developing their technical skills and their training skills.

Recommendation 4: BBSRC should work with the learned societies, other funding bodies and HEIs to encourage and support careers and high-quality training for UK researchers, bioimaging facility managers and technical staff.

Table 3.1 - The benefits and challenges of different training mechanisms available to the UK bioimaging community. Different mechanisms are best suited to different aspects of bioimaging.

Mechanism	**MOOCs**	**On-The-Job, One-to-One in the Lab**
Benefits	• Many students can benefit at once • Convenient for both teachers and students • No limitations based on location or discipline • Can build networks of learners who share best practise • Ideal for teaching theory • Little funding required for AV equipment and maintenance • Ideal for beginners but also for advanced theoretical understanding • Access to training as and when required • Easy to scale up, training for 10 or 100 students can be provided using the same materials	• Can be done when and where needed • Student has influence on the content of the session so they get the best outcomes • Provides hands-on practical experience and potentially follow-up support • Provides experience of the specific equipment (down to make and model) used in that lab • If the trainer is a regular user then little preparation is required and costs are minimal • Passes on practical expertise that other approaches may not
Challenges	• Requires student self-motivation • Can become outdated if not maintained • No central directory or repository for bioimaging-related MOOCs • No recognised accreditation or standardisation • Lack of practical experience	• Dependent on availability of trainer • Misunderstandings and errors propagate as each student later becomes the trainer • May not provide underpinning theory that allows the student to appreciate the practicalities of the technology • Impossible to accredit or standardise • Difficult to scale up from one-on-one, so resource and time intensive
Level	• Ideal for beginners but also for advanced theoretical understanding • Can provide both broad and deep training	• Ideal for those starting to use specific equipment and may be used to teach a particular method or technique associated with that technology • Generally provides deep training
Access	• Access for all researchers	• Access for one student at a time
Funding	• Little funding required for AV equipment and maintenance • Could come through institutions, learned societies, e.g. RMS or SEB, or funding mechanisms such as BBSRC STARS scheme	• Funding general part of day-to-day lab costs, i.e. equipment access and consumables

Mechanism	**Local/Central Facility Training**	**Training Course/School**
Benefits	• Can be done when and where needed • Student has influence on the content of the session so they get the best outcomes • Provides hands-on practical experience • Provides experience of the specific equipment (down to make and model) used in that facility • The trainer is an expert user so little preparation is required and costs are minimal • Passes on practical skills that other approaches may not • Assuming continued trainer development, the training will be up-to-date and high quality	• Covers both theory and practical experience • Access for many students at once, enables cohort building • Provides hands-on experience of one or more pieces of equipment; may provide time for students to user their own samples • Trainer(s) are experts • Assuming continued trainer development, the training will be up-to-date and high quality • Possible to have accreditation • Longer courses allow a wider range of topics to be completely covered, and more time for individual participants to ask specific questions which fit their own learning needs. • Can include inspirational speakers • Can lead to networks within the field
Challenges	• Difficult to accredit or standardise • May not provide the theoretical underpinning that allows the student to truly appreciate the practicalities of the technology • Requires the availability of staff able to deliver the training	• Requires a large amount of organisation • Courses may be over-subscribed • Requires travel for trainers and students • Time limited • Training can be expensive
Level	• Ideal for those starting to use specific equipment(s) • Generally provides deep training • Suitable for training of PhD/PDRA/ researcher level with a facility manager/ facility staff	• Ideal for those starting to use the technologies covered and may be used to introduce various associated methods or techniques • Generally provides broad training
Access	• Access for one student at a time	• Access for several students at a time
Funding	• Funding general part of day-to-day facility costs, i.e. equipment access and consumables	• Funded through a spectrum of methods, including research council support (e.g. BBSRC STARs scheme) or student fees, or cost-recovery models and industry sponsorship • Costs include the time of the trainer(s), resources for participants, accommodation, equipment and facility access, and consumables.

4. Future Requirements and Emerging Trends in UK Bioimaging

Given the fast rate of change of bioimaging technologies, researchers still experience challenges and limitations with regards to developing and new technologies. The UK does have a history of early adoption and continuation of this will be essential if future UK bioimaging is to remain world-class.

Enabling Technologies

Within our community survey, enabling technologies such as improved detectors/cameras, novel labelling and probes, and laser technologies, are considered as having been very impactful in recent years and important for future bioimaging advancement (see Figure 4.1).

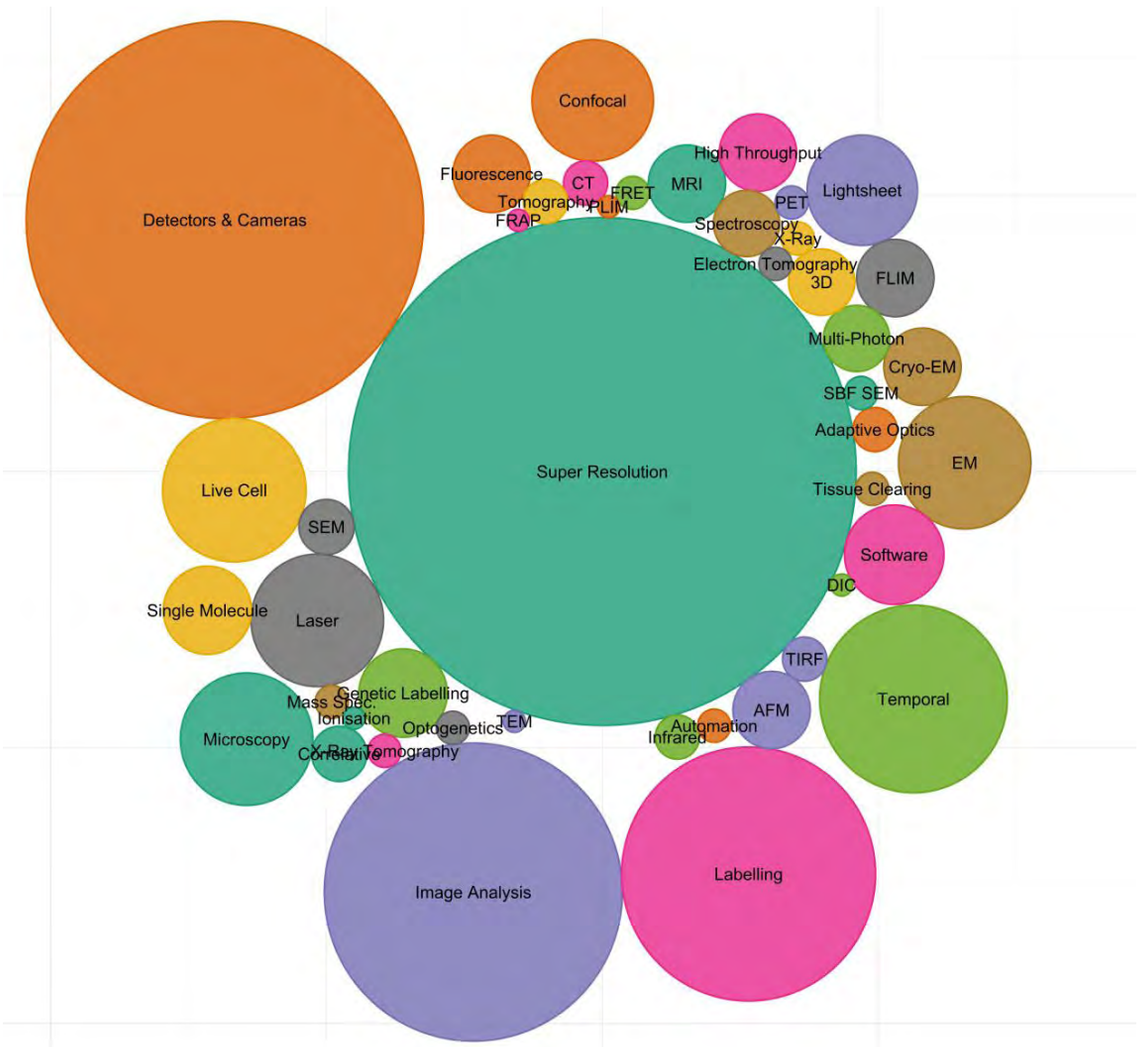


Figure 4.1 - Responses to the community survey question, 'What imaging technologies have been most impactful in recent years?' Each disc represents one technology and the size of the disc is representative of the number of respondents using that technology. Colour and position of discs are random.

Future developments in these technologies may help combat various limitations raised in the community survey, such as challenges with sample preparation; spatial, including depth, temporal and spectral resolution/range, sensitivity, throughput, in vivo and non-invasive approaches, and labelling, among other notable areas.

During consultation for this review, sample labelling was identified as a highly impactful area both in the past and potentially in the future. Genetic approaches to labelling, such as optogenetics, are able to open up new experimental avenues that were previously unachievable. Eight percent of the

community survey respondents explicitly mentioned label-free methods; these present an emerging and potentially important development in the coming years. This is further reflected in conversations with industry bioimaging users who are also looking for non-invasive and 'real world' bioimaging environments to decrease the gap between the lab and the consumer/user-facing focus.

Similar to enabling technologies, data and its associated management, e.g. analysis, storage and sharing, are seen as being the most important developments in the near future with 51% of community survey respondents highlighting the importance of future developments in aspects of data management (see Figure 4.1). This is indicative of data technologies, such as image analysis algorithms, being a significant current limitation, which is confirmed by the responses from the community. If not tackled appropriately, these areas will be a putatively terminal limitation for future bioimaging and, in turn, across bioscience and the bioeconomy. Data management and analysis are covered in detail in Section 5 (below).

Enabling technologies, such as detectors, lasers and probes, are an essential part of the bioimaging ecosystem. Support given for the development and improvement of these enabling technologies will have significant effects upon bioimaging technologies.

Emerging Technologies

With a technology backdrop as broad as is the case for bioimaging (see Figure 1.1), and with such a wide field of impact, it is difficult to identify emerging and important technologies without accidentally dismissing other complimentary technologies or alternative approaches that may have equal impact in the future. Bioimaging technologies will be impacted by advances in hardware, including laser technologies, adaptive optics and new detectors; by sample preparation, tissue clearing and labelling technologies; developments in light microscopy, electron microscopy, spectral imaging, tomography and medical imaging; and also by data infrastructure and analysis technologies (see Figure 4.2 for the community survey responses). Throughout this report we provide just a few examples of emerging technologies from a wide range of new tools and methods currently available or in development.

Whilst the development of new super-resolution techniques will continue to push the boundaries, the normalisation of super-resolution technologies, bringing them in-house and increasing their accessibility across the biosciences, will enable these methods to go far beyond their current level and to have increasing impact across the board. This is similar to the impact of confocal technologies in recent years, which has seen a broad impact that supports all bioscience, enabling in-house, day-in-day-out experiments that were once extremely difficult or impossible for scientists to conduct.

Whilst changes in spatial resolution have been impactful in the past, it is still a current limiting factor and will be important for future bioscience; spatial field of view, and in particular depth, are of equal importance. Recent and future developments in light sheet microscopy, including lattice light sheet microscopy, and mesoscopy technologies, will allow high resolution, large depth imaging of whole organs, large tissues, spheroids, organoids and even whole organisms. With these new imaging systems will come an ever increasing complexity inherent in images that will require new, specific algorithms and image processing methods.

Recent and future developments in volume EM will allow even higher resolution deep imaging of tissues and model organisms. In particular, the automation of image acquisition in the SBF-SEM, FIB-SEM and array tomography systems results in thousands of images being collected in a matter of days. These techniques are being used to reveal, for example, the architecture and connectivity of the brain, the changes in immune cell organelles during an immune response, and the architecture of developing tissues in healthy and diseased animals and plants. Advances in detectors and in massively-parallel imaging in the SEM will increase sensitivity and speed, resulting in huge data output (>1TB per hour) that will require further investment in automated data handling and analysis.

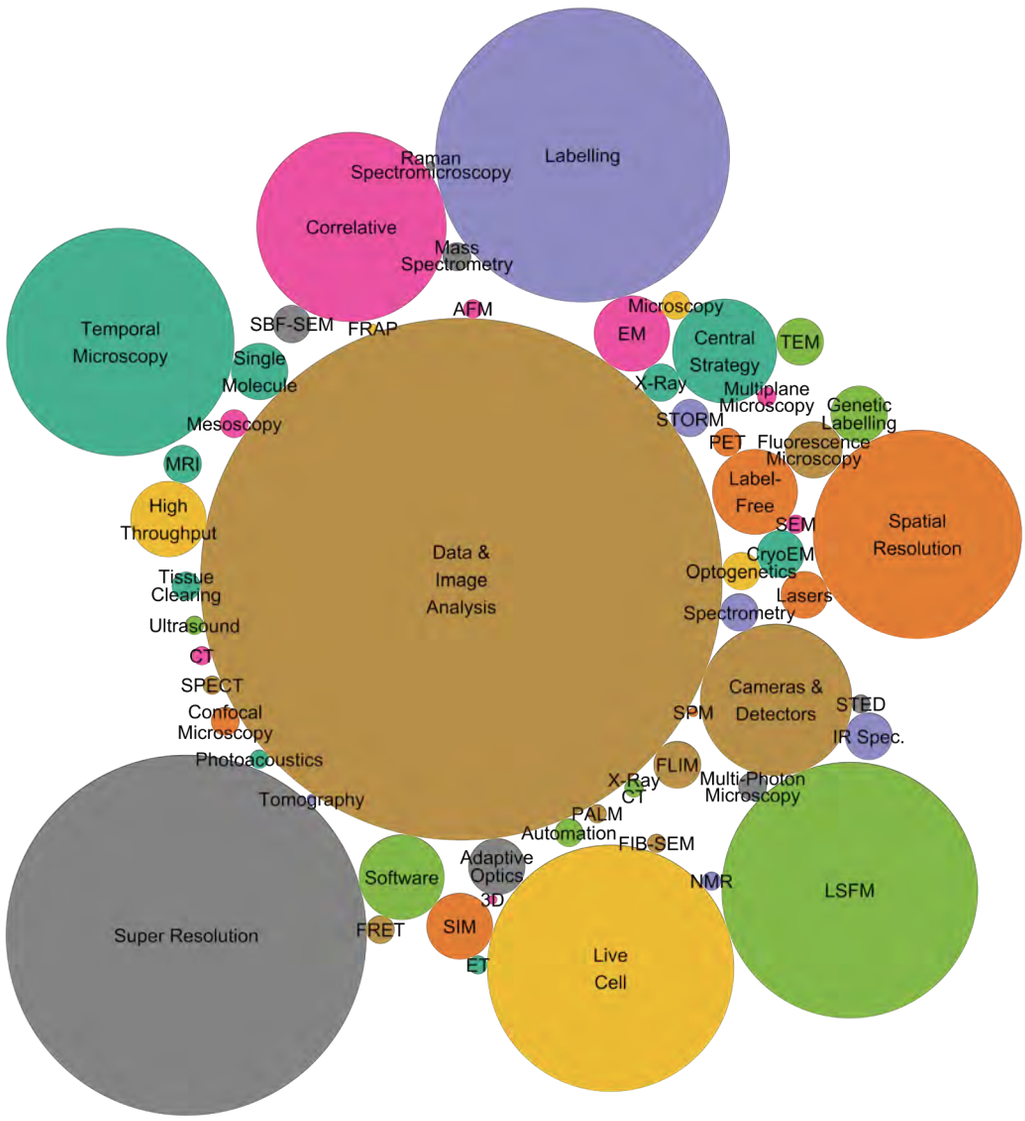


Figure 4.2 - Responses to the community survey question 'What imaging technologies are likely to have impact in coming years?' Each disc represents one technology and the size of the disc is representative of the number of respondents using that technology. Colour and position of discs are random

The recent development of phase plates and direct electron detectors for use in cryo-EM structural studies now enables researchers to solve non-repeating structures to approximately a three Angstrom resolution. With increased use and continued refinement of hardware and image processing techniques, the achievable resolution will increase further in the near future. Such studies have a high global impact as it becomes possible to image molecular structures at approaching atomic resolution, without the need for X-ray crystallisation. It is essential that the UK continues to have a strong presence in this field by investing in the latest technology and pushing the development of new ideas.

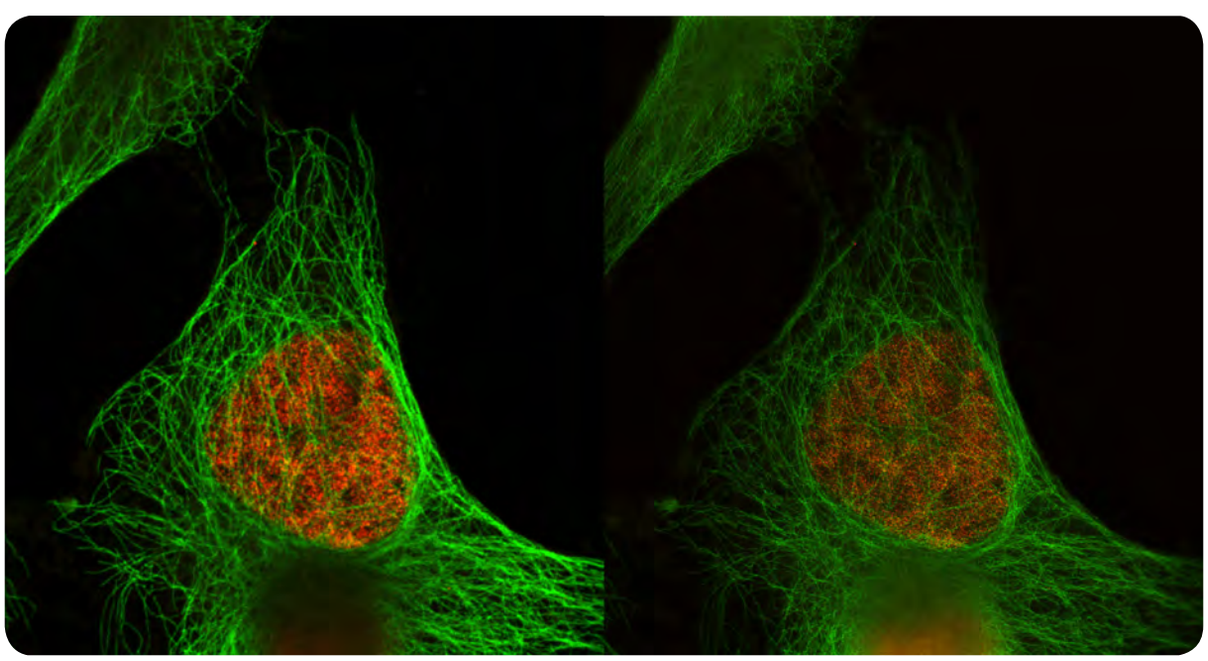
The increasing output of macromolecular structures from cryo-EM will inevitably lead to the ability to visualise docking of macromolecular structures into native cell structures, to investigate the function of the macromolecules in a biologically relevant setting. Future developments are therefore likely to focus on cryo-imaging of whole cells and tissues, which is technically challenging. Developments in cryo sample preparation, cryo light microscopy, cryo FIB-SEM and cryo soft X-ray tomography (beamline at Diamond Light Source) will be essential to deliver this science.

Further, the integration of, or correlation between, different data will be a clear driver for future bioscience. The correlation and integration of light microscopy and electron microscopy (CLEM) is perhaps the most established example, and even here experiments will become more complex as

3D data is generated in e.g. SPIM and volume EM, or SR and cryo-EM. Less explored, but with huge potential, is the integration of 'omics' with quantified bioimaging experiments, or data from other imaging or non-imaging experiments that will reveal depths of information currently inaccessible. For example, quantified multi-label imaging of proteins in a cell could be combined with biochemical or metabolic information from those proteins to reveal new information regarding protein role and action in the cell. Also, bioimaging experiments could be combined with genome engineering techniques to report on endogenous levels of proteins and provide more accurate quantitative information on protein numbers, assembly or complexes, and dynamics. This integrative approach will lead to a paradigm shift from genomic-inspired understanding to a quantitative phenomic-inspired understanding derived from bioimaging.

Bioimaging is a fast developing field with new technologies and improvements in core equipment, enabling technologies, data management and image analysis occurring regularly. The UK bioimaging community is aware of core emerging research and technologies and the UK bioimaging landscape puts the UK in a prime position to capitalise on these emerging trends. The UK bioimaging community and landscape must be appropriately supported to ensure that the adoption of new technology is timely and efficient. Failure to support the UK bioimaging technology landscape, community and supporting structures would lead to a detrimental effect on all UK bioscience.

Recommendation 5: BBSRC should encourage community driven meetings regarding new and emerging technologies that would allow interaction between developers, industry, facility managers, and users.



HeLa cells with fluorescently labelled cytoskeletal tubulin (green) and the nuclear located histone (red), imaged with conventional confocal microscopy (left) or Stimulated Emission Depletion microscopy (STED, right). A confocal microscope creates an optically sectioned image by raster scanning a focused laser beam through a sample to excite fluorescent molecules, but prevents fluorescence generated outside of the focused spot from reaching the microscope detector. STED is a super-resolution technique that uses a second, donut shaped laser that is superimposed upon the confocal laser to prevent fluorescence from being generated in the outer shell of the focused spot. This effectively shrinks the volume of the focused spot beyond that which is achievable with the best microscope objectives resulting in an image with improved resolution. Credit: Laura Zanetti-Domingues, Science and Technology Facilities Council

5. Bioimaging Data Management and Analysis

The UK bioimaging community recognises that data is a current and future limitation: analysis algorithms and software are required to fully utilise bioimaging data; storage infrastructure needs must be met to cope with the rapidly increasing amounts of bioimaging data being produced by modern methods; finally, tools for sharing imaging data and deposition in public repositories must be developed in order to create a collaborative and open research community across the UK.

With increase in throughput, resolution and field of view, has come a phenomenal increase in the amount of data produced through bioimaging. Technologies are now able to routinely collect terabytes of data per hour and petabytes per year, which must be managed, stored and analysed appropriately. This has in turn, led to an increased need for data handling, image analysis and data skills amongst the bioimaging community.

Image Analysis

Being able to generate biological images, analyse and then interpret them is extremely important and of great value in its own right. Image analysis technologies continue to advance apace, allowing researchers to visualise and measure samples in ways not before possible, including in three and four dimensions, and often using continuous real-time measurements. However, further breakthroughs may be enabled by being able to integrate image data with other data types, for instance genomic and transcriptomic data.

Bioimage analysis and, more widely, all data technologies, including those required for storage and sharing, are seen as limiting factors by the community. Importantly, the community also see data technologies as being of high potential in the future development of bioimaging (see Figure 4.2), meaning that they provide both a risk and an opportunity. If not tackled appropriately, areas of data management and analysis may become a terminal limitation for future bioimaging and, in turn, for bioscience more widely and the bioeconomy.

UK bioimaging has excellent bioimage analysis and quantification, informatics and management of research, supported by world-class software and data expertise, such as the Software Sustainability Institute[16]. Despite the overall strength of UK bioimage analysis, key analysis areas are lacking in support and technical expertise, for example there is a lack of bioimage analysis tools for electron microscopy modalities. These gaps in UK bioimage analysis can be reduced through collaboration with the wider image analysis communities beyond BBSRC's remit. Responses from consultations indicate that several community-driven aspects, such as data standards, will be important to future bioimage analysis solutions.

Further, cross-disciplinarity will be essential to the development of robust algorithms with reproducible outputs, the validation of new tools and the development or maintenance of user-friendly software and platforms. Expertise from computer scientists, engineers and mathematicians will be needed to develop and integrate advanced approaches to automatic data analysis, from image analysis challenges such as registration, segmentation, annotation, cross-modality data integration to advanced computer vision techniques, and attempts to extract the maximum amount of information from data by automated data mining, and machine learning.

[16] **http://software.ac.uk/**

For the development of new algorithms and image analysis approaches, open source or clear licensing is vital to community take-up, adaptation and further development of methods. Algorithms and software licensed under open licenses allow for the whole UK bioimaging community to benefit from the method and, further, to improve and/or tailor the method. Shared development of enhancements and bug fixing decrease the onus of responsibility on the original author of the code and help to improve maintenance and sustainability of the code.

Whilst funding body and academic publisher encouragement of open source licensing for image analysis algorithms solutions will have a positive impact by disseminating new techniques, continued support of software/plugin development and maintenance will also be required to maintain the UK's high standard of bioimaging data services.

Image analysis is an essential part of the quantitative bioimaging pathway. The bioimaging community must work with computer scientists, engineers, physicists and mathematicians to exchange analysis techniques with other disciplines and to develop new techniques that solve problems unique to bioimaging. Encouraging open source algorithms and software, open standards and metadata, and open access data will be important in enabling this trans-disciplinary sharing.

Recommendation 6: Continued support of algorithm and software development is vital, as it underpins the ability of the UK research community to extract meaningful results from microscopy data. Targeted calls such as TRDF are a key component, as is support via responsive mode grants. Cross-council funding, particularly with EPSRC and MRC, is likely to be particularly important due to the interdisciplinary nature of the work.

Data Storage and Sharing

In addition to challenges around analysis there is strong community support for the development of data storage and data sharing tools and infrastructure. Bioimaging technologies are now able to produce terabytes of raw data per hour and this is rapidly increasing with further developments in the field. This must be stored and often shared across institutions or even between institutions and across the globe.

Such massive storage and sharing needs require a greatly improved data infrastructure than currently available across the UK and will require cooperation across disciplines and with both funding bodies and institutions. The costs for developing a new infrastructure will be high but a renewed data infrastructure will benefit not just the bioimaging community but all science and research across the UK.

Along with the physical infrastructure, well-trained and well-equipped technical staff must be available. Such network and database engineers will provide a vital source of support and technical expertise for the management, handling and transfer of massive data. Such technical staff are already present in many universities, often associated with other disciplines such as astrophysics or digital humanities. Close cooperation within institutions will make this expertise more widely available to the bioimaging community.

First steps are being made towards bioimaging specific data infrastructure needs through the development of platforms, such as the world leading Open Microscopy Environment[17] (OME) in the UK. OME is focussed on the development of open-source software and data format standards for the storage and manipulation of biological microscopy data (see Box 5.1).

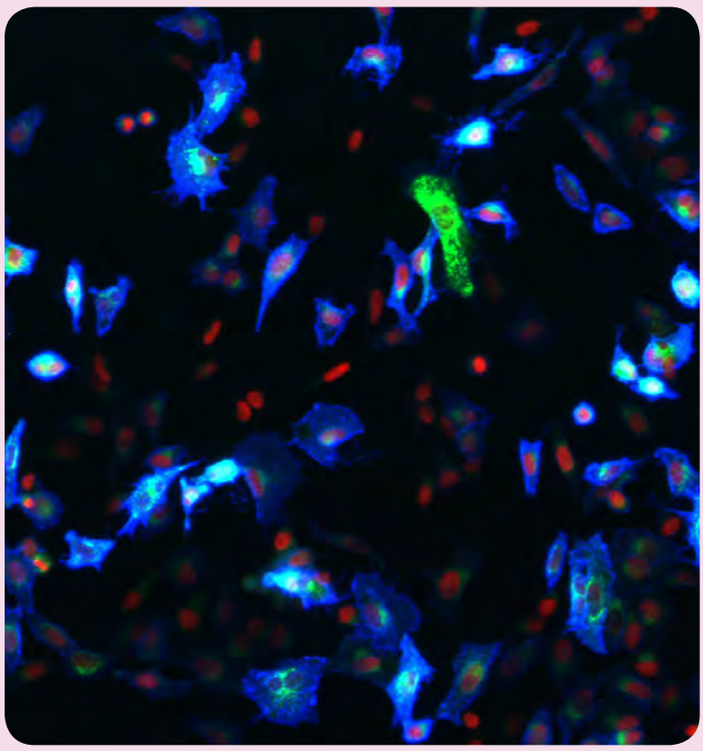
[17] **https://www.openmicroscopy.org**

Box 5.1 Open Microscopy Environment

Since 2000, the Open Microscopy Environment (OME) has built open source interoperability tools for biological image data. OME has three components–an open data model for biological imaging, standardised file formats and software libraries for data file conversion, and software tools for image data management and analysis.

The OME Data Model provides a common specification for scientific image data. It provides ways of describing and annotating all aspects of most imaging and screening experiments, the imaging systems themselves, and common analytic metadata, like regions-of-interest, feature vectors and unique identifiers.

The OME-TIFF file format and the Bio-Formats file format library provide an easy-to-use set of tools for converting data from proprietary file formats. These resources enable access to data by different processing and visualization applications, sharing of data between scientific collaborators and interoperability in third party tools like Fiji/ImageJ.



Confocal microscopy images of HeLa cells. Credit: Image Data Resource public domain, see Nature Cell Biology 14, 764–774 (2012), produced as part of study **http://dx.doi.org/10.1038/ncb2510**.

The Java-based OMERO platform includes server and client applications that combine an image metadata database, a binary image data repository and high performance visualization and analysis. The current release of OMERO (5.2.3) includes a single mechanism for accessing image data of all types via Java, C/C++ and Python and a variety of applications and environments (e.g., ImageJ, Matlab and CellProfiler).

With these tools, OME delivers open, enterprise-scale platforms for accessing, sharing, processing and publishing large image datasets to a large, diverse, and growing scientific community. OME's tools are now used daily, by scientists around the world, to enable the processing, analysis, sharing and publication of digital image data.

Professor Jason Swedlow, Dundee University

OMERO has now been adopted in several ways and by several groups across the world. Commercial uses of the system include the Journal of Cell Biology DataViewer[18] whilst academic examples include the UK-led Electron Microscopy Data Bank (EMDB[19]; see Box 5.2) an international public imaging repository that has undergone extension and development utilising OMERO technologies. The EMDB and the newer EMPIAR[20] repository, which archives 2D data underpinning the maps and tomograms in EMDB, are unique across the world. At present, EMPIAR is the only repository able to archive data produced by certain emerging EM techniques; without these repositories vital scientific data might be lost.

UK data infrastructure research and development such as OMERO, EMDB and EMPIAR all contribute not only to UK bioimaging but to global bioimaging, maintaining the UK's position as a world leader. Such repositories and tools allow for the creation and adoption of shared data standards and open access of images, thus enabling full exploitation of imaging data and integrative approaches between different modalities.

[18] **http://jcb-dataviewer.rupress.org**
[19] **https://www.ebi.ac.uk/pdbe/emdb/**
[20] **https://www.ebi.ac.uk/pdbe/emdb/empiar/**

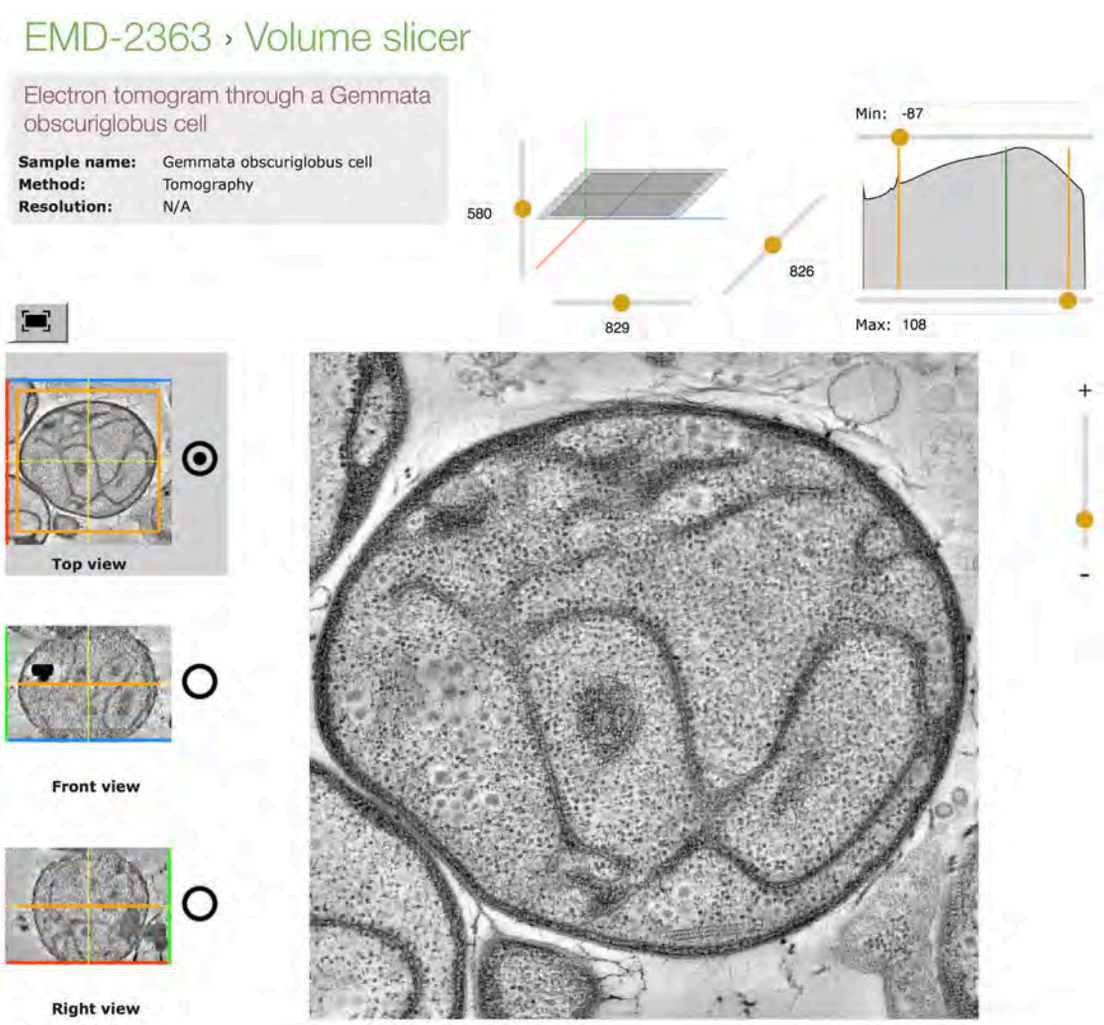
Box 5.2 Electron Microscopy Data Bank

The Electron Microscopy Data Bank (EMDB) was established at EMBL-EBI in 2002 in response to community requests. EMDB is now the standard repository for 3DEM and electron tomography reconstructions, and many journals have made deposition to EMDB mandatory for publication. The 3DEM community very enthusiastically supports EMDB. Deposition of EM maps and tomograms to EMDB is not yet mandatory, although several journals do insist on it.

EMDB is already having an impact in disseminating 3D structural information about biomacromolecular complexes, molecular machines and cells and cell components. Once this data becomes more easily accessible/usable to non-experts, especially when integrated with other sources of biological data, there is huge potential for new knowledge discovery and inspiring new lines of research.

In 2009, a joint BBSRC grant between PDBe and OME enabled an exchange of software and expertise, allowing OME to add support for EM data and allowing PDBe to utilise OME tools for data inspection and presentation. As part of the grant, PDBe and OME also organised a workshop for community experts to discuss data management challenges in 3DEM.

Gerard Kleywegt & Ardan Patwardhan, European Bioinformatics Institute



Electron tomogram through a Gemmata obscuriglobus cell revealing that these cells are neither compartmentalised nor nucleated as the spaces created by the membrane invaginations are all interconnected. This is based on serial section electron tomography. The specimen is fixed, embedded in resin and physically sliced using an ultramicrotome. A 3D reconstruction of each section is obtained using electron tomography and the series of 3D reconstructions are aligned to one another to form a giant 3D reconstruction. The tomogram has been archived in EMDB (accession code EMD-2363) which makes it accessible in a variety of ways to users, including through the interactive, web-based "volume slicer" tool shown here (**http://www.ebi.ac.uk/pdbe/emdb/3dslice/EMD-2363**). Credit: Gerard Kleywegt, European Bioinformatics Institute EMBL-EBI

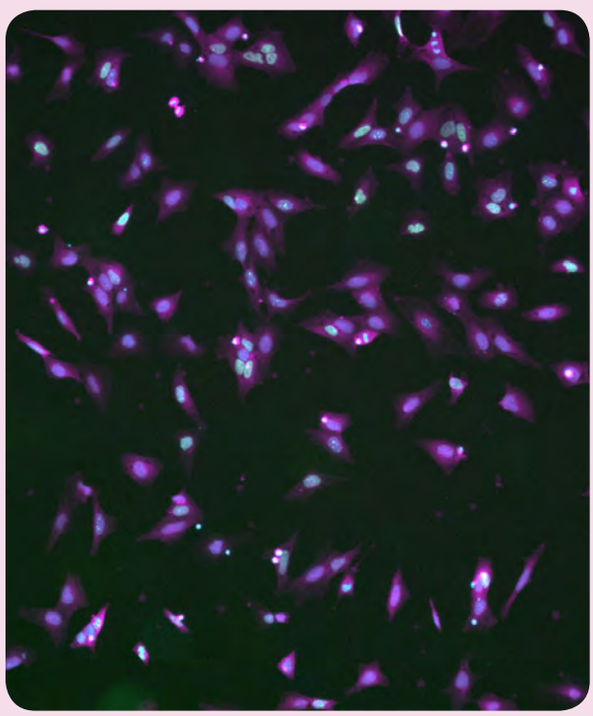
Open data, including shared, open standards and data formats, is an untapped and potentially tremendous resource of scientific knowledge. With modern bioimaging methods producing terabytes of data, scientists are only scratching the surface with analyses that are designed to answer only their own research questions. By making all data available to the wider bioimaging and bioscience communities, it can be reused and reanalysed to allow data produced to answer one research question to begin to answer other questions. Moreover, using data mining and meta-analysis techniques, we can begin to produce new hypotheses and research questions. Successful open data does, however, rely on a strong infrastructure of high-speed networks and large, open data storage and repositories.

A recent large BBSRC capital award is enabling the establishment of a new UK-led Image Data Resource (IDR; see Box 5.3) through collaboration between Dundee University, EMBL-EBI and the University of Cambridge. In addition to being an important resource for the UK bioimaging community, this project can be considered as a proof-of-concept for the new Euro-BioImaging Hub Data Repository and will thus have European and potentially global impact.

Box 5.3 Image Data Resource

To demonstrate the capability and utility of publishing scientific image data, we used OMERO and Bio-Formats to build an Image Data Resource (IDR). This resource holds >42 TB of image data from >20 studies in 36M images, and includes all associated experimental (e.g., genes, RNAi, chemistry, geographic location), analytic (e.g., submitter-calculated image regions of interest and features), and functional annotations. Wherever possible, metadata in IDR links to external resources that are the authoritative resource for that metadata (Ensembl, NCBI, PubChem, etc.). Datasets in human cells, Drosophila and fungi are included. The IDR also holds the full Mitocheck dataset, a comprehensive chemical screen in human cells, and the imaging data from Tara Oceans, a global survey of plankton and other marine organisms.

Wherever possible, functional annotations (e.g., "increased peripheral actin") have been converted to defined terms in the EFO, CMPO or other ontologies, always in collaboration with the data submitters. Over 89 % of the functional annotations have links to defined, published, controlled vocabularies.



Human induced pluripotent stem cells (iPS cells). Credit: Image Data Resource public domain, see Nature 546, 370–375 (15 June 2017), produced as part of study **http://dx.doi.org/10.17867/10000107**.

The IDR runs from EMBL-EBI's Embassy cloud resource, and is, as of this writing, being updated to provide computational resources for analysing the image datasets it holds. The IDR project aims to demonstrate the scientific value of building and maintaining repositories of image data, integrated with all experimental and analytic metadata.

Professor Jason Swedlow, Dundee University

The data infrastructure challenges faced by the UK bioimaging community, and wider UK research community, are not limited to the UK. The same infrastructure requirements and limitations are seen across the world and, given the international nature of science, infrastructure improvements and developments in the UK must maintain an awareness of global infrastructure changes. Such cross-nation infrastructure needs may be met through close collaborative working with international partners through transnational projects such as Euro-BioImaging.

The UK's data infrastructure is not suitable for the increasingly large amount of data produced by bioimaging technologies. Both the hardware required for storage and sharing data and the software required to make data storage, management and sharing available and accessible to the entire community, are required to meet future bioimaging needs.

Recommendation 7: BBSRC should work with other research councils, relevant government departments (e.g. BEIS, HMT), HEFCE, UK HEIs and the global community to develop a coherent approach for the replacement, upgrade and renewal of the UK's data infrastructure as required for bioimaging.

Data Integration

In June 2014 a joint collaboration strategy on image data was announced[21] between Euro-BioImaging, a Europe-wide infrastructure project, and ELIXIR[22], that should also serve to lay the foundations for data integration between imaging data and other life-science data, such as bioinformatics data. The aspiration of the collaboration strategy is to support access to biological image data and link it to biomolecular data already held at ELIXIR.

To enable the integration of diverse data types presents many challenges; not least the development of automated image analysis software to process images at scale and with consistency, as well as the usual data-sharing challenges of interoperable formats, standards and metadata inter alia. However, the potential returns from being able to do this are great; this could transform some areas of science where the individual data types already exist, enabling new knowledge generation and adding value to provide a more holistic view of biological systems.

This is further reflected in the community survey where correlative approaches either between different imaging modalities or between imaging data and molecular data are highlighted in relation to a number of the questions asked and are present in the responses as an important emerging approach.

Due to the importance of integration across different techniques, for example, correlation of imaging with 'omics' data, should any aspect of the UK bioimaging technology backdrop and those enabling technologies, including data, fall behind the global cutting edge, many areas of bioscience research would be negatively impacted.

Integration of data from imaging and non-imaging experiments is an important emerging trend across the biosciences and will be enabled by open standards for data and improved data infrastructure technologies.

Data Skills

Extraction of biological understanding from new and developing imaging technologies is unlikely to be served by existing algorithms, but by the design and application of new and bespoke algorithms by experienced and able researchers in bioimage analysis. Such researchers will require not only computer science skills and literacy, experience with software development and user interfaces, but a core biological knowledge required to understand the context of any analysis.

The community identified a need for a new approach to statistical and computational tools for bioimaging, where researchers will need to compute correlations across multiple massive datasets that cross imaging modalities and even extend out of the imaging domain across, for example, genomics

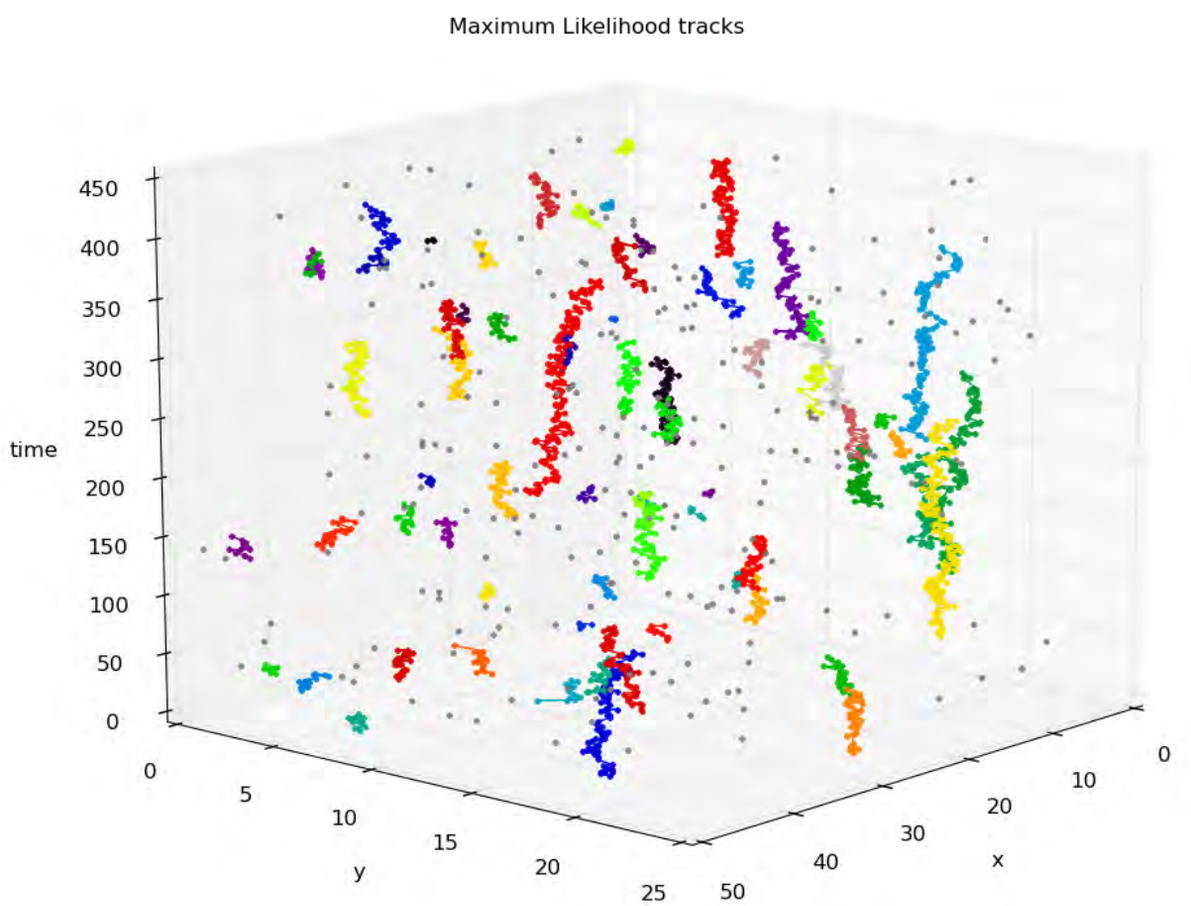
[21] **http://www.eurobioimaging.eu/content-news/euro-bioimaging-elixir-image-data-strategy**

[22] **https://www.elixir-europe.org/**

and proteomics data. Again, this requires a community of well-trained biologists, bioinformaticians and computer scientists who are able to effectively communicate and collaborate to develop new algorithms and tools.

Bioinformatics still tends to be driven towards genomic and transcriptomic data sets, however bioimage bioinformatics is of growing importance and initiatives will be needed to encourage researchers to train and move in this direction. There is a real risk of sitting on vast amounts of data and only being able to understand a fraction of the potential information. This could well be one of the biggest limitations in bioscience today. Even current image analysis is very mono-directional with much of the image being ignored. Mining this data could unlock a wealth of information and drive new scientific discoveries.

It is also critical for biological scientists to be given access to improved training in image analysis. With the advent of user-friendly programming packages it is possible for biologists to use image analysis algorithms that suit their particular data and biological question. However, it is crucial that biologists understand the underlying principles of the analysis in order to choose the correct approaches and use them appropriately, and this requires education. Additionally, an understanding of the process of developing new algorithms and image analysis tools, and how to communicate needs with computer scientists, is required if biologists require a novel solution. Unfortunately there is little training currently available in the fundamental concepts of image analysis, which can make these requirements difficult.



The maximum likelihood traces of simulated single-molecule microscopy data obtained with the Biggles tracking algorithm. Molecules that are observed over time are shown in colour, while observations that are identified as spurious are shown in grey. Single particle trackers are algorithms that use a sequence of single molecule microscope images and identify the motion of molecules. This enables the understanding of biological processes, such as cell signalling. Conventional trackers do produce a single trace for each molecule and cannot capture the uncertainty that comes with the tracking process. In any measurement process, uncertainties are normally captured by providing the measurement error. The Biggles algorithm does the same for tracking: it gives a tracking solution and also the uncertainty of that solution together with likely alternatives. So, Biggles gives a measure of confidence for the tracking results and the conclusions drawn from it. Credit: Laura Zanetti-Domingues, Science and Technology Facilities Council

Training in this area must encompass two directions of information flow: first, to introduce those with specialist technical programming knowledge (people from a computer science or engineering background) to biological imaging approaches, and second, giving researchers with a biological background enough programming knowledge to carry out effective and accurate analysis. The first will foster new methods development, and build a community of developers. It is perhaps best approached by cross-disciplinary grant funding or targeted 'Sandpit' or 'Ideas Lab' events. For the second, post-graduate skills development could be addressed by targeted DTCs/CDTs, while later career biologists would benefit from training programmes aimed at broadening data skills. These could include training in the use of appropriate software (e.g. ImageJ, Python) and the correct use of algorithmic approaches.

Data skills and training are required across the biosciences community to enable high-quality quantitative bioimaging. This includes theoretical understanding of image analysis as well as practical skills and expertise.

Recommendation 8: Training should be provided both to those with computer science, mathematical, statistical and engineering backgrounds as well as those with biological backgrounds to enable two-way information flow. This community of developers and data–literate biologists would benefit from innovative cross-disciplinary funding opportunities.

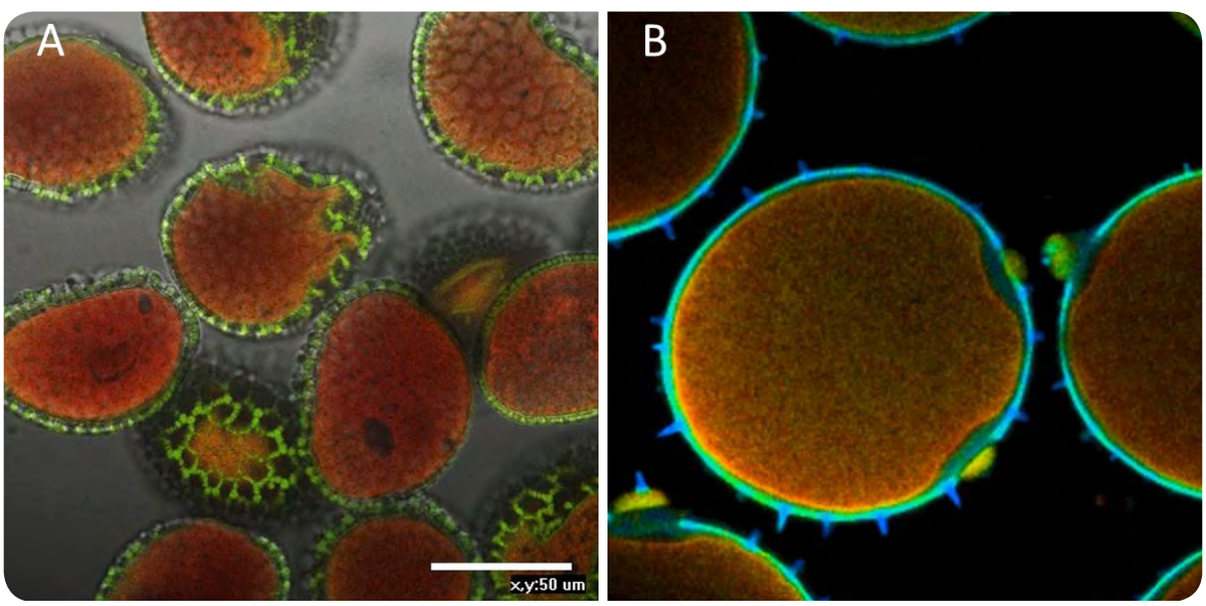
6. Technology Development and the UK Bioimaging Industry

Bioimaging Technology Development in the UK

Bioimaging technology research and development in the UK has already led to new commercial ventures and impacted the global bioimaging industry (Box 1.3, section 1). The Technology Touching Life consultation[23] identified imaging technology and methods development in the life sciences as one of several key areas where research councils working together could lead to significant impact and maximise existing investments in research. This included, for example, the development of new labelling and label-free approaches; multimodal and correlative studies; enhanced sensitivity and detectors and new non-invasive or *in vivo* methods.

An important part of advancing bioimaging research and helping to add value to UK GDP through commercialisation of this research is by enabling academic-industry interaction to foster knowledge exchange and support collaborative R&D. Due to the rapidly developing interrelatedness and complexity of the scientific challenges to which bioimaging technologies and methods are being applied, this area of technology development is becoming increasingly multidisciplinary and multisectoral.

Evidence collected through this review suggests that academic-industry collaborations in bioimaging have considerable engagement from the physical sciences, engineering, computing and mathematics. However, the community would benefit significantly from broadening the breadth of engaged disciplines particularly in regards to the physical sciences, chemistry and computer sciences. There is now a greater need to support closer, sustainable interactions between technology developers and users across multiple sectors and disciplines, particularly in terms of skills and technology development. For this reason, this section has been informed not just through feedback from the academic community, but primarily through in-depth interviews with over 12 companies spanning the spectrum of users and developers, SMEs to multi-national companies.



Auto-fluorescence from pollen particles imaged on a custom built two-photon confocal setup. Combining this excitation modality with advanced imaging techniques, such as fluorescence life-time imaging microscopy, unique properties of the pollen can be observed which would remain hidden in a simple white light or confocal image. A: combined image of autofluorescence and transmitted light channels from lily pollen particles; B: Fluorescence Lifetime Imaging of the autofluorescence from pumpkin pollen particles. These images come from a study of pollen aerosols and their effects on human health. Credit: Laura Zanetti-Domingues, Science and Technology Facilities Council

[23] **http://www.bbsrc.ac.uk/documents/1509-tech-touching-life-consultation**

The community survey responses and industry conversations demonstrated that current academic-industry collaborations in bioimaging focus predominantly on the development and testing of equipment and/or new systems. With further support, there is an opportunity to advance UK bioimaging capability and research through ensuring these collaborations also focus on software technology, particularly for image analysis and modelling.

Bioimaging technology and methods development requires expertise beyond the biosciences. A successful technology developer has to possess skills in one or more areas, including mathematics, engineering, computing, physics, chemistry and/or biology. Whilst it is impossible to have significant expertise in all of these disciplines, it is essential that both bioimaging technology developers and users can communicate skilfully within multidisciplinary teams.

Successful imaging technology and methods development requires a true multidisciplinary approach. Support and training are required to maintain effective links across traditional discipline boundaries and between academia and industry.

Technology Providers

The UK-based bioimaging technology development industry is relatively small in terms of manufacturing in the UK with many larger companies choosing to locate these activities overseas, particularly in Germany, Japan and the USA. However, it was clear that the UK is viewed by the global bioimaging industry as a strong place for collaboration with regards to technology development and a very wide range of active collaborations were cited; a large proportion of which are developed and sustained as a result of pre-existing relationships. The focus of these relationships was predominantly in the context of: novel fluorescence microscopes, such as light sheet and super-resolution solutions; researching new electron microscopy techniques; and producing high-end microscopy parts such as lasers and detectors; proof-of-concept work; beta-testing of new technologies; and the development of user interfaces and software to support data handling and analyses.

Comparing responses from the academic and industrial communities in the UK, it is evident that the community would benefit from the provision of further support to help foster and catalyse opportunities for collaborative R&D and knowledge exchange. In particular, conversations with industry revealed the importance of Europe, more specifically the UK, for the development of new technologies; testing and evaluation of new commercial systems; and consultation for software production.

This is in contrast to the perception that the UK academic bioimaging community has only a weak link with industry (as the majority of larger bioimaging technology companies are located elsewhere in the world).This disparity is perhaps due to the UK academic bioimaging community being excellent at translating their research to a commercial concept, but the post-competitive research and development often occurs outside of the UK.

Bioimaging companies consulted during the course of this review stated that UK bioimaging facilities at universities/institutes and research campuses, play a critical role in UK academic-industrial collaborations, and in significantly strengthening the overall UK bioimaging capability. The industrialists interviewed recognised the essential role of UK bioimaging facilities in acting as hubs, not just of technologies, but of training, skills and expert advice that allow new models and novel technologies to be rapidly adopted, tested and developed further by the bioscience community. A specific example relating to training was the use of these facilities for the sharing of knowledge and practise on sample preparation methodologies, tools and techniques, including environmental considerations for emerging technologies. Added value could be gained from such facilities if there was increased support for enabling industry access to these facilities, particularly in the form of pilot project funding.

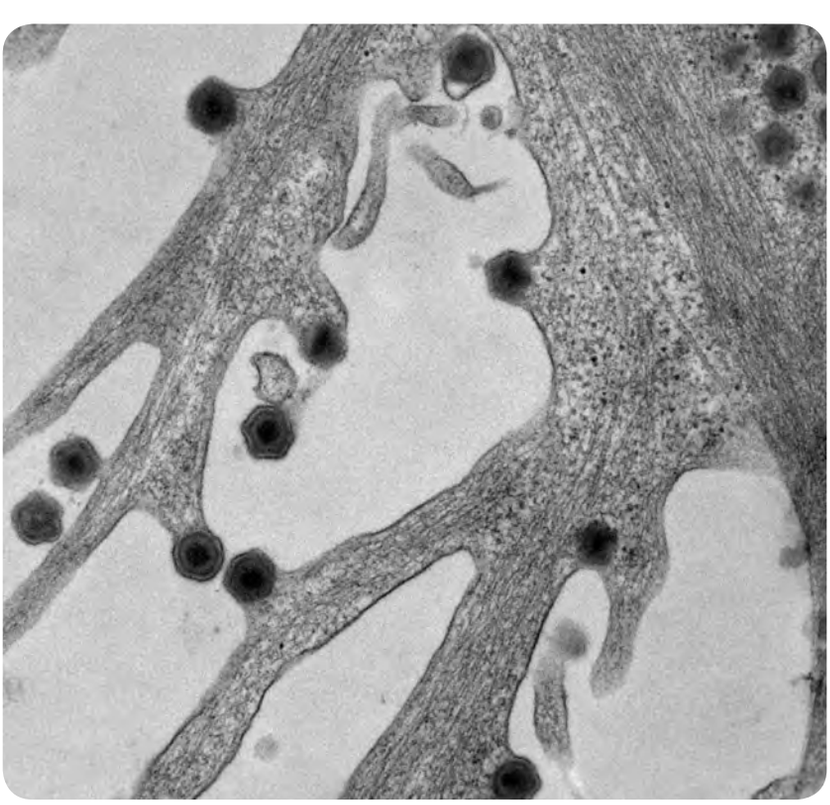
All of the technology development companies in the UK consulted for this review cited the following primary challenge facing both developers and users across academia and industry: on the one hand advanced, enabling novel technologies require quick uptake in order to keep UK bioscience world leading, but on the other hand standard 'workhorse' equipment must be maintained and must use state-of-the-art enabling technologies, such as cameras and lasers, to continue to support a significant proportion of essential and world-class bioscience.

Strong bioimaging facilities across the UK are valued by the UK bioimaging technology industry as hubs of technologies, training and expertise. Support for committed arrangements between UK bioimaging facilities and UK and global bioimaging technology companies will help to strengthen the bioimaging technology development in the UK.

Recommendation 9: Increase support for multidisciplinary and multisectoral networking activities between UK academic and industrial developers, and users, with a specific focus on funding for pilot projects.

Bioimaging Users

Bioimaging across the academic and private sector is an essential component of research which underpins the entire bioeconomy, for example in seed production, crop protection, food quality and safety, drug delivery, veterinary medicine, ecological conservation, through to cosmetics and beyond. The imaging modality and technological advancement is different for each application and many utilise classical technologies such as confocal microscopy. However, the foci for many industrialists engaged with academics in bioimaging are sample preparation, labelling and environmental control during imaging to bring 'real world' samples under the microscope in as close to their original state as possible. As described in Section 3, these are key areas of research for all users of bioimaging and the move from static imaging of fixed samples to live, continuous imaging of living cells, tissues and organisms is important for both academic and industrial bioscientists. One example is the need to develop label-free technologies to mitigate obtrusive labelling molecules when imaging food samples for production and food safety testing.



Vero cell infected with African swine fever virus at 20 hours post infection. Mature virions travel to the cell membrane and bud to exit the cell. The sample was prepared using standard chemical fixation and imaged in a transmission electron microscope. Credit: Pippa Hawes, The Pirbright Institute

Evidence collected during the interview and community engagement stages of this review also suggests that higher spatial resolution could be an area for increased academic-industry interaction. Interestingly, although increased spatial resolution was a particular challenge for academic researchers, this was not viewed as such a limitation for industrial researchers. However, a better understanding of the calibration, quantification and confidence of data captured at standard resolutions is essential across both spheres. It was identified that for industrialists it is often temporal resolution or time-lapse imaging which can be of greater importance, for example imaging changes such as hydration in a skin substitute over time, post-application of a cosmetics product. This might require a combination of label-free imaging, environmental control during imaging and time-lapse imaging capture. For those industrial researchers who do require higher resolution imaging the temporal resolution may become a lesser constraint, for example, the 3D imaging of food products utilising tomography techniques may require high resolutions in 3D but is a static system and, as such, temporal imaging is not required.

Another pre-competitive area highlighted in the consultation process was the importance of turning 'data to knowledge' through advanced modelling and data technologies for users. There were many areas for focus within data analysis and modelling, including but not limited to: incorporating data from different modalities; increasing predictive capability for screening and monitoring applications; standards and formats; and automated analysis to remove user variance.

A further area identified for potential pre-competitive collaboration was that of standards and regulation. Whilst the challenges and opportunities in these areas transcend both users and developers, much of the evidence collected suggested an urgent need for users in particular to engage more with regulators. Increased interaction with regulators to help inform and regulate novel ways in which bioimaging technologies can be utilised and exploited, could help add value to UK GDP, further supporting the bioeconomy.

Many areas have been identified where complementary and synergistic working already occurs between academia and industry, however, these could be further built upon and there are still many untapped opportunities providing scope for much greater impact and benefit to the bioeconomy.

Recommendation 10: Facilitate discussion between academics and industrialists, working with regulators, and the British Standards Institute, to increase the use and validity of bioimaging tools and technologies across the breadth of UK industry and bioeconomy.

7. UK Bioimaging in an International Context

Bioimaging in the UK

The UK bioimaging community is well equipped when considered in an international context. There are few bioimaging technologies that are not represented in the UK's bioimaging technologies backdrop. UK bioimaging facilities are seen by both the UK bioimaging academic and industrial communities as excellent focal points for the community, providing training, skills, expertise and, of course, technologies. Furthermore, UK technology development has a strong international standing with UK universities being involved in all levels of bioimaging technology development with both UK and international companies.

The comparative strength of UK bioimaging facilities and the technology backdrop can be seen in comparing, for example, the RMS facilities database[24] against the first generation of Euro-BioImaging (EuBI) candidate nodes[25]. All of the technologies or modalities included in the nodes are currently available in UK bioimaging facilities with the exception of a few lesser-used techniques.

UK Bioimaging Community Coordination

BioImagingUK is a key network for the bioimaging community in the UK. It has supported networking of the community, and developed strategy for this community in terms of defining priorities and focussing on key areas such as careers, skills and training (see Box 7.1). This network also provides a mechanism by which the bioimaging community can respond collectively to important surveys or consultations.

Box 7.1 BioImagingUK Aims & Activities

1. To develop and exploit new imaging technologies – driving development of and access to state-of-the-art imaging instrumentation.
2. To devise and help implement mechanisms to enable shared access to the general and specialized expertise based in life sciences and medical imaging laboratories and facilities throughout the UK.
3. To engage our departments, universities, and funding bodies to develop career models for the personnel that develop, maintain, and enable advanced imaging technology for the life and medical sciences.
4. To define new training programmes, to provide the foundation for the next advances in life sciences and medical imaging within the UK.
5. To work inclusively to define short and long-term strategy statements to our research funding bodies, in order to help articulate funding requirements and priorities.

BioImaging UK Website (2017)

Indeed, the BioImagingUK network and representatives from the medical imaging community submitted a joint response to the 2014 BIS Capital Consultation[26], the 2015 Nurse Review of Research Councils[27] and more.

[24] **https://www.rms.org.uk/network-collaborate/facilities-database.html**

[25] **http://www.eurobioimaging.eu/content-news/euro-bioimaging-appoints-its-hub-and-nominates-first-generation-nodes**

[26] **http://www.bioimaginguk.org/index.php/BIS_Submission_Biological_and_Medical_Imaging**

[27] **http://www.bioimaginguk.org/index.php/Nurse_Review_of_Research_Councils**

The Facility Managers Meetings have been running since 2007 and now attract over 170 delegates with more than half being from core facilities and many others from industry. These meetings enable the flow of knowledge on best practices, latest developments, and form a strong network across the community. Access to this group helped create significant momentum behind BioImagingUK and is now being replicated by the electron microscopists for both life and material sciences.

UK Bioimaging and International Links

Whilst the UK community is well-coordinated and networked at a national level, it is important to consider the international context: who should the UK community be working with, on which aspects and through what mechanisms? In order to consider these questions it is useful to look at examples of established activities in other countries or broader European and international activities. An informed view as to what would be beneficial for the UK research community can be built by comparing and contrasting these mechanisms and schemes; the following paragraphs introduce some international examples.

Euro-BioImaging

Euro-BioImaging[28] (EuBI) is a large-scale pan-European research infrastructure project on the European Strategy Forum on Research Infrastructures (ESFRI) Roadmap. The EuBI mission is to build a distributed imaging infrastructure across Europe that will provide open access to innovative biological and medical imaging technologies for European scientists. The infrastructure established by EuBI will consist of a set of geographically distributed but strongly interlinked imaging facilities (Nodes), linked through a central Hub, which will also provide training and support for the community. By providing access to training in imaging technologies and through sharing of best practice and imaging data, the vision is that EuBI will become an engine that will drive European innovation in imaging research and technologies.

There are currently seventeen full members and three observers on the Interim Board (IB). The full members are: Austria, Belgium, Bulgaria, Czechia (formerly the Czech Republic), Finland, France, Hungary, Israel, Italy Netherlands, Norway, Poland, Portugal, Slovakia, Spain, United Kingdom and EMBL (as an intergovernmental organisation). Observers on the Interim Board are Deutsche Forschungsgemeinschaft (DFG; awaiting official mandate to represent all of Germany), Denmark and Sweden.

The UK currently has three representatives on the interim board of EuBI, one representing the funding bodies (BBSRC and MRC); and two academic members who represent the biological and medical imaging communities respectively.

At present, EuBI has approved the proposal for a tripartite coordinating Hub - hosted by Finland (statutory seat and governance), EMBL Heidelberg (for biological imaging) and Turin, Italy (for medical imaging). The UK has interests in the Data Repository aspects of the Hub. Following a call in 2013 for expressions of interest to become a EuBI node, the Board has also ratified the nomination of 28 imaging facilities from ten countries plus EMBL, as candidates to become the first generation of EuBI Nodes.

The UK declined to put forward a national Node(s) at this stage, preferring to take stock of our national position first, and then decide how the UK research community could best be served – an important aspect of this review. The original call for Nodes did not allow for submissions reflective of the diversity of imaging technologies and expertise present in the UK. Furthermore, since the call for Nodes in 2013, the UK imaging capabilities and installed technologies have advanced significantly, so having an opportunity to evaluate key facilities and areas of current strength in imaging research and technology, and consider future needs is valuable. This is something which this review is intended to help inform.

[28] **http://www.eurobioimaging.eu/**

In the coming months, it will be important for the UK to decide on the extent of UK engagement in the EuBI project, and if the UK is engaged, which aspects would be important to us. As demonstrated by the first generation of EuBI Nodes, the majority of imaging technologies that would be accessible through EuBI are already available in the UK. Therefore it is important to ascertain whether the level of access in the UK is adequate for some of the more specialist regional or national facilities, or whether access to nodes through EuBI would provide further important access to such technologies for UK researchers.

However, although there is currently access to the majority of cutting-edge technologies in the UK at present, the rate of development of technology is high, and it is important that the UK is able to keep up with this rate of development as this in turn will enable crucial scientific discoveries. While this could be achieved through provision of funding for equipment within the UK, EuBI could also provide a route to accessing these cutting-edge technologies in the future, as they appear in the wider European landscape.

Leishmania parasites, transmitted by blood-feeding sandflies in 90 countries worldwide, cause chronic disease in man and other mammals. The parasites move using a long flagellum which is lost following introduction into the mammalian host. A scanning electron microscope image shows the structure of theTrypanosoma brucei bloodstream form. Credit: Peter O'Toole, The University of York

If it is the case that access within the UK to specific technologies is acceptable, then ascertaining the added value of EuBI is key. Indeed, involvement in a project which has the potential to foster further collaboration between UK researchers and their European counterparts engaged in the programme could be valuable. Additionally, there are aspects to the project related to training and data management, storage, analysis and sharing that, in community terms, could be valuable to have collaboration at a European level.

There is, however, a risk in engagement in the programme to some degree as, although UK researchers would have access to nodes across the EuBI partner countries, researchers from all partner countries would have reciprocal access to any UK facilities put forward as nodes, potentially placing an additional burden on UK facilities. Finally, a very important consideration is one of cost; EuBI will likely require significant financial contributions and the funding available for bioimaging will be limited. Careful consideration must be given as to how the needs of the UK community can be best served; balancing the requirements for funding support through traditional research council mechanisms (for research, equipment and training) with the benefits of participation in large-scale international activities. Given the substantial resource requirements of the latter (funds and staff), the added value of such activities must be clear.

In summary when considering the extent of engagement of the UK in Euro-BioImaging, specific attention should be paid to the following points:

- Provision of and access to, imaging facilities and equipment on a pan-European basis, assessing what is accessible through Euro-BioImaging versus what equipment can already be accessed within the UK
- The degree to which international collaboration is enabled and benefits accrue for UK biological and biomedical imaging researchers by participation in this programme
- The access to training resources that will be offered through this programme
- The benefits of addressing challenges such as data management on a European scale and the importance of UK engagement in such efforts

Benefits of International Engagement

Through consultation with the UK bioimaging community and through analyses of the UK's bioimaging landscape and infrastructure it is clear that the UK has a very strong technological backdrop. Thus, for most imaging technologies, UK scientists should be able to identify sites within the UK that can, in principle, provide access to any particular technology, providing they have the resources to do so. As such, engagement and international collaboration must have benefits for the UK beyond access to equipment or methods in order to be cost effective for the UK bioimaging community. For example, the community of image analysis and management technology developers is a global community, so engagement with this community may have benefits for UK-based developers and users of these tools.

A key benefit of international engagement and collaboration for the UK bioimaging community is access to integrated, collaborative networks of researchers. Such networks provide access to facilities that are actively developing novel technologies and methods, including the development of new labelling and sample preparation techniques. A global network of like-minded researchers opens up access for the UK bioimaging community to world-class expertise and technical skill, for new technologies but also for the extension and improvement of existing technologies and methods. Further, international collaboration and engagement can provide access to accredited training and knowledge exchange for researchers and technical staff at all levels.

It is clear that international collaboration and large scale programmes provide extremely useful mechanisms to access high-quality facilities and technology across the world, and to network and collaborate with highly-skilled researchers from other countries, sharing research methods, equipment and best practice.

In order to utilise international expertise to support UK bioimaging, the UK must maintain strong research relations with countries such as Australia, Belgium, China, France, Germany, Japan, the Netherlands, Singapore and the USA. While there are a number of means to foster engagement with imaging communities in these countries, EuBI could provide one route to fostering such engagement, particularly through its participation in the Global BioImaging[29] EC-funded project (see later), as access to researchers and networks in many of these countries will be enabled.

Smaller scale international relationships can be built and sustained through funding from BBSRC's International funding schemes[30]. These include support for short introductory visits (including training for staff), long-term two-way exchanges over a period of years, and international workshops to bring together experts from specific fields. Furthermore, at least for the time being, the UK bioimaging community can also access networking opportunities offered by the European Commission such as COST actions.

BBSRC needs to give careful consideration to engagement in European and International imaging programmes, such as Euro-BioImaging, to ensure that UK resources are deployed most effectively for the benefit of the UK research community.

Recommendation 11: BBSRC should consider the future level of UK engagement in European (particularly post-Brexit) and International networks, such as Euro-BioImaging, CTLS and COST, and support UK researchers' engagement as appropriate. Additionally, BBSRC should remain engaged in the development of these networks and consider its role as a national funder in providing input to the priorities of such networks.

[29] **http://www.eurobioimaging.eu/global-bioimaging**

[30] **http://www.bbsrc.ac.uk/research/international/**

Bioimaging: A Global Area of Research & Collaboration

As shown throughout this report, bioimaging in the UK is supported by a strong community; a diverse but well supported technologies backdrop; world class research in supporting methods and data; and positively recognised facilities. However, in order to truly appreciate how the UK can best position itself in a global context it is important to understand how competitor and collaborator countries and organisations operate.

For example, large programmes or facilities in Europe that may be of interest, include the Core Technologies for Life Sciences (CTLS) meetings which bring together representatives from various biological core facilities, including microscopy, cytometry, genomics, proteomics/metabolomics, protein production, and biophysics/molecular interactions. They consider best practice and opportunities for closer working, not just between countries, but also between technologies and can collectively argue for the needs of the sector(s). Also of interest is the model of beta testing of equipment at EMBL Heidelberg (see Box 7.2), and the close relationship between this facility and imaging and microscope manufacturers across a spectrum of technology development activities.

Box 7.2 European Molecular Biology Laboratory (EMBL)

EMBL is an intergovernmental organisation to which the (currently 22 full) member states pay an annual subscription. For the UK, the contribution is provided by the MRC and BBSRC on behalf of the UK life sciences community.

Given EMBL's inherent European nature it is able to act as a central site for the delivery of training and skills and this is accomplished through a large number of bioimaging-related courses jointly run by EMBL and EMBO. EMBL is also able to host many international scientists, including a large number of UK scientists, for collaborative visits, allowing the exploitation of EMBL's state-of-the-art technologies.

Indeed, EMBL Heidelberg, particularly the Advanced Light Microscopy Facility (ALMF), provides a unique environment in terms of the range of training and levels of infrastructure available, the nature of which is not accessible at many imaging facilities internationally. The ALMF offers a collection of state-of-the-art light microscopy equipment and image processing tools. The facility was set up as a cooperation between EMBL and industry to improve communication between users and producers of high-end microscopy technology. The ALMF supports in-house scientists and visitors in using light microscopy methods for their research and regularly organises in-house and international courses to teach basic and advanced light microscopy methods. In this context, EMBL and EMBO provide a powerful resource for imaging researchers.

The VIB in Belgium has multiple microscopy centres throughout the country. There are two major lead centres (Ghent and Leuven). Both centres have their own significant user bases and as such both provide excellent LM and EM facilities at both sites. However, both centres have formed unique areas of complementary excellence. Ghent focusses on the latest volume EM technologies and Leuven concentrates on the very latest super-resolution light microscopy technologies. The sites meet frequently and organise courses together. The distance between the two sites is such that it is possible for PIs to use equipment at either site, although difficult for live cell work where samples need to be set up on site of the microscope.

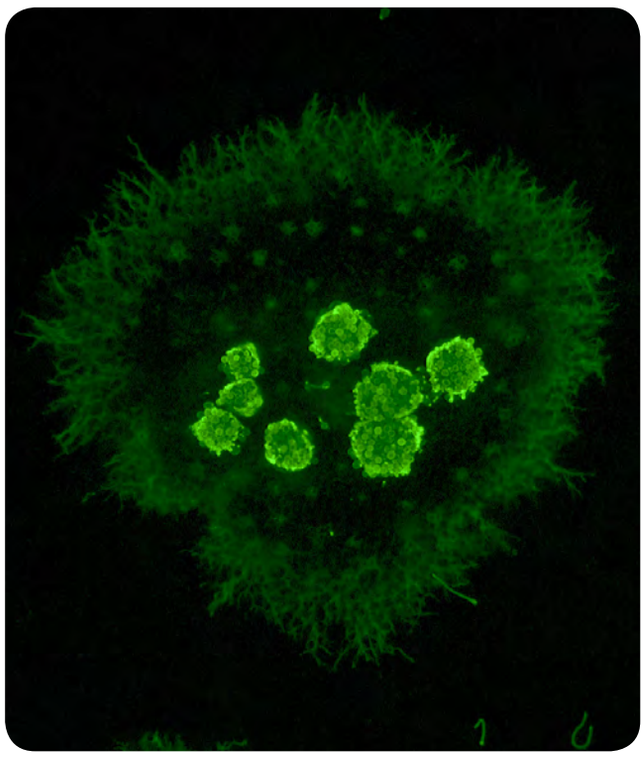
German BioImaging, with its close connections to industry, and France Bioimaging were also recognised as important examples of excellence and good practice during consultation for this review.

Germany is an internationally recognised focus of strong biosciences research including in bioimaging. Germany has access to the headquarters and research centres for some of the largest bioimaging technology companies in the world. Like the UK, Germany boasts well organised and supported bioimaging facilities and a mobilised community. The German BioImaging network is the German equivalent of BioimagingUK and is currently supported by the German Research Foundation, DFG.

In 2012/2013 German Euro-Bioimaging submitted a bid to the German Federal Ministry of Education and Research (BMBF) for a distributed and coordinated national infrastructure, whilst viewed positively this was not included in the BMBF roadmap. In January 2016 a further proposal for a distributed and coordinated national infrastructure offering open access to very advanced bioimaging technologies was again submitted to the BMBF. With this document, the "German BioImaging-Research Infrastructure" seeks inclusion in the National Roadmap for Research Infrastructures. At the time of writing, the outcome was not yet known.

DFG is currently an observer on Euro-BioImaging, awaiting an official mandate to represent the whole of Germany and the German bioimaging communities.

France BioImaging is a National Infrastructure in the Biology and Health programme. The programme organises a national, coordinated infrastructure of bioimaging facilities and bioimaging development laboratories through a series of nodes.



The image shows an infection site of Asian soybean rust fungus on a leaf. Single fungal spores germinate on the surface, penetrate the leaf and colonize in the plant tissue. A net of fungal hyphae grows in the plant cells and millions of new spores will be produced and released on the leaf surface within a week. The fungal structures were stained with a fluorescent dye to distinguish them from plant tissue. Microscopy is used to screen plants for fungal infections, which are not always visible in bright light. Credit: Nadine Ilk-Maintz, The Sainsbury Laboratory, NRP Image Library, Norwich Research Park.

France BioImaging is both well-funded and coordinated, with national standards and evaluation criteria for imaging facilities, national training programmes, and regular national meetings. Split into five work packages, France BioImaging manages bioimaging instrumentation and methods, high-throughput and automation of systems, labels and probes, image analysis and data management and training and skills, for the French bioimaging community.

Further, a number of respondents to the community survey noted the Janelia Research Campus[31] in the USA as a good example of a productive, state-of-the-art, technology development environment, which has produced some significant advances in imaging technology; including super-resolution techniques and light sheet microscopy methods (see Box 7.3).

In addition to building links across Europe, during its Preparatory Phase Euro-BioImaging has developed collaboration agreements with several international partners including the Australian Microscopy and Microanalysis Research Facility (AMMRF) & the Australian National Imaging Facility, as well as India-BioImaging. Such agreements will form the basis of shared services and infrastructure across the globe including training platforms, data repositories and facility exchange programs. This has formed part of a European Union Horizon 2020 programme: the Global BioImaging (GBI) Project. More specifically, agreements between EuBI and facilities such as AMMRF in partner countries have led to shared knowledge and best practice regarding training resources such as the MyScope[32] training portal, developed by AMMRF.

[31] **https://www.janelia.org/**

[32] **http://www.ammrf.org.au/myscope/**

Box 7.3 Janelia Research Campus, USA

The Janelia Research Campus in the USA was founded by the Howard Hughes Medical Institute, which brings together scientists from all disciplines to work on the development of new imaging methods and research on neuronal circuits. The campus boasts a "uniquely innovative, collaborative atmosphere" that focuses on high-risk, long-term, pioneering research.

Janelia provides a shared support infrastructure of expert, flexible staff and state-of-the-art equipment. This shared support is designed to complement and extend those facilities found in Janelia's fifty-plus labs. Janelia is currently home to over 500 researchers at all levels and 'Janelians' come from all over the world with over 150 visiting researchers every year.

Janelia is a unique example of access as it has received large amounts of funding and is a dedicated research campus bringing together all of its researchers and expertise, technologies and techniques and supporting services into a concentrated centre of innovation.

The community survey responses show that Janelia is recognised as an international example of excellent access to bioimaging resources, although the community is aware that this has been enabled due to extraordinary amounts of funding.

Participation in EuBI enables access for UK scientists not just to European partners but also, through these agreements, to other international groups via GBI. Future plans for GBI include developing working with imaging infrastructure experts from across the globe to share technology development, training, knowledge and data management resources. Key countries for interaction with the GBI include Japan, the USA, Argentina and South Africa, as well as the aforementioned Australian and Indian agreements.

Many of these European and wider international programmes are still in the relatively early stages of development and are evolving rapidly. This presents the UK with an opportunity to engage and influence these efforts, although it is not yet clear which will be the most beneficial for the UK, and the extent to which we should participate. In all cases however, the UK has to be mindful of the capacity and resources we have to participate, and we must be driven by our scientific goals.

There are many excellent international resources for bioimaging, whether they be single-sited institutes, distributed institutions within or across countries, or national networks. Many offer different expertise and operate according to different models, (e.g. depending on whether the collaboration is for technical development or discovery science, or both); hence a flexible approach to interactions is required which can accommodate this diversity and the speed of evolution of international programmes.

Recommendation 12: BBSRC should provide flexible mechanisms for UK researchers (within BBSRC's remit) to visit and collaborate with a diversity of international imaging centres of excellence.

8. Enabling Future World-Class Bioscience

Bioimaging is a field that enables world-class research across all of the biological sciences. Research projects utilising different types of bioimaging are seen throughout the BBSRC-funded portfolio, from ageing through to synthetic biology, and at all scales of life, from single molecules to whole organisms. Bioimaging technologies and methods, including image analysis and data sharing, operate across BBSRC's remit and strategic priorities. In this section we have highlighted a selection of examples of future areas that bioimaging will underpin and the key technologies, interactions and infrastructure that will be required to facilitate these studies.

World-Class Bioscience

Increases in both spatial and temporal resolution are key to future bioimaging. Along with new probes and detectors, increasing resolution will enable imaging of endogenous levels of proteins and lipids, e.g. from in locus tagging using genome engineering. This will also lead to more quantitative approaches as researchers gain more information on the number of molecules involved in specific steps.

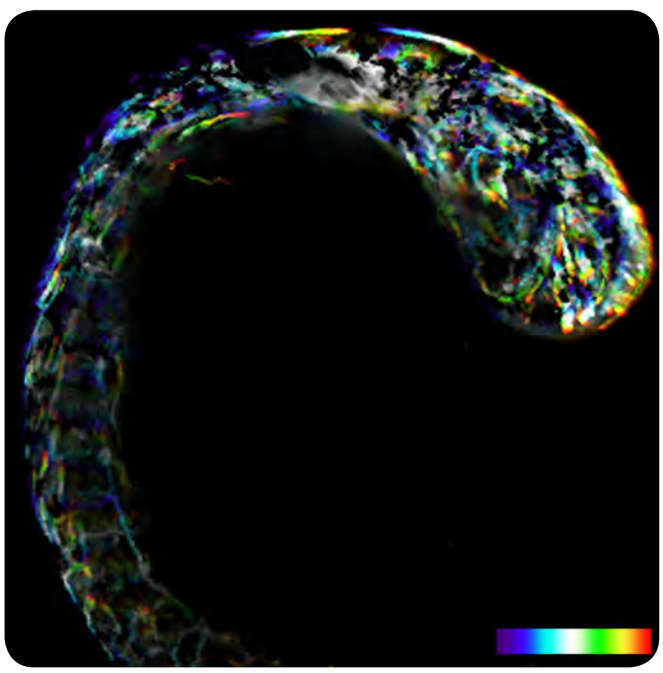


Image shows the movement of neural crest cells in a zebrafish embryo during early development (27-44h). The image is time-coded projection of a time-lapse series using different colours to show the position of cells during the experiment (purple at the start, red at the end). The data were acquired using a light sheet microscope and processed using ImageJ.
Credit: Dylan Bergen, University of Bristol.

Further improvements in quantitation, e.g. through improvements in bioimage analysis and annotation, integration of imaging data with other biological data, e.g. genomics and proteomics data, will enable new and more complete understanding of biological systems from the point of view of genotypes, phenotypes and environment. This integrative approach will lead to a paradigm shift from genomic-inspired understanding to a quantitative phenomic-inspired understanding derived from bioimaging. The development and deployment of resources that make well-organised, annotated comprehensive imaging datasets publicly available will spur the development of analytic tools that integrate data from different studies, and stimulate the growth of a whole new field of bioinformatics.

Similarly, improvements in bioimaging and bioimage analysis leading to the quantitative tracking of single cells within populations and/or single molecules within cells will allow a mechanistic understanding of dynamics and equilibria that have, until now, only been studied at a population level (see Box 8.1). Therefore, improvements in technology and analysis and/or the integration of data from a multitude of technologies (see Section 4) will enable true multi-scale approaches to biological problems.

Agriculture & Food Security

Future imaging, including better spatial and spectral resolution and improved depth penetration, will allow bioscientists to better understand the spatial distribution of small molecules within whole and living cells and analyse whole organs or organisms, e.g. living plant roots. More complex image analysis and machine learning methods look to enable genuinely high-throughput phenotyping across scales, from cell to organism. Miniaturisation of sensors and portability of technology will allow easier whole plant or animal imaging in situ in an agricultural environment.

Box 8.1 Enabling Future World Class Bioscience

We are interested in describing signalling networks that regulate the mammalian cell cycle. Historically most cell cycle research has been carried out in large populations using population-based biochemical assays, e.g. western blots; but these methods mask cell-to-cell differences in cell cycle state and protein levels. Population-based methods instead give a portrait of the "average cell" in a population – which may not even exist! Moreover, when using such techniques, it is impossible to track the cell fate decisions taken by a single cell over a period of time; such as the decision between proliferation and quiescence. In order to understand cell-to-cell differences, and individual cell fate decisions it is critical to study large numbers of single cells; which is where bioimaging comes in.

We use an iterative cycle of single-cell imaging and mathematical modelling to explain how cells make the decision to proliferate and enter the cell cycle. Specifically, we use automated microscopy to follow the levels and localization of key signalling proteins in single cells over the course of many cell cycles. Why hasn't this been done before? The technology needed to image and quantify the dynamics of proteins in living cells is relatively new and relies heavily on automation and computer vision. In fact, our research would be impossible without automated bioimaging and sophisticated image analysis tools.

Currently our research is able to quantify the behaviour of hundreds of single cells over reasonable periods of time (2-3 days), but the length of our experiments is always where we face limitations. The future will lie in being able to do longer and longer experiments, recording single cells over many days and even weeks. For us, it is not super-resolution or high throughput that will make the difference but time period. Furthermore, while there have been stunning recent improvements in the computer vision technologies used to track individual cells, and automatically quantify single cell phenotypes, there is still a need to develop even more advanced tracking and image recognition algorithms. These are the technological challenges that will hopefully be addressed in the future.

Dr Chris Bakal, Institute of Cancer Research.

Industrial Biotechnology

Increases in throughput for bioimaging, driven by a requirement in the academic bioimaging community, will have a massive effect across the biotechnology community. Increased throughput and the associated developments in labelling, sample preparation and analysis will allow, for example, massive screening assays for antimicrobials, pesticides or pharmaceuticals.

Bioscience for Health

The ability to map biochemical pathways over space and time and across length scales, i.e. cells, tissues, and organisms, will allow researchers to develop a fuller understanding of the processes involved in the maintenance of health across the life course, such as metabolism and immunology.

Technology Development

Bioimaging is a range of technologies, from sample preparation and labelling, through to explicit imaging equipment and image analysis. Advances in any one area of this field will have a positive effect on all other areas of technology and method development as well as on the adoption of new technologies in the wider biosciences community. As such, whilst a large part of bioimaging is technology development, support of bioimaging research and the bioimaging community will lead to advances in genetic control and optogenetics, physical understanding of biological samples, systems approaches and synthetic biology, to name but a few.

Advances in bioimaging will continue to stimulate and enable world-class bioscience across and beyond the BBSRC remit. It is essential that the UK's currently strong bioimaging landscape is maintained and that the community and equipment needed is well supported by the BBSRC.

The UK Bioeconomy

As mentioned throughout this report, bioimaging underpins all areas of bioscience, in turn having an impact on the UK's bioeconomy. For example, food research, including food safety and security, is carried out in both academic and industrial research centres, relying on various forms of bioimaging: microscopy, spectrometry and tomography. In consultations with industry members this review found that industrial imaging relies heavily on sample preparation and labelling, data management and analysis and temporal/spatial constraints, e.g. spatial resolution or time-lapse imaging; these are the same challenges faced by the academic community. By encouraging further technology and method development and adoption within the academic community, there will be a positive effect on the wider bioeconomy as industrial researchers acquire these advances through existing collaborations, literature and community meetings or conferences.

Future bioimaging will underpin many aspects of the bioeconomy and is an essential component of the impact of bioscience on industry. Support of UK bioimaging is essential to the continued strength and expansion of the UK bioeconomy.

Interaction with Other Disciplines

Key to integration across data sources and imaging modalities is the interface between traditional disciplines. Further development of shared knowledge and common standards across the bioimaging and wider biosciences community will not only enable broader data integration and correlative studies but will open up bioimaging data to the wider scientific community.

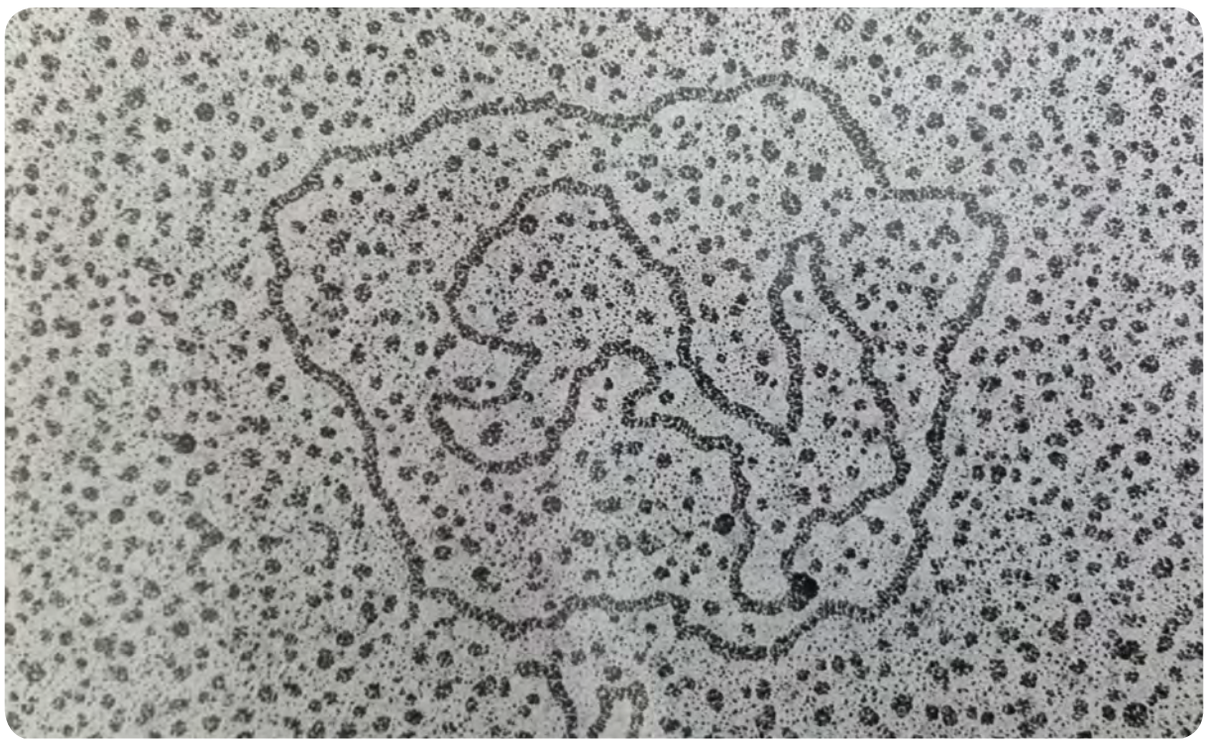
Similarly, sharing data and standards with physicists, chemists and material scientists allows the transfer of knowledge between, for example, astronomers and bioimage analysts, such as object tracking techniques, or allows for example, condensed matter scientists to analyse the physical properties of particular cells or tissues, leading to the development of mathematical models from which hypotheses can be formed. Maintaining sharing and standards and this level of knowledge and skills transfer will enable further advances in bioimaging.

Interactions with computer scientists and mathematicians, for example, can open up meta-analyses of existing bioimaging data through information mining, machine learning, mathematical models and statistical approaches as well as the implementation of tools and techniques from these disciplines. Such interactions can also introduce new lab protocols, help automate processes, and in general change the way bioscientists are able to capture and work with raw data.

Such interactions are already occurring, for example in the application of single molecule microscopy to understanding molecular interactions, where the approaches of astronomers, mathematicians, engineers, computational and computer scientists are leading to increasingly robust, quantitative and scalable data analysis, management and interpretation critical to address the grand challenges.

Most imaging experiments generate 'big data', i.e. large, complex, heterogeneous, rich datasets that are ripe for mining and integration with genomic and other data. Expert data scientists will be required to make the most of experimental imaging data.

Working closely with chemists is leading to new developments in organic, inorganic and genetically encoded probes, sample preparation and mounting methods. For example, the development of fluorogenic probes for super-resolution imaging such as silicon-rhodamine conjugates of phalloidin, as well as of artificial amino acids used for bio-orthogonal labelling of proteins has only been possible thanks to interdisciplinary teams with a strong chemical bent. These interactions are vital for developing new techniques for existing technologies and also for developing appropriate and optimal techniques for new and emerging technologies.



Electron Micrograph of DNA plasmid from yeast. Credit: Bruce Pearson, Institute of Food Research, NRP Image Library, Norwich Research Park

There is significant scope to ensure integration of imaging modalities to include BBSRC-relevant work that extends to areas that lie beyond the scope of this review. Examples include experimental workflows that use whole animal imaging for both fundamental science as well as veterinary and clinical applications.

Many larger projects now exploit light and electron microscopy for cell and model organism experiments (e.g. zebrafish and rodents imaged using multiphoton imaging, light sheet microscopy, and volume-based EM methods such as SBF-SEM) the outcomes of which are then integrated with large animal experiments in pigs, or human imaging facilities, such as MRI. This provides a translational pathway based around imaging that also aligns to "One Health" initiatives relevant to BBSRC. The infrastructure for this requires substantial cross-funder communication and integration that includes multiple research councils, charities, and the NHS/NIHR. For example, The Roslin Institute works with the University of Edinburgh to provide diverse animal imaging modalities, and is linked to the Edinburgh Super-Resolution Imaging Consortium to provide molecular level analysis.

Similar scenarios can be considered for plant work where fundamental molecular cell biology using imaging has direct relevance and translation to field-scale experiments and trials. Such integrated approaches to small and large scale imaging are an opportunity for future research correlating molecular and cellular phenotypes with whole organism outcomes.

Bioimaging is a cross-disciplinary field, as recognised in previous government and research council reports, and building communications and networks across disciplines is vital to the continued success of UK bioimaging.

Recommendation 13: BBSRC should work with other funding bodies to ensure that cross-disciplinary projects focussed on the development of new bioimaging technologies, methods and analyses can be facilitated, and to encourage the exchange of knowledge and expertise across disciplinary boundaries.

Recommendation 14: BBSRC should encourage cross-disciplinary networks and communities at the local, grass-roots level as a mechanism for community self-organisation, collaboration and spreading of standards and best practise.

Future UK Bioimaging Infrastructure

The UK bioimaging infrastructure is both broad and deep (see Sections 1, 2, 4, 5 and 6) and must remain so in order to support further UK bioimaging advances, enable future world-class UK biosciences and underpin the UK bioeconomy.

Whilst access to new and cutting-edge developments in bioimaging must be available to those bioscientists who require them, it cannot come at the expense of broad access to workhorse technologies that support the majority of experimental research by UK bioscientists. Likewise, funding of new, advanced technologies should not compromise support and maintenance of workhorse equipment, such as confocal microscopy (see Section 2). This requires a fine balance of different access methods and supporting systems to enable access to all areas of bioimaging for all UK bioscientists, both academic and industrial (see Sections 1, 2, 4 and 6).

The wheat (Triticum aestivum) cultivar Vuka is susceptible to yellow rust disease. This image shows a leaf ruptured by emerging spores post-infection with the yellow rust fungus (Puccinia striiformis f. sp. tritici). Imaged by cryo-scanning electron microscopy and false-coloured using Photoshop. Credit: Kim Findlay, John Innes Centre, NRP Image Library, Norwich Research Park

Whilst the current UK bioimaging backdrop and infrastructure is strong, this has arisen through huge effort and large investment by the community and funding bodies. Maintaining and developing these requires continued support of the community, technologies and data. Without maintenance the strength of UK bioimaging will diminish in a matter of years; it is reasonable to expect gaps in the UK bioimaging technologies and skills landscape to form within two years due to the rapid rate of change in both enabling and imaging technologies.

Recommendation 15: BBSRC should work with the UK bioimaging community, including learned societies, other funding bodies, HEIs and HEFCE to ensure that UK bioimaging is receiving the support and funding necessary to maintain a world-class environment that will, in turn, enable world-class bioscience in the UK.

The UK's institutional and regional bioimaging facilities will be a key aspect of finding this balance, acting as access points for technologies, workhorse and advanced, training, skills and expertise. Core bioimaging facilities also allow the sharing of best practise through networks of facility users and the sustainable maintenance of high-end equipment. These core bioimaging facilities were acknowledged as a key aspect of UK bioimaging throughout our consultations.

However, access to technology and expertise requires resources: a facility that has obtained a new, advanced imaging technology cannot make it available to large portions of the UK bioimaging community without funding and resources to do so. Technology experts that provide guidance on how to use advanced imaging technology, time on a system, and maintenance of a system are all real costs of sharing technology that are not necessarily covered through current funding mechanisms.

Complementary to enabling access to technologies, methods and expertise comes the transfer of expertise and skills; the training of new users in existing technologies and methods, and the training of existing users in new technologies and methods (see Sections 2 and 3). Without a strong training and skills base, the UK bioimaging and bioscience communities will fall behind in the adoption of new technologies and methods, which will in turn hinder biosciences and the bioeconomy in the UK.

Being able to generate, share, analyse and mine biological images and the resulting data is extremely important and an essential part of any bioimaging infrastructure. The UK has established world-recognised strength in sharing technologies through repositories and databases, analysis approaches, including cross-disciplinary, problem-driven collaborations. We also have an awareness of the need for shared standards and further development of the e-infrastructure and algorithms available to the UK bioimaging community (see Sections 5 and 6). It is vital that the UK supports its bioimaging infrastructure with a strong e-infrastructure and enables future bioimaging through the development of imaging standards, analysis platforms, new algorithms and informatics.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Conclusions

Section 1: Bioimaging in the UK

- Through intense community effort and recent, large investment, the UK produces world-class bioimaging-related research, underpinning all of the biosciences.
- Bioimaging is a cross-disciplinary field with interactions across the sciences. The UK is effective at developing the necessary collaborations and cross-disciplinary communication needed for bioimaging.
- UK bioimaging development has led to notable technologies that have been commercialised and are now used worldwide. Further, UK bioimaging expertise is regularly accessed by the private sector to solve core industrial problems to the benefit of the wider bioeconomy.
- The UK bioimaging landscape encompasses a breadth of technologies and combines broadly impacting standard tools, such as confocal microscopes, and state-of-the-art technologies such as cryo-EM.

Section 2: The UK Bioimaging Infrastructure

- The UK has worked hard to develop a strong bioimaging technologies backdrop; however, without continued support and funding this could quickly weaken. Support and funding must enable the procurement of both commonplace and state-of-the-art technologies.
- UK bioimaging has recently coalesced forming community-driven, researcher-led organisations such as BioImagingUK and the Facility Managers Meetings. Strong support of these community bodies already comes from the research councils, Wellcome Trust and learned societies but must be maintained in years to come.
- UK access to bioimaging resources occurs through various scales of access: from in-lab equipment, through to local core facilities, right up to high-end equipment in national centres. Each mechanism of access has its benefits and a distributed network of varying resources is essential to continued access in the UK.

Section 3: UK Bioimaging Training and Skills

- The future of UK bioimaging is reliant not just on technologies but on a well-trained and highly skilled community of developers, users and technical staff. As such, high-quality training must be well supported by all those with a vested interest in UK bioimaging. Our goal should be to ensure there is sufficient bioimaging capability in the UK with opportunities for training at all levels, and sustainable career pathways.

- Training biologists to, for example, understand and develop code is just one side of training across disciplines; computer scientists, mathematicians, engineers, chemists and physicists must also be trained in understanding bioscience.

- Bioimaging is a skills heavy research area: the technology, methods development and the use of bioimaging require different levels of cross-disciplinary knowledge and expertise, including, for example, image analysis experience. Training and skills development is essential at all career stages and across the disciplines. Training can be supported through various mechanisms but available training and skills resources must be well advertised and accessible to the whole community.

- Most mechanisms of training require some level of monetary support, especially in bioimaging where time on equipment and consumables are required for practical training. Funding is currently available from multiple sources and for multiple purposes. The UK bioimaging community must be supported in accessing the funds and resources available to the community.

- Training and expertise can be effectively disseminated through the UK's bioimaging facilities. In order to maintain a high quality of training, facility managers should be constantly developing their technical skills and their training skills.

Section 4: Future Requirements and Emerging Trends in UK Bioimaging

- Enabling technologies, such as detectors, lasers and probes, are an essential part of the bioimaging ecosystem. Support given for the development and improvement of these enabling technologies will have significant effects upon bioimaging technologies.

- Bioimaging is a fast developing field with new technologies and improvements in core equipment, enabling technologies, data management and image analysis occurring regularly. The UK bioimaging community is aware of core emerging research and technologies and the UK bioimaging landscape puts the UK in a prime position to capitalise on these emerging trends. The UK bioimaging community and landscape must be appropriately supported to ensure that the adoption of new technology is timely and efficient. Failure to support the UK bioimaging technology landscape, community and supporting structures would lead to a detrimental effect on all UK bioscience.

Section 5: Bioimaging Data Management and Analysis

- Image analysis is an essential part of the quantitative bioimaging pathway. The bioimaging community must work with computer scientists, engineers, physicists and mathematicians to exchange analysis techniques with other disciplines and to develop new techniques that solve problems unique to bioimaging. Encouraging open source algorithms and software, open standards and metadata, and open access data will be important in enabling this trans-disciplinary sharing.

- The UK's data infrastructure is not suitable for the increasingly large amount of data produced by bioimaging technologies. Both the hardware required for storage and sharing data and the software required to make data storage, management and sharing available and accessible to the entire community are required to meet future bioimaging needs.

- Integration of data from imaging and non-imaging experiments is an important emerging trend across the biosciences and will be enabled by open standards for data and improved data infrastructure technologies.

- Data skills and training are required across the biosciences community to enable high-quality quantitative bioimaging. This includes theoretical understanding of image analysis as well as practical skills and expertise.

Section 6: Technology Development and the UK Bioimaging Industry

- Successful imaging technology and methods development requires a true multidisciplinary approach. Support and training are required to maintain effective links across traditional discipline boundaries and between academia and industry.

- Strong bioimaging facilities across the UK are valued by the UK bioimaging technology industry as hubs of technologies, training and expertise. Support for committed arrangements between UK bioimaging facilities and UK and global bioimaging technology companies will help to strengthen the bioimaging technology development in the UK.

- Many areas have been identified where complementary and synergistic working already occurs between academia and industry, however, these could be further built upon and there are still many untapped opportunities providing scope for much greater impact and benefit to the bioeconomy.

Section 7: UK Bioimaging in an International Context

- It is clear that international collaboration and large scale programmes provide extremely useful mechanisms to access high-quality facilities and technology across the world, and to network and collaborate with highly-skilled researchers from other countries, sharing research methods, equipment and best practise.

- BBSRC needs to give careful consideration to engagement in European and International imaging programmes, such as Euro-BioImaging, to ensure that UK resources are deployed most effectively for the benefit of the UK research community.

- There are many excellent international resources for bioimaging, whether they be single-sited institutes, distributed institutions within or across countries, or national networks. Many offer different expertise and operate according to different models, (e.g. depending on whether the collaboration is for technical development or discovery science, or both); hence a flexible approach to interactions is required which can accommodate this diversity and the speed of evolution of international programmes.

Section 8: Enabling Future World-Class Bioscience

- Advances in bioimaging will continue to stimulate and enable world-class bioscience across the BBSRC remit. It is essential that the UK's currently strong bioimaging landscape is maintained and that the community and equipment needed is well supported by the BBSRC.

- Future bioimaging will underpin many aspects of the bioeconomy and is an essential component of the impact of bioscience on industry. Support of UK bioimaging is essential to the continued strength and expansion of the UK bioeconomy.

- Bioimaging is a cross-disciplinary field, as recognised in previous government and research council reports, and building communications and networks across disciplines is vital to the continued success of UK bioimaging.

- Whilst the current UK bioimaging backdrop and infrastructure is strong, this has arisen through huge effort and large investment by the community and funding bodies. Maintaining and developing these requires continued support of the community, technologies and data. Without maintenance the strength of UK bioimaging will diminish in a matter of years; it is reasonable to expect gaps in the UK bioimaging technologies and skills landscape to form within two years due to the rapid rate of change in both enabling and imaging technologies.

Recommendations

Section 2: The UK Bioimaging Infrastructure

Recommendation 1: BBSRC should consider regular bioimaging technology and resource funding initiatives, helping to renew existing facilities, invest in emerging instrumentation and encourage wider access to the UK's bioimaging capability within a rapidly changing landscape.

Recommendation 2: BBSRC, working in partnership with others, should continue to support community-driven organisations and encourage their leadership in terms of training and skills, community resources and meetings.

Recommendation 3: BBSRC should facilitate a broad range of shared access mechanisms across all BBSRC-funded bioimaging equipment and facilities.

Section 3: UK Bioimaging Training and Skills

Recommendation 4: BBSRC should work with the learned societies, other funding bodies and HEIs to encourage and support careers and high-quality training for UK researchers, bioimaging facility managers and technical staff.

Section 4: Future Requirements and Emerging Trends in UK Bioimaging

Recommendation 5: BBSRC should encourage community driven meetings regarding new and emerging technologies that would allow interaction between developers, industry, facility managers and users.

Section 5: Bioimaging Data Management and Analysis

Recommendation 6: Continued support of algorithm and software development is vital, as it underpins the ability of the UK research community to extract meaningful results from microscopy data. Targeted calls such as TRDF are a key component, as is support via responsive mode grants. Cross-council funding, particularly with EPSRC and MRC, is likely to be particularly important due to the interdisciplinary nature of the work.

Recommendation 7: BBSRC should work with other research councils, relevant government departments (e.g. BEIS, HMT), HEFCE, UK HEIs and the global community to develop a coherent approach for the replacement, upgrade and renewal of the UK's data infrastructure as required for bioimaging.

Recommendation 8: Training should be provided both to those with computer science, mathematical, statistical and engineering backgrounds as well as those with biological backgrounds to enable two-way information flow. This community of developers and data–literate biologists would benefit from innovative cross-disciplinary funding opportunities.

Section 6: Technology Development and the UK Bioimaging Industry

Recommendation 9: Increase support for multidisciplinary and multisectoral networking activities between UK academic and industrial developers, and users, with a specific focus on funding for pilot projects.

Recommendation 10: Facilitate discussion between academics and industrialists, working with regulators, and the British Standards Institute, to increase the use and validity of bioimaging tools and technologies across the breadth of UK industry and bioeconomy sectors.

Section 7: UK Bioimaging in an International Context

Recommendation 11: BBSRC should consider the future level of UK engagement in European (particularly post-Brexit) and International networks, such as Euro-BioImaging, CTLS and COST, and support UK researchers' engagement as appropriate. Additionally, BBSRC should remain engaged in the development of these networks and consider its role as a national funder in providing input to the priorities of such networks.

Recommendation 12: BBSRC should provide flexible mechanisms for UK researchers (within BBSRC's remit) to visit and collaborate with a diversity of international imaging centres of excellence.

Section 8: Enabling Future World-Class Bioscience

Recommendation 13: BBSRC should work with other funding bodies to ensure that cross-disciplinary projects focussed on the development of new bioimaging technologies, methods and analyses can be facilitated, and to encourage the exchange of knowledge and expertise across disciplinary boundaries.

Recommendation 14: BBSRC should encourage cross-disciplinary networks and communities at the local, grass-roots level as a mechanism for community self-organisation, collaboration and spreading of standards and best practise.

Recommendation 15: BBSRC should work with the UK bioimaging community, including learned societies, other funding bodies, HEIs and HEFCE to ensure that UK bioimaging is receiving the support and funding necessary to maintain a world-class environment that will, in turn, enable world-class bioscience in the UK.

Glossary of Acronyms

AFM – Atomic Force Microscopy

ALERT – Advanced Life Sciences Research Technology Initiative

BSCB – British Society for Cell Biology

CLEM – Correlative Light and Electron Microscopy

CRISPR – Clustered regularly-interspaced short palindromic repeats

Cryo-EM – cryo Electron Microscopy

CT – Computed Tomography

DIC – Differential Interference Contrast

DTC – Doctoral Training Centre

EBI – European Bioinformatics Institute

ELIXIR – European Life-Science Infrastructure for Biological Information

EM – Electron Microscopy

EMBL – European Molecular Biology Laboratory

EMDB – Electron Microscopy Databank

EMPIAR – Electron Microscopy Pilot Image Archive

ET – Electron Tomography

EuBI – Euro-BioImaging

FIB-SEM – Focused Ion Beam SEM

FIJI – ImageJ with plug-ins

FLIM – Fluorescence Lifetime Imaging Microscopy

fMRI – Functional MRI

FRAP – Fluorescence Recovery After Photobleaching

FRET – Förster Resonance Energy Transfer

FTIR – Fourier Transform Infrared Spectroscopy

GW4 – Great Western Four Consortium

IDR – Image Data Resource

LSCM – Laser Scanning Confocal Microscopy

LSFM – Light Sheet Fluorescence Microscopy

MOOCs – Massive Open Online Course

MRI – Magnetic Resonance Imaging

N8 – North England Eight Consortium

OME/OMERO – Open Microscopy Environment/OME Remote Objects

OPT – Optical Projection Tomography

PDRA – Post-Doctoral Research Associate

PET – Positron Emission Tomography

RC – Research Councils

RM – Responsive Mode Funding

RMS – Royal Microscopical Society

SBF-SEM – Scanning Block Face SEM

SDCM – Spinning Disc Confocal Microscopy

SEB – Society for Experimental Biology

SEM – Scanning Electron Microscopy

SIM – Structured Illumination Microscopy

SIMS – Secondary Ion Mass Spectrometry

SPECT – Single Photon Emission Computed Tomography

SPIM – Single/Selective Plane Illumination Microscopy

SPM – Scanning Probe Microscopy

STED – Stimulated Emission Depletion

STORM – Stochastic Optical Reconstruction Microscopy

TEM – Transmission Electron Microscopy

TIRF – Total Internal Reflection Fluorescence

Annexes

Table of Contents

A. Expert Review Group Members

- Dr Mark Carver (FujiFilm)
- Dr Lucy Collinson (The Francis Crick Institute)
- Dr Susan Cox (King's College London)
- Dr Andrew French (The University of Nottingham)
- Dr Pippa Hawes (The Pirbright Institute)
- Professor Patrick Hussey (Durham University)
- Dr George Littlejohn (University of Exeter, now Plymouth University)
- Dr Peter O'Toole (University of York)
- Dr Andrey Revyakin (University of Leicester)
- Professor Peter Shaw (John Innes Centre)
- Professor David Stephens (University of Bristol)
- Professor Jason Swedlow (University of Dundee, Euro-BioImaging Interim Board)
- Professor Michael White (The University of Manchester)
- Dr Laura Zanetti-Domingues (STFC Central Laser Facility)
- Dr Timo Zimmermann (Centre for Genomic Regulation, Barcelona Spain)

B. Supplementary Data

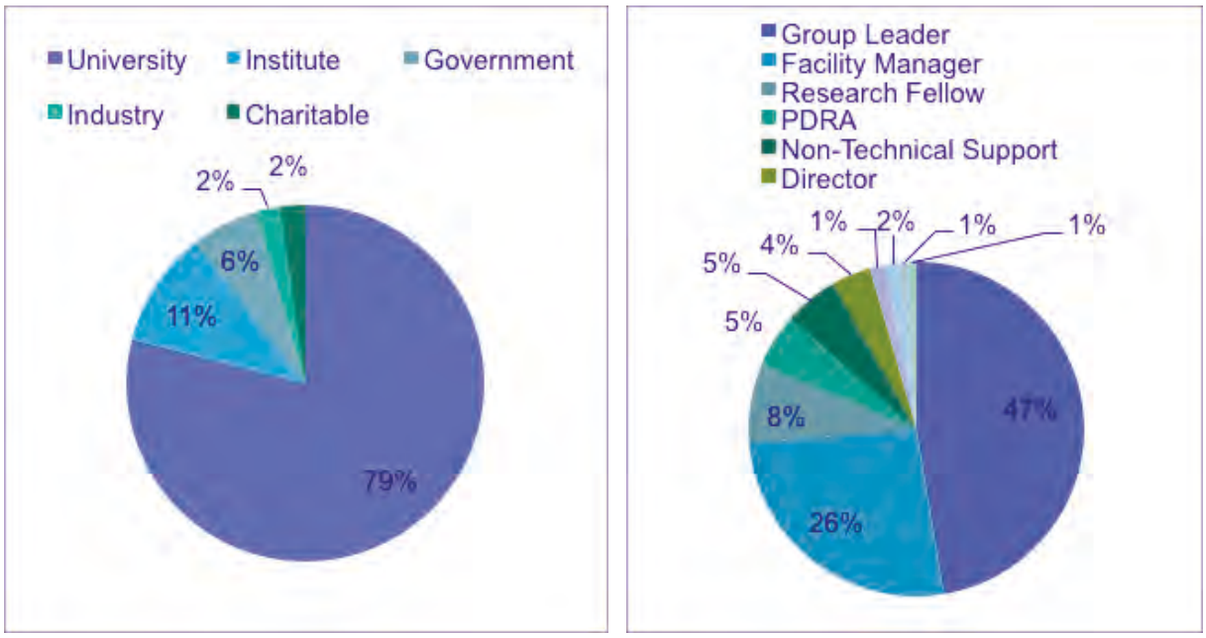

Figure B.1 - Respondents to the community survey binned by sector (left panel) and position (right panel). Respondents could select multiple answers for each question. Responses from 133 persons were collected for this question, of which 62 were answering on behalf of themselves, 49 were responding on behalf of a department, institute or facility and the rest were a combination of the two.

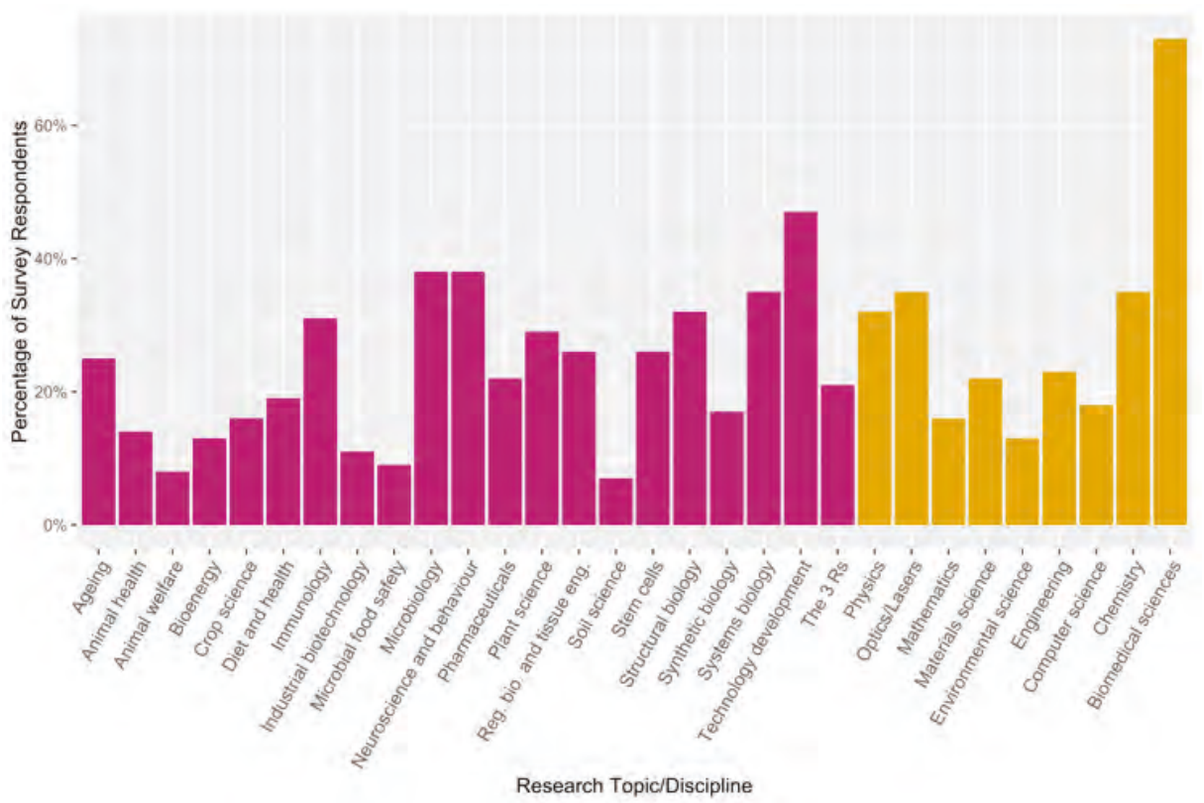

Figure B.2 - Respondents to the community survey binned by BBSRC strategic areas (pink) and non-biosciences research areas (yellow). Respondents could select multiple answers for each question. Responses from 133 persons were collected for this question, of which 62 were answering on behalf of themselves, 49 were responding on behalf of a department, institute or facility and the rest were a combination of the two.

Successful Models of Networking or Access available to UK Bioimaging			
Local/Regional	*Central/National*	*International*	*eResources*
University of York, The Imaging & Cytometry Laboratory	*Rutherford Appleton Laboratory (RAL)	Royal Microscopical Society (RMS)	Micro-Manager
Edinburgh Super-Resolution Imaging Consortium (ESRIC)	*Diamond Light Source	European Molecular Biology Laboratory (EMBL), Advanced Light Microscopy Facility	OMERO
University of Oxford, Micron	*Central Laser Facility (CLF)	OpenSPIM	Bio-Formats
Exeter Imaging Network	BioImagingUK	Euro-BioImaging	ImageJ/FIJI

*Harwell Science and Innovation Campus

Table B.1 – Examples of successful models of networking, enabling access and community sharing of UK bioimaging resources. These examples were captured from the community survey and have been categorised by 'Local/Regional', e.g. internal to one institution or shared by a small number of geographically close institutions; 'Central/National', i.e. intended to be used in a national manner, such as those facilities at the Harwell Science and Innovation Campus; 'International' models, whether they be societies, networks, shared knowledge or international collaborative efforts; and 'eResources', e.g. software or data infrastructure projects that usually have a global digital presence and no physical presence.

C. Recent Large Investments

Recent Large Investments & Funding Initiatives with a Bioimaging Focus			
Funding Initiative	*Funders Involved*	*Level of Funding (£M)*	*Year*
Next Generation Optical Microscopy Initiative	MRC, BBSRC, EPSRC	26.45 (2.45 BBSRC)	2012
Cancer Imaging programme	MRC, CRUK	50	2008-13
ALERT	BBSRC	14.5 (capital only)	2013-14 and 2016
Shared Equipment Funding Committee	Wellcome Trust	2.5 per annum	2011-14
Electron Bio-Imaging Centre (eBIC), Diamond	Wellcome Trust, MRC, BBSRC	15.6 (3 BBSRC)	2011-14
Strategic Investments	Wellcome Trust	4.0 - Micron Oxford (Oxford University) 2.5 - development of super-resolution microscopy (Cambridge)	2011-14
OME/OMERO	Wellcome Trust, BBSRC	9.41 (1.51 BBSRC)	2002-15
Big Data Strategic Investment	BBSRC	1.79 - Next Generation Image Data Repository	2014
Electron Microscopy Data Bank	BBSRC	0.63	2009-2012
Cryo-EM equipment to support world-leading structural biologists across the UK	Wellcome Trust	20	2017
Total		**>£140M (since 2011)**	

Table C.1 – Examples of recent large investments (since 2011) and funding initiatives with a bioimaging focus; these investments are from several UK funding bodies but impact the whole UK bioimaging community. This is not an exhaustive list and does not include bioimaging research or equipment funded through standard responsive mode applications for any of the funders.

D. BBSRC Mechanisms of Support and Funding

BBSRC Mechanisms of Support and Funding	
Activity	*BBSRC Support Mechanisms*
Equipment Funding	**Responsive Mode** (relatively small scale) Dedicated Initiatives e.g. ALERT (mid-range equipment), Next Generation Optical Microscopy Initiative (NGOMI) National Capability Grants (BBSRC Institutes)
Skills and Training	**Centres for Doctoral Training** (Post Graduate) **Fellowships** (PDRA) **STARS** (small-scale training)
Networking and Collaboration	Networks, e.g. **BioImagingUK**, EM UK ESFRIs e.g. **Euro-BioImaging**, **ELIXIR** Partnering Awards & International Workshops Conference session/special interest meeting sponsorship
Industry Engagement	**Industrial Partnership Awards** **'Stand-alone' LINK** **Follow on Fund** (FoF)

Table D.1 – Example BBSRC mechanisms of support and funding, grouped by 'activity': funding for new or replacement equipment, development of skills and training, development of networks and collaborative groups and engagement with industry.

E. Community Consultation Questions

BBSRC bioimaging review survey

Background

Imaging is increasingly important for driving bioscience research discoveries. In recent years there have been significant changes in the UK bioimaging research landscape, including new scientific drivers, significant technological developments in imaging, a number of large-scale investments and the establishment of an identifiable community with interest in imaging.

In response to these developments BBSRC is conducting a **science-led** review of bioimaging. The review group will provide advice to BBSRC on our support for UK bioimaging, allowing us to ensure that our research community remains at the forefront of imaging-driven research and innovation.

As part of this review, BBSRC is conducting a survey to gather the views of researchers with an interest in bioimaging. All information submitted will be treated in confidence.

How to complete the survey

The survey comprises **20** questions and responses are welcomed from departments, HEIs, other bioscience research organisations, scientific societies, industry and other relevant BBSRC stakeholders. Responses from individuals will be accepted, but those from larger groupings are strongly encouraged.

1. **What sector do you work in? (please tick one)**

   - University
   - Institute
   - Government
   - Industry
   - Charitable
   - Other - please specify

2. **What is your position within the organisation you work in? (please tick one)**

   - group leader
   - industry R&D
   - facility manager
   - technical staff
   - research fellow
   - PDRA
   - postgraduate student
   - Other – please specify

3. **Who are you submitting this response on behalf of? (please tick one)**

   - myself
   - facility users (specify the facility)
   - my department (specify)
   - my institution or organisation (specify)
   - another organisation e.g. learned society (free text)

Please note that it will be assumed that answers you provide to the following questions are representative of those you are responding on behalf of.

About your research

These questions are designed to identify your research interests relevant to bioimaging, the methods and techniques you use, and the ways in which you access imaging facilities and resources.

4. Which broad area(s) of bioscience do you work in?

- BBSRC research topics

Which other areas (if any) do you work in?

- Biomedical sciences
- Mathematics
- Chemistry
- Engineering
- Physics
- Optics/Lasers
- Computer science
- Environmental science
- Other (please specify)

5. Please provide examples of the specific biological question(s) that imaging helps you to address?

6. What imaging techniques do you use and how do you currently access the imaging technology you need?

Where possible, include an indication of the number of researchers using the imaging technology in the group you are responding for (e.g. your department or institute).

Please include one entry for each technique utilised (up to 10 possible entries).

7. What specialist imaging support do you need in order to conduct and develop your research?

- sample preparation
- technical assistance
- data analysis
- experimental design
- other (please specify)

8. What technical limitations related to imaging technologies do you currently experience?

Please rank the limitations in terms of their importance.

- spatial resolution
- time resolution
- sensitivity (signal to noise)
- data analysis
- information mining

If there are other significant technical limitations not listed above that you experience, please include them here and assign a rank using the scale.

9. **What are the key computational platforms/software tools that you currently use to support research in imaging?**

Please give details of the limitations of current tools and specify the nature of these tools in terms of whether they are licensed e.g. open source/commercial/licensed/no licence.

10. **Do you currently collaborate with researchers outside your broad research field to develop new imaging methods (e.g. mathematicians, physicists, chemists, computer scientists)?**

Please provide brief details of the collaboration(s), how it was established and what it enables that you could not otherwise achieve

11. **Are you a technology developer?**

How do you engage end users in the technology development pipeline?

12. **Do you have any current or recent collaboration(s) in imaging or development of imaging technology with industrial partners e.g. beta testing?**

Please provide brief details of the collaboration(s); including the industrial partner, role of the collaborator, purpose of collaboration, and length of the collaboration.

13. **What have been the major developments in imaging that have impacted your research, particularly in the last five years?**

Horizon scanning

These questions are designed to identify research challenges, emerging trends and future needs within the imaging community.

14. **What do you consider will be the potentially important developments in imaging tools and methods and how do you see them developing in the next five to ten years?**

15. **What tools are needed to underpin the image analysis of the future?**

16. **Looking across BBSRC's remit and strategic priorities, what scientific breakthroughs could be enabled by emerging developments in imaging technologies? What grand challenges should the bioscience imaging community aim to tackle?**

17. **What do you consider to be examples of successful models of enabling access to and community sharing of imaging resources, both within the UK and overseas?**

Please comment on types of resource (e.g. equipment, software, data storage, technical support) and different modalities and ranges of scale (e.g. lab, departmental, university, consortia, regional, national, international).

18. **How could the bioimaging research community respond to address industry requirements and wider societal drivers in the future?**

Final Comments

19. **We would welcome any other comments you have that we should take into consideration for the BBSRC Review of Bioimaging.**

20. **Would you be willing to be contacted again regarding the review?**

Acknowledgments

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Biotechnology and Biological Sciences Research Council
Polaris House
North Star Avenue
Swindon
SN2 1UH
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