TURKU BIOIMAGING

{ More than you can imagine }

PREFACE

The iconic Turku BioImaging “Black Book” is back in this fourth edition!

Turku BioImaging (TBI) is an umbrella organization for “all things imaging” on the Turku campus in Finland. TBI covers the whole spectrum of imaging, from nanoscale and cellular imaging to small animal and medical imaging - “from atoms to anatomy”. TBI also has a central role in coordinating imaging across Finland.

Imaging is the most used methodology in life science research. This book gives an overview of the imaging technologies and services available in Turku for scientists. Included are technology overviews, contact information, and information on TBI educational and image analysis services.

The services presented are available to any scientist, local or external, academic or industrial, based on open access principles. This book also presents the imaging infrastructures that provide this open access in practice.

We hope you enjoy this little exploration into the fantastic world of imaging!

Turku BioImaging Operations Team in 2023, from left: Junel Solis, Jiri Funda, Dado Tokic, Anna Jalo, Pasi Kankaanpää, Irina Belaia.

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1. INTRODUCTION TO TURKU BIOIMAGING

Turku BioImaging is the "home" of imaging

Turku BioImaging (TBI) is an interdisciplinary science and infrastructure organization that develops and manages imaging in Turku and Finland. TBI unites imaging expertise from biology and medicine and from academia and industry.

TBI was established in 2007 and formalized into a concrete organization of the University of Turku and Åbo Akademi University in 2019. TBI is independent, allowing it to support imaging broadly across the campus and different infrastructures.

https://www.bioimaging.fi/

What does Turku BioImaging do?

Imaging coordination and funding. Locally, TBI coordinates collaboration of different imaging service providers. Nationally, TBI coordinates Turku activities in Biocenter Finland BioImaging (chapter 5) and holds its vice-chairmanship. Internationally, TBI leads Euro-BioImaging Finland (chapter 5), the European service organization in Finland consisting of the top imaging facilities from 6 universities and 3 university hospitals. TBI also works closely with the international headquarters of Euro-BioImaging ERIC. Together, these different levels of coordination form a synergistic landscape of imaging in Finland, where

different facilities have non-overlapping areas of specialization. This coordination is critically required for funding to be obtained for imaging in Turku and Finland. TBI coordinates the most significant imaging funding proposals in Finland. To Turku, TBI has in recent years brought in approximately 9 000 000€ for microscopes and other imaging instruments, staff salaries and service development.

Image data services. Image data management and re-use, and image data processing and analysis with both conventional and deep-learning tools, have been ranked as perhaps the most significant area of modern bioimaging. This is also an area that effectively links together biological and medical imaging. This is one of the key areas of operation of TBI. TBI provides open access image analysis, consultation and training services and maintains specialized servers for image data (chapter 2). TBI also works actively with companies in Turku and elsewhere to provide and develop image data solutions that bridge academia and industry.

Imaging education and events. TBI established the Turku international MSc Programme in Biomedical Imaging (chapter 3), and coordinates much of its activities and related national and international collaboration, as well as takes care of some of the teaching duties in the program. In addition, TBI arranges several one-off imaging courses every year for instance in the area of image analysis, as well as arranges bigger imaging events, such as the European Light Microscopy Initiative congress in Turku in 2022. TBI also develops Ocul-AR, a smart phone app for learning and teaching microscopy, based on augmented reality.

Research program in imaging. TBI directs Field of View, a new research program in Turku focused on how imaging can be applied to obtain meaningful discoveries in biology and medicine (chapter 6). Field of View brings together expertise from different areas of imaging, promotes image data solutions, and connects researchers and students.

Associated imaging facilities. TBI-associated imaging facilities provide open access services to imaging technologies, ranging from molecular and cellular imaging and high content analysis to whole animal and human imaging (chapter 4). All technologies listed in this book (chapters 8 – 13) are available in Turku.

Why is Turku BioImaging needed?

Turku is the imaging capital of Finland! Turku has a long history in imaging, including the development of Nobel-winning super-resolution microscopy and the establishment of Euro-BioImaging. Today, Turku houses the Euro-BioImaging headquarters, leads Euro-BioImaging Finland, runs a respected international MSc program in imaging, and has world-class operations in the newest area of imaging, image analysis and data management, including deep learning solutions. Imaging overall is the most widely needed methodology in life science, used by over 90% of researchers.

Turku BioImaging is needed to capitalize on Turku's unique position in imaging, and to maintain and develop the imaging services needed by Turku's life scientists. TBI enables open access for everyone to imaging instruments, education and training, and collaborative multi-disciplinary networks. Importantly, TBI itself provides open access services in the area of imaging that surveys show is among the most crucial, but where services are otherwise not available in Turku: image analysis and data management (chapter 13).

Most of the funding for imaging is granted only if imaging is carefully coordinated across Finland's various imaging organizations. TBI is the entity in Finland with the knowhow and experience to carry out this coordination.

Who are in Turku BioImaging?

Turku BioImaging consists of a **Management Team**, an **Operations Team**, a **Steering Committee**, and **associated facilities**.

The **Management Team** (see photos on the next page) leads TBI strategically. The **Operations Team** (see photo in Preface) coordinates operations and provides services in infrastructure development, education, image analysis and data management. The **associated facilities** are core facilities in Turku that operate in the area of imaging and provide open access services: Cell Imaging and Cytometry Core, Turku PET Centre, Medisiina Imaging Centre, Laboratory of Electron Microscopy, Scanning Electron Microscopy, Turku Screening Unit, and Turku Center for Disease Modeling. The Management and Operations Teams work together with the associated facilities and support them.

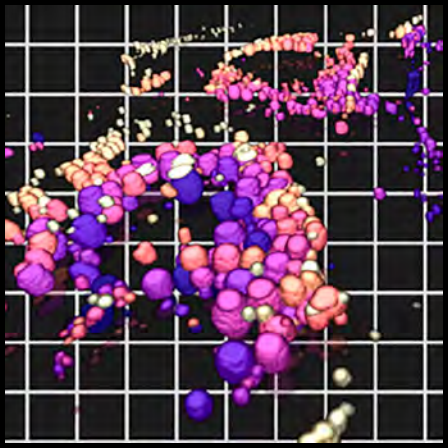
TBI is overseen by a broad-based **Steering Committee**, consisting of imaging experts across the campus.

All researchers, teachers, students, infrastructure specialists and others on the Turku campus that work with, study, or are interested in imaging form together the broader **TBI community**.

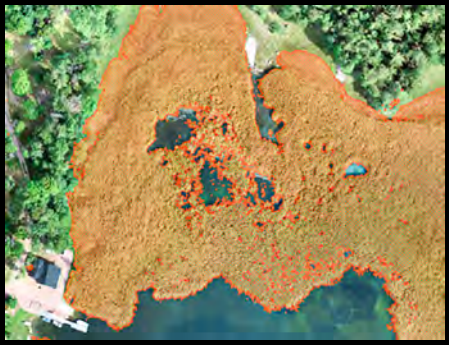
TBI's Management Team: **Pasi Kankaanpää**, *Head of Biological Imaging;* **Tiina Saanijoki**, *Head of Medical Imaging (on leave in 2023, substitute Jiri Funda);* **Guillaume Jacquemet**, *Chair of the TBI Steering Committee. The two heads, Kankaanpää and Saanijoki (Funda), lead TBI's Operations Team.*

Contact: tbi-office@bioimaging.fi

2. TURKU BIOIMAGING IMAGE DATA SERVICES



Lipid droplets inside a cell segmented using StarDist.



AI prediction of reed growth using drone images.

Turku BioImaging provides image data management, image analysis consultation and image-analysis-as-a-service to anyone looking to make the most of their image data. All services are open access to both academic and private sector users. TBI's image data services were established in April 2021 as part of the services of TBI's Operations Team.

TBI creates customized image analysis pipelines to ensure consistency and reliability of results. TBI specializes in the application of deep learning methods for complex image data, independent of its source. For example, TBI works with image data from different microscopes, medical imaging devices, cameras, and drones. TBI's image data services are part of the Euro-BioImaging services of the Finnish Advanced Microscopy Node, and through Euro-BioImaging funding is also frequently available for researchers to use TBI's image analysis services. TBI also has a special focus to develop image data analysis services for companies in the Turku region and beyond.

Image data services provided by Turku BioImaging include:

- Imaging experiment design and analysis consultation
- Image data management
- Processing and analysis as a service
- Use of artificial intelligence and deep learning when appropriate
- Two- and three-dimensional visualization and analysis
- Training in data management and image analysis

- **Dedicated open access service for image data analysis and management.**
- **Services range from collaborative development to full service.**

Contact: image-data@bioimaging.fi

More information: https://bioimaging.fi/image-data-team

3. MSC PROGRAMME IN BIOMEDICAL IMAGING

BIMA students during the Bioimaging and Microscopy course.

Master's Degree Programme in Biomedical Imaging (BIMA) is an international program jointly administered by University of Turku and Åbo Akademi University. The program is part of the Institute of Biomedicine at the University of Turku, and Cell Biology/Biosciences at Åbo Akademi University, thus formed around spearhead expertise areas in Turku. BIMA aims to train professionals that will have a thorough theoretical understanding of diverse imaging technologies along with practical skills in a wide range of imaging methods and applications.

Program strongholds

BIMA stands on the broad imaging strongholds in Turku and comprises a truly interdisciplinary array of prominent research groups and departments. The local collaborators are the national Turku PET Centre, Turku Bioscience Centre, Turku Center for Disease Modeling, Turku University Hospital, and Turku BioImaging. Additionally, BIMA has collaborators in the Nordic countries, Europe, and the USA. BIMA offers courses and internships with international experts. The interdisciplinary curriculum provides graduates with an excellent basis for careers in many different areas of life sciences, both in academic research and industry.

Content of BIMA

The curriculum consists of major subject studies and selectable studies such as fundamental and advanced microscopy, instrumentation, *in vivo* imaging, image analysis, multimedia presentation as well as lecture series and hands-on courses. BIMA provides students with good practical skills in imaging methods ranging from molecular and cellular to tissue and clinical imaging.

Who may apply and when?

Application opens annually in January and is intended for foreign and Finnish students with a lower university degree equivalent to a Finnish B.Sc. degree in life sciences or relevant areas of biomedical sciences, such as physics, chemistry, or engineering. All applicants must prove that they have adequate English skills according to the program requirements.

- **Two-year MSc program taught in English, 120 ECTS credits.**
- **Annual intake max. 20 students.**

Contact: bima-office@bioimaging.fi

More information:
https://www.bioimaging.fi/msc-in-biomedical-imaging/

4. TBI-ASSOCIATED IMAGING FACILITIES

Cell Imaging and Cytometry Core

The Cell Imaging and Cytometry (CIC) Core is a centralized imaging facility that offers support and instrumentation for both conventional and advanced light microscopy and flow cytometry, with additional capabilities for nanoscale imaging using techniques, such as super-resolution and atomic force microscopy. CIC is one of the core facilities of the Turku Bioscience Centre, a joint organization of Åbo Akademi University and the University of Turku. CIC serves approximately 200 users every year, with services open to both national and international academic and industrial users. In addition to state-of-the-art instrumentation, CIC offers theoretical and hands-on training, experiment design consultation and image analysis services.

https://bioscience.fi/services/cell-imaging

Turku PET Centre

Turku PET Centre employs short-lived positron emitting isotopes for a number of *in vivo* imaging techniques that are in high demand in clinical diagnostics and practice as well as in biomedical research. The center, which is a Finnish National Research Institute, provides high-end research, diagnostics, and clinical *in vivo* imaging services for the whole country. Currently, Turku PET Centre employs over 200 staff members and investigators with expertise in radionuclide production, radiochemistry, preclinical and clinical imaging, and research in various fields. Apart from PET tracer and drug discovery and development, image analysis and modelling, Turku PET Centre has research expertise especially in the fields of translational, cardiovascular and metabolic research, neuroscience, and oncology. The research modalities include tissue autoradiography, PET, PET/CT, PET/MRI and MRI

(3T) imaging and digital ultrasound. All research is performed in compliance with guidelines and quality requirements, e.g. EU directives and current GMP, GLP and GCP guidelines.

www.turkupetcentre.fi

Medisiina Imaging Centre

Medisiina Imaging Centre is a core facility which provides access to modern bioimaging instruments including microscope whole slide scanners, confocal and epifluorescence microscopes, laser capture microdissection and micro-CT. Medisiina Imaging Centre is one of the core facilities of the Institute of Biomedicine, Faculty of Medicine, University of Turku. The access to instrumentations of Medisiina Imaging Centre is open to both the academic and industry users.

https://www.utu.fi/en/university/faculty-of-medicine/institute-of-biomedicine/core-facilities/medisiina-imaging-centre

Laboratory of Electron Microscopy

Laboratory of Electron Microscopy (EM) is a core facility that offers full service for transmission electron microscopy (TEM) examination and data analysis. The laboratory of EM is one of the core facilities of the Institute of Biomedicine, Faculty of Medicine, University of Turku. The laboratory offers access to EM-related techniques including plastic embedding and ultrathin sectioning for conventional TEM, correlative light and electron microscopy (CLEM), immuno electron microscopy and electron tomography. In addition to providing access to state-of-the-art technologies, the facility offers services needed for specimen preparation, training in TEM operation and consultation related to EM experiments. The equipment and methods offered by the laboratory of EM apply to medical and biological research as well as in materials sciences and are open to both academic and industrial users.

https://www.utu.fi/en/university/faculty-of-medicine/institute-of-biomedicine/core-facilities/laboratory-of-electron-microscopy

Scanning Electron Microscopy

The Materials Research Infrastructure (MARI) at the Department of Physics and Astronomy, Faculty of Science, University of Turku provides access to advanced Scanning Electron Microscopy (SEM) imaging. SEM is used for high-resolution imaging to obtain compositional and elemental information of the sample surface or near-surface region. The facilities also include several sample preparation options, such as sputter coater for depositing thin metal or carbon films, plasma cleaner for surface activation and a broad ion beam mill for sample cross-sectioning or polishing. The access to instrumentations of MARI is open to both the scientific and the business community, including use in biosciences.

https://mari.utu.fi/en/equipment/sem/

Turku Center for Disease Modeling

Turku Center for Disease Modeling (TCDM) provides state-of-the-art imaging facilities and advanced animal models for disease modeling studies. TCDM offers access to MRI, PET, X-ray, ultrasound, and optical imaging supporting both academic and industrial-associated non-clinical research. TCDM is a research service organization at the Faculty of Medicine, University of Turku, and is part of the national Biocenter Finland Model Organisms and FinGMice networks.

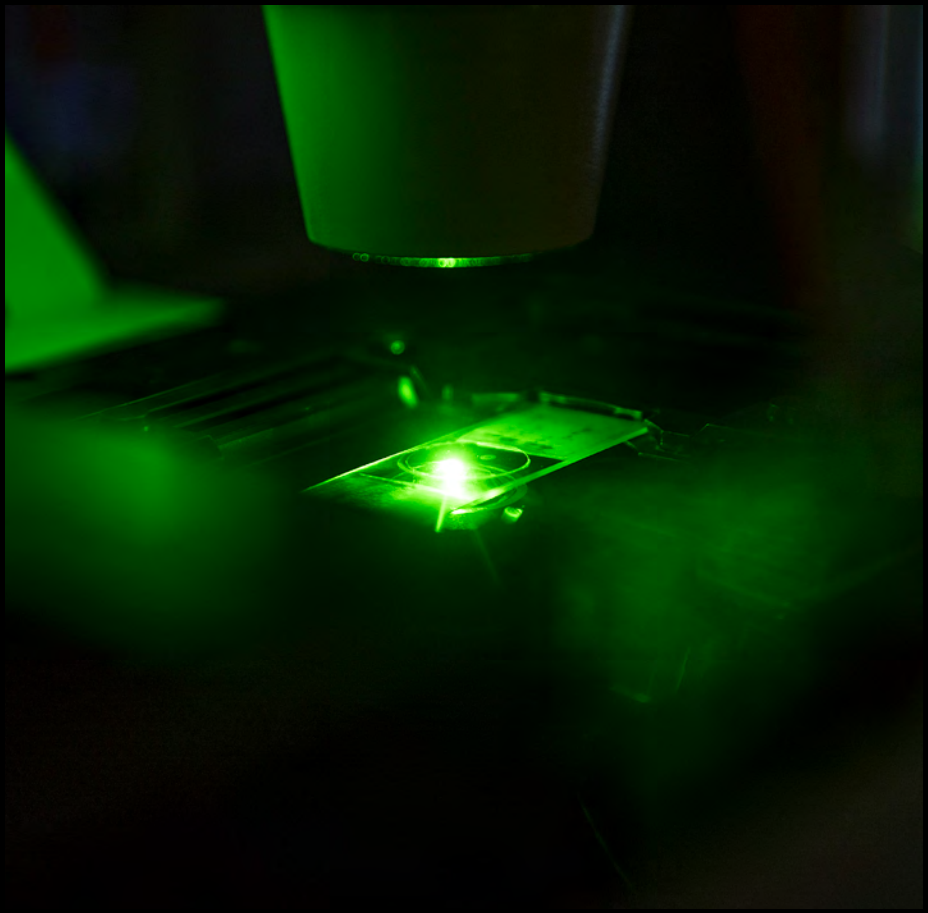
https://www.tcdm.fi/

Turku Screening Unit

The Turku Screening Unit provides services and expertise in optimizing conditions and automation routine experiments using acoustic dispensing and automated pipetting of reagents with High Throughput Imaging of cells, tissues and animal models, High-Content Screening in oncology and medicinal chemistry with virtual screening and wet-lab validation. The Turku Screening Unit is affiliated with four laboratories across the bioscience campus in Turku.

https://bioscience.fi/services/screening/services/

In addition, other affiliated facilities, such as Auria Biobank and the Turku University Hospital, offer supporting and related services.



Microscope, captured by C2 company.

5. IMAGING RESEARCH INFRASTRUCTURES

Open access to imaging technologies, services and training is provided by large multi-sited research infrastructures that operate both nationally and internationally. These infrastructures are carefully coordinated in Finland to enable synergies and to avoid overlaps. The infrastructures and their coordination are a major task of Turku BioImaging, and a requirement for continued funding for new imaging equipment and imaging facility staff salaries.

For most of the TBI-associated imaging facilities described in the previous chapter, being part of various research infrastructures is critical to enable their operations and development. Thus, without the national and international infrastructures, there would be hardly any facilities providing local imaging services in Turku. This is why it is also crucial for researchers to use and acknowledge the research infrastructures appropriately in their work.

The most central research infrastructures for imaging are *Euro-BioImaging* and *Biocenter Finland*, presented below, but also many other infrastructures are important for imaging and imaging-related services.

Biocenter Finland BioImaging

BF
Biocenter Finland

Biocenter Finland Biological Imaging Infrastructure (Biocenter Finland BioImaging, BF BioImaging), is a platform of Biocenter Finland that focuses on biological imaging service provision and collaboration in Finland. Biocenter Finland is a distributed national research infrastructure that provides open technology access for the

Finnish research community through 15 different platforms. Biocenter Finland consists of 5 Biocenters in 6 Finnish universities and it is on the national roadmap of research infrastructures.

BF BioImaging consists of 5 Nodes: Turku BioImaging, Helsinki BioImaging, Tampere BioImaging, Oulu BioImaging and Eastern-Finland BioImaging. Imaging facilities and their services from the participating Nodes that are considered suitable for national level access are part of BF BioImaging. These consist mainly of numerous technologies of advanced light and electron microscopy. BF BioImaging harmonizes access practicalities between units, and the platform also has several working groups that develop different aspects of imaging across Finland, such as quality management, education, image analysis and data management.

The chair of BF BioImaging is Eija Jokitalo from Helsinki BioImaging. TBI Head of Biological Imaging, Pasi Kankaanpää, is the vice chair of BF BioImaging and leads the Turku Node of the infrastructure. Of the Turku facilities, Cell Imaging and Cytometry Core, Laboratory of Electron Microscopy, Turku BioImaging Operations Team (image data services) and the Turku Screening Unit are associated with BF BioImaging.

https://www.biocenter.fi/technology-platform-services/biological-imaging

Euro-BioImaging ERIC

Euro-BioImaging ERIC (European Research Infrastructure Consortium) is a pan-European research infrastructure that provides open access to imaging technologies, training, and data services for both academic and industrial researchers. Euro-BioImaging ERIC was established by the European Commission in 2019, following years of preparatory work that in Finland was led by Turku BioImaging. Euro-BioImaging ERIC is hosted by Finland, and the “headquarters” (Hub) are located in Turku. Community-specific sections of the Euro-BioImaging Hub for biological and biomedical imaging are located at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany and in Torino, Italy, respectively.

Euro-BioImaging offers its services through a network of 35 Nodes spread across its 16 member states and EMBL. Altogether, the Nodes comprise more than 170 imaging facilities and offer access to more than 100 biological and biomedical imaging technologies. Euro-BioImaging is also the coordinator or a partner in numerous large EU projects that develop imaging and provide funding for researchers to access imaging services.

Euro-BioImaging ERIC is its own legal entity, and does not belong to any university, although it works closely with both universities in Turku and also rents offices and other services from them. The General Director of Euro-BioImaging ERIC is Prof. John Eriksson. The service-providing Nodes of Euro-BioImaging belong to their owner universities/organizations and are linked to Euro-BioImaging ERIC through Service Level Agreements.

www.eurobioimaging.eu

Euro-BioImaging Finland

Euro-BioImaging Finland is the Finnish service organization of Euro-BioImaging (see above). Euro-BioImaging Finland consists of two multi-sited Nodes: The Finnish Advanced Microscopy Node (FiAM) and the Finnish Biomedical Imaging Node (FiBI). Both Nodes offer academic and industrial researchers open access to biological and biomedical imaging technologies, services, and training. Euro-BioImaging Finland is led by Turku BioImaging, and it is on the national roadmap of research infrastructures.

Euro-BioImaging Finland is among the most popular service providers in Euro-BioImaging. It specializes in full service packages of 3D imaging that include image analysis and data management. The available services cover the full spectrum of imaging modalities from the molecular level to the organism level. Euro-BioImaging Finland comprises Finland's top imaging facilities from 6 universities and 3 university hospitals.

Euro-BioImaging Finland and its Nodes have an open access policy, which in practice means that any academic or industrial user is able to use the services of FiAM and FiBI. All services are open to local, national, and international users. The prices and reservation procedures are readily available online.

https://eurobioimaging.fi/

Finnish Advanced Microscopy Node of Euro-BioImaging

Finnish Advanced Microscopy Node (FIAM) is a multimodal and multi-sited research infrastructure. FiAM has been operational since 2016 and it specializes in providing biological imaging and microscopy technologies and services accessible in Helsinki, Turku, and Oulu.

FiAM's services include open access to state-of-the-art imaging technologies, including laser scanning and spinning disk confocal microscopy, super-resolution imaging (STED, STORM, and TIRF), live cell imaging, a vast array of electron microscopy methods (2D and 3D Electron Microscopy, Correlative Light and Electron Microscopy), mesoscopic imaging (SPIM and OPT), high-content imaging, image data analysis, as well as consultation, instrument user training, and image data management.

FiAM has three partners operating under the names Helsinki BioImaging (University of Helsinki), Turku BioImaging (University of Turku and Åbo Akademi University), and Oulu BioImaging (University of Oulu). These Node partners provide an impressive range of modern imaging and microscopy technologies and expertise, and in addition, they have their own unique imaging specializations. Of the Turku facilities, Cell Imaging and Cytometry Core and Turku BioImaging Operations Team (image data services) belong to FiAM. FiAM is led by Turku BioImaging.

https://eurobioimaging.fi/FiAM/

Finnish Biomedical Imaging Node of Euro-BioImaging

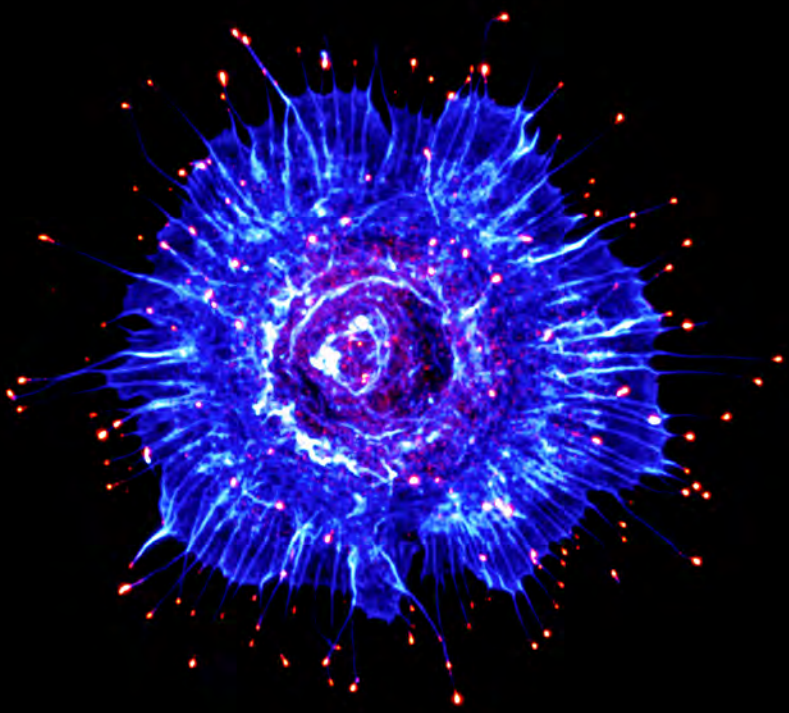
The Finnish Biomedical Imaging Node (FiBI) was accepted as part of Euro-BioImaging in 2020. FiBI comprises the four leading Finnish *in vivo* imaging facilities: Turku PET Centre, Kuopio Biomedical Imaging Unit, NEUROIMAGING Research

Infrastructure, and Helsinki *In vivo* Animal Imaging Platform.

FiBI specializes in a broad selection of advanced *in vivo* imaging technologies covering all major biomedical imaging modalities from mouse to man. The spearhead technologies include: 1) positron emission tomography (PET) imaging and PET tracer development, 2) preclinical high-field magnetic resonance imaging (MRI), 3) magnetoencephalography (MEG), and 4) preclinical optical imaging.

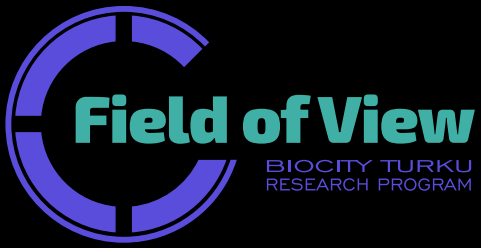
The research application areas entail key areas relevant to major public health threats, such as cardiovascular diseases and obesity, neurological diseases, cancer, infection, and inflammation. The key strength of FiBI is its versatile multimodal imaging platform for both animal and human studies, which enables real-time monitoring and the possibility of simultaneously acquiring molecular, functional, and anatomical information, and, importantly, clinical translation. FiBI is led by Turku PET Centre/TBI.

https://eurobioimaging.fi/FiBI/



The rose by Monika Vaitkevičiūtė.

6. FIELD OF VIEW RESEARCH PROGRAM



Field of View is a new research program of BioCity Turku, the Turku umbrella for life sciences that funds several research programs focused on various research topics. Field of View, established in 2022, focuses on how imaging can be used to make meaningful discoveries in biology and medicine. The key aims of Field of View are to bring together expertise from different areas of imaging, promote novel image data management and analysis solutions, and connect researchers and students to foster new ideas and collaborations. Field of View also aims to facilitate funding acquisition, develop imaging education, and broaden knowledge of imaging beyond academia.

The activities of Field of View include organizing an annual Turku Imaging Day from 2023 onwards, organizing regular group leader lunches and organizing various other imaging-related events and activities, such as special workshops. Field of View is also open to any suggestions from its member community, such as guest lectures or special workshops.

The directors of Field of View are the heads of Turku BioImaging, Pasi Kankaanpää and Tiina Saanijoki (on leave in 2023 and replaced by Jiri Funda).

Anyone on the Turku campus working with imaging is welcome to join Field of View! Equally welcome are entire research groups and individual persons working with imaging, as researchers or technical staff. Field of View members currently comprise 24 research groups from both medicine and biology, and several individual members. Join Field of View here:

https://link.webropolsurveys.com/S/164BEE530FECC617

https://www.bioimaging.fi/field-of-view/

7. TBI FOR INDUSTRY

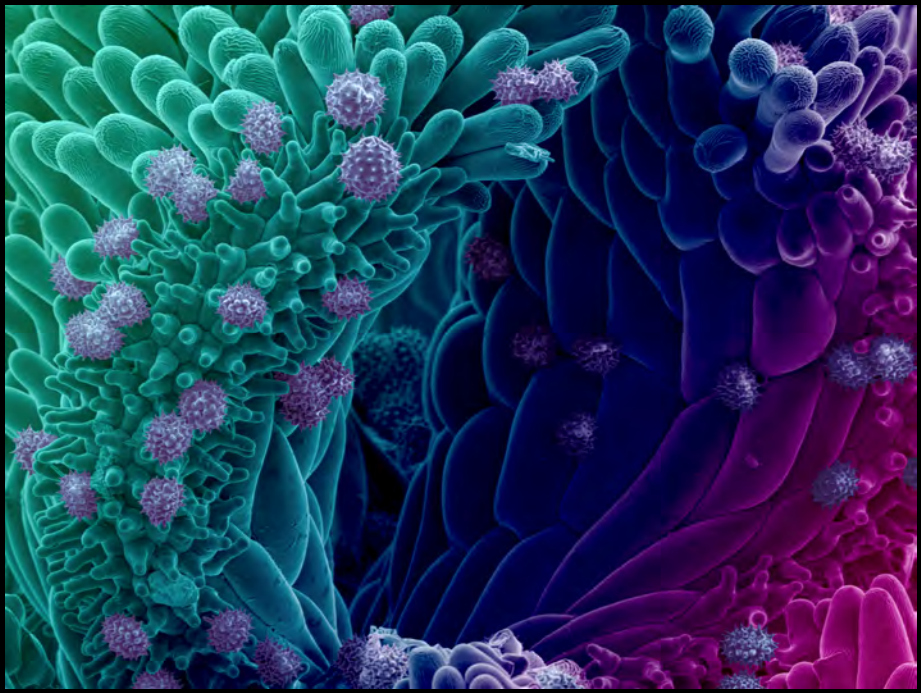
TBI engages in close collaboration with biotechnology, pharmaceutical, and life science industries particularly in the Turku region with the aim to strengthen the role of imaging and image data in R&D work of the business sector. Imaging expertise and support provided by TBI is of great benefit especially to small companies, which do not have the range and depth of resources in-house. In practice, TBI serves as a hub for expert advice, instrument access, training, image analysis, image data management, and optimal usage of image data. By utilizing modern image analysis and processing methods, such as deep learning and cloud computing, and by mining old image data for new information, companies can for example speed up their product development and quality management processes, pave the way for new innovations, and even renew their business. Typically, the industrial bioscience community uses TBI services with new methods and novel technologies to be rapidly tested, adopted, and developed further and, as such, TBI can accelerate the translation of industrial R&D activities into improved healthcare products and services.

Moreover, TBI strives for diverse interaction between bioimaging master's program students and the industry and aims to connect international imaging students with local companies from early on. Cultivating these ties builds up the imaging expertise in the companies over time, ensures companies' access to the brightest minds, and reinforces the transfer of knowledge and exchange of ideas that further strengthens the local innovation ecosystem.

How does it work?

If you have any questions or queries, TBI is always happy to help. Feel free to contact us through TERTTU collaboration platform

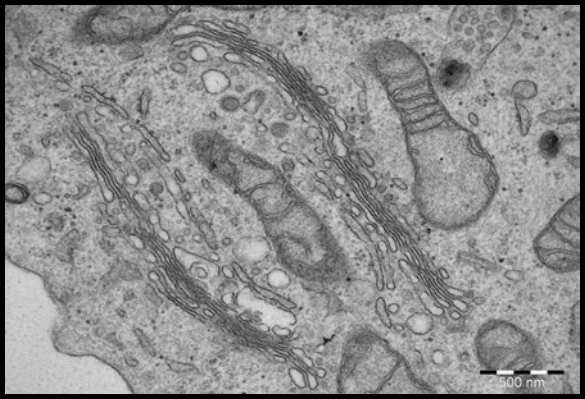
(https://innovations.healthcampusturku.fi/) or by email (tbi-office@bioimaging.fi) and we will be sure to get back to you as soon as possible.



Pollen, captured by Daniel Gütl.

8. NANOSCALE IMAGING

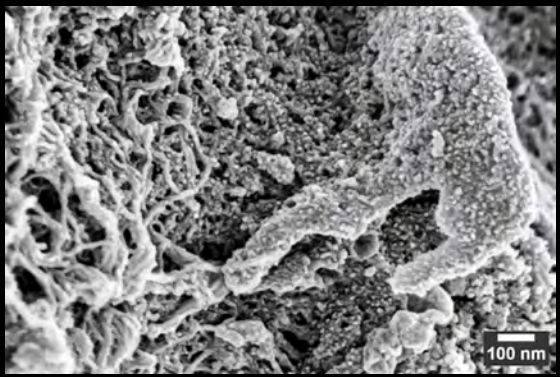
Electron microscopy



TEM image of a cultured cell prepared by conventional plastic embedding and thin sectioning protocol.

What is it for?

Electron microscopy is the method of choice if detailed structural information at nanometer resolution is required from samples of cells, tissues, nanoparticles, viruses, bacteria, macromolecules, and other related materials. The Laboratory of Electron Microscopy at the Institute of Biomedicine, University of Turku, is a core facility that provides electron microscopy and sample preparation services. Available techniques include conventional transmission electron microscopy (TEM),



Secondary electron micrograph of actin fibers and lamellipodia.

immuno electron microscopy, correlative light and electron microscopy (CLEM) and electron tomography. Scanning electron microscopy (SEM) is available at the Material Research Infrastructure (MARI), Department of Physics and Astronomy, University of Turku.

How does it work?

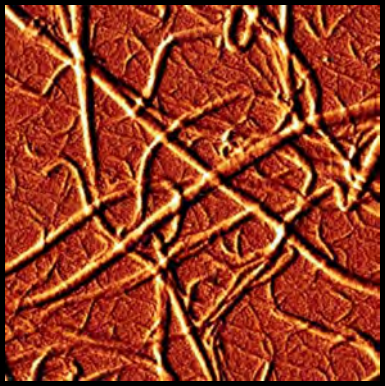
Electron microscopy uses an electron beam to visualize the sample. Use of electrons, instead of photons, allows imaging at nanometer resolution. TEM visualizes the interactions of electrons transmitted through an ultrathin (60-100 nm) section of a specimen. In SEM, a focused electron beam is scanned over the sample surface and an image is derived from secondary or backscattered electrons emitted from the specimen, allowing the imaging of more arbitrarily shaped samples. For conventional TEM, biological samples must usually be fixed with aldehyde, dehydrated, and embedded in epoxy or another appropriate resin before being cut into thin sections. In addition, cellular components need to be stained with heavy metals for a reasonable contrast. For conventional SEM, samples are dehydrated and often coated with a thin layer of conductive material, such as gold or carbon. However, in suitable conditions, non-coated and insulating samples can also be imaged with

SEM. Macromolecules or nanoparticles can be imaged with or without fixation and staining depending on the sample type.

Contact: sem@utu.fi

- **High resolution imaging for a wide range of samples.**
- **Special techniques available for localization of antigens, correlative microscopy and 3D imaging.**

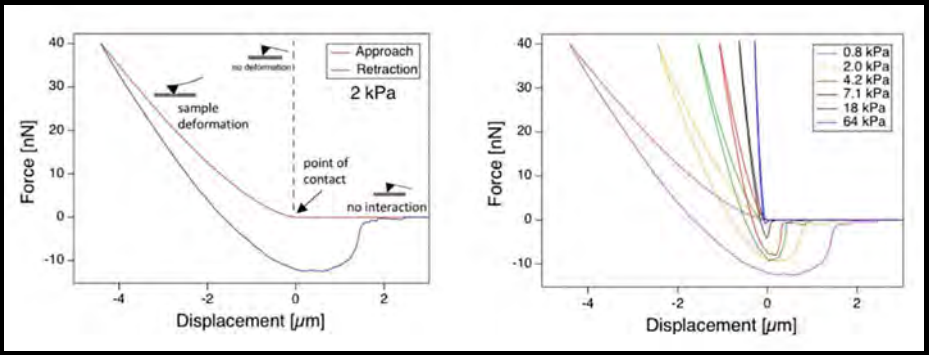
Atomic force microscopy



Collagen fibrils imaged with AFM.

What is it for?

Atomic Force Microscopy (AFM) is primarily used to image surface topography. With functionalized probes, it can also be used to measure specific binding forces between molecules such as receptors and ligands, or between cells and a substrate. AFM imaging is suitable when the resolution of optical microscopy is not sufficient, when a sample needs to be imaged under native physiological conditions, or when the type of sample preparation required for electron microscopy is not possible. In addition, AFM can be used to manipulate objects, e.g. to study the effects of specific mechanical stimuli on cells.



Nanoindentation curves: (Left) Approach and retraction curves showing the points of contact. (Right) Multiple approach curves on substrates of different stiffness.

AFM is also used to test the mechanical properties of the sample in a process called force spectroscopy. With this process, it is possible for instance to test binding forces between proteins or cells, or to perform indentation on a sample and obtain its Young's modulus as a measure of the sample stiffness. In biology, AFM can be performed thanks to the introduction of a liquid cell that allows working on many samples that require a liquid media and even on living cells.

How does it work?

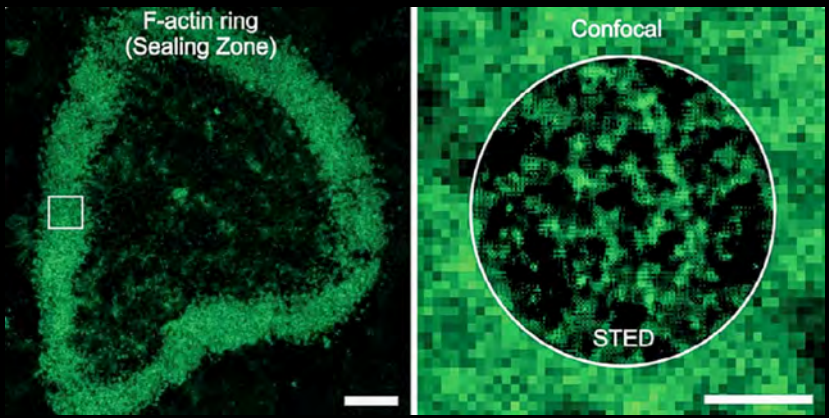
AFM is a type of scanning probe microscopy technique, in which a sharp tip on a flexible spring-like cantilever mechanically scans over a specimen's surface and senses the forces between the tip and the surface. Such forces cause the cantilever to bend, and the deflection is measured using a laser beam reflected from the cantilever. The AFM can be operated in liquid and under physiological conditions, making it possible to study living biological

specimens. The technique is label-free, making sample preparation straightforward. Biological AFM is often coupled to optical microscopy.

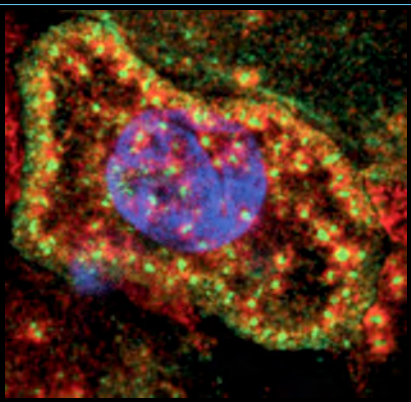
Contact: microscopy@bioscience.fi

- **Mechanical probing can be used for visualizing the topography of a surface, its mechanical properties and biological affinity.**
- **Possible to image biological samples in liquid with nanometer resolution.**

STED microscopy



A thick actin ring specific to bone-resorbing osteoclasts is expressed (left). Zoomed-in STED image reveals interconnected F-actin mesh-like structures, which are not visible in a confocal image. Scale 10 µm (left) and 1 µm (right).



F-actin (green), vinculin (red), and nucleus (blue) are shown in human osteoclasts cultured on a glass surface. At STED resolution, structures of vinculin surrounding F-actin podosomes are revealed.

What is it for?

Stimulated Emission Depletion (STED) microscopes provide improved optical resolution (super-resolution) and are the instrument of choice when the resolution of normal confocal microscopy is insufficient and electron microscopy is not suitable. Compared with conventional confocal microscopy, STED microscopy provides a 3 – 10 fold improvement in resolution, going down to 30 nm in lateral (x-y) resolution using the 2D-STED mode and down to 75 nm in axial resolution (z-resolution) when using the 3D-STED mode. A STED instrument can be used in a similar manner to a confocal fluorescence microscope, and thus can provide non-invasive imaging of (living) specimens in three dimensions (3D).

How does it work?

STED microscopy is a type of confocal fluorescence microscopy. Compared with the diffraction-limited resolution by conventional wide field and confocal fluorescence microscopes (180 – 300 nm), STED can provide a resolution beyond the limit, down to 30 nm in biological samples. In STED microscopy, a doughnut-shaped high-power laser, called a STED beam, is overlaid on an excitation laser spot. Under the doughnut, spontaneous fluorescence

emission is suppressed, and the size of an effective emission spot is reduced. This is how the resolution is improved in STED microscopy. In the case of 3D-STED the depletion laser includes one extra beam shaper that creates the necessary vertical polarization for the laser to deplete the excitation laser above and below its focal point.

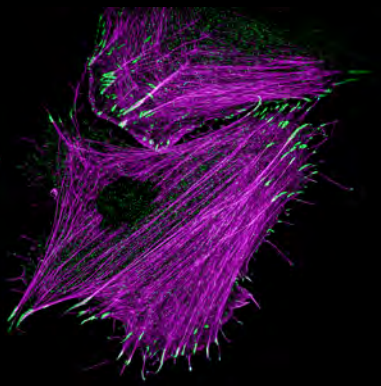
- **Super-resolution technique for specimens stained fluorescently with high density of labelling fluorophores.**
- **Based on the stimulated emission depletion-phenomenon.**

Contact: microscopy@bioscience.fi

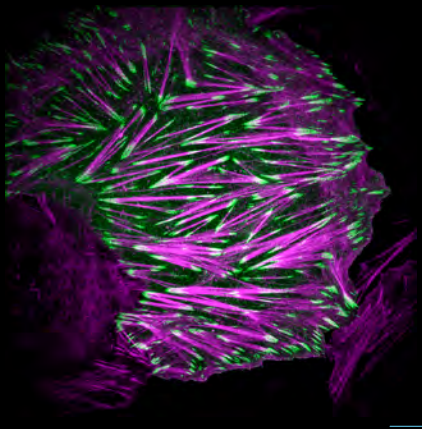
Structured illumination microscopy

What is it for?

Structured illumination microscopy (SIM) is a super-resolution method that doubles the spatial resolution in all three dimensions. Therefore, using SIM, it is possible to resolve structures spaced at approximately 100 nm. SIM is generally easy to use, suitable for a wide variety of biological samples and is compatible with most fluorophores with the conditions that they are relatively resistant to photobleaching and non-blinking. The SIM microscope in Turku is based on a widefield microscope, and its performance is strongly affected by sample thickness and out-of-focus light. It is, therefore, best to avoid samples thicker than 20 µm with this technique. As SIM is compatible with most fluorophores, four color channels can be accommodated. However, an optimal resolution requires precise tuning of the oil refractive index that can be different for distinct channels. SIM is commonly used for live cell imaging. That said, 3D SIM often requires the acquisition of hundreds of images per time point (depending on the volume imaged) and can be phototoxic. Careful optimization of the acquisition parameters is often required when using SIM on live samples.



Cancer cell stained to visualize its focal adhesions (green), its actin cytoskeleton (magenta) and filopodia tips (cyan) was imaged using structured illumination microscopy.



Cancer cells stained to visualize their focal adhesions (green), and their actin cytoskeleton (magenta) were imaged using structured illumination microscopy.

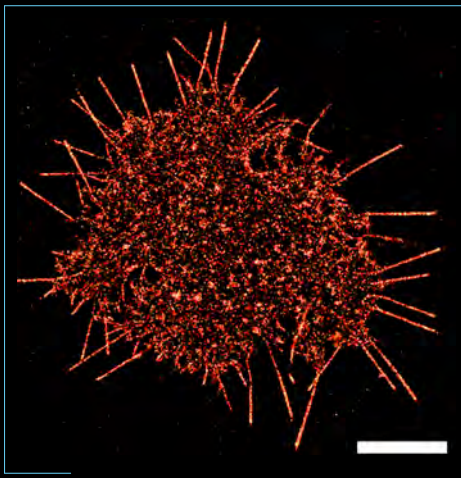
How does it work?

When using SIM, the sample is illuminated using a patterned light. In the Turku setup, 15 images per plane are taken using a different pattern for each focus plane and are then combined by a computer algorithm to reconstruct a 3D super-resolved image. The Turku SIM microscope uses parallel lines generated using a grid that shifts (5 shifts) and rotates (3 rotations).

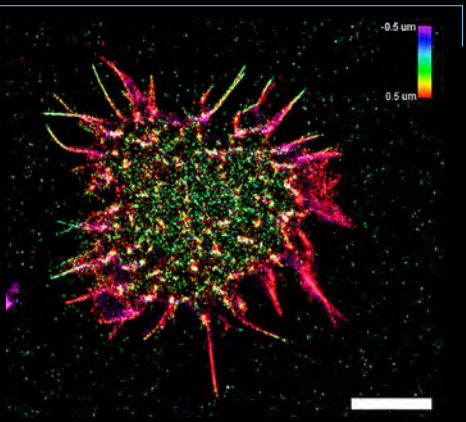
- **Around 100 nm resolution in X, Y, and Z.**
- **Easy to use, suitable for a wide variety of biological samples and is compatible with most fluorophores.**

Contact: microscopy@bioscience.fi

Single molecule localization microscopy



2D dSTORM image of activated B-cell stained for F-actin with Alexa Fluor 647 – phalloidin.



3D dSTORM image of activated B-cell stained for F-actin with Alexa Fluor 647 – phalloidin. Scale bars = 5 µm. Images were acquired in TIRF imaging mode by Thomy Garnier on an ONI Nanoimager that is available for use at the CIC.

What is it for?

Single Molecule Localization Microscopy (SMLM) is a super-resolution microscopy technique that can be used to answer questions related to the molecular organization at a spatial resolution below the classical diffraction-limit of light of ≈200 nm in the lateral direction and ≈600nm in the axial direction.

How does it work?

SMLM relies on the stochastic switching of fluorescent molecules between a dark non-fluorescent OFF state, and a bright fluorescent ON state. In the limit where only a few sparsely located molecules are in the bright fluorescent ON state, it is possible to determine the centroid location of each of these single molecules. By combining centroids of molecules from repeated acquisition of several thousands of images, it is possible to reconstruct a single super-resolution image. Using SMLM, a lateral spatial resolution of ≈50 nm can routinely be achieved, while further improvements down to ≈10 nm is possible following extensive optimization with sample labelling, imaging, and data analysis. It is also possible to improve the axial resolution, down to about 50 nm, by e.g. distortion of the shape of the point spread function in the z-direction.

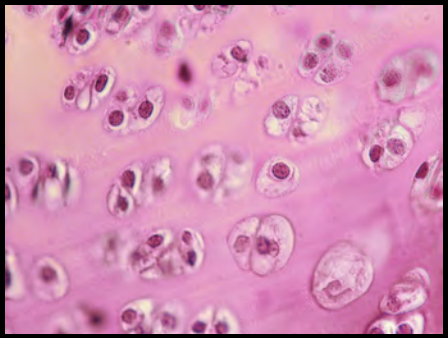
In practice, SMLM is often performed in a TIRF imaging mode although widefield imaging is also possible but at the expense of lower signal-to-noise ratio. SMLM can be performed using fluorescent proteins and dyes in combination with specialized imaging buffers that are designed to stabilize the dark OFF state, by minimizing irreversible photo-bleaching, while also maximizing the number of photons that are emitted in the ON state. A favored specimen for SMLM is fixed cells which have been specifically labeled for a molecule of interest with the fluorescent dye Alexa Fluor 647, and imaged in TIRF mode in an aqueous imaging buffer that combines oxygen scavenging, e.g. a pH buffered solution that combines glucose, and the enzymes glucose oxidase and catalase, with a reducing agent such as β-mercaptoethanol.

- **Established super-resolution imaging technique that is readily available on dedicated ONI Nanoimager microscope at the CIC.**
- **Primarily compatible with imaging of fixed samples.**

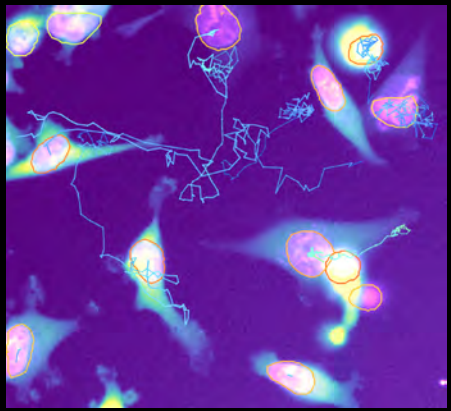
Contact: microscopy@bioscience.fi

9. CELLULAR IMAGING

Widefield microscopy



Widefield microscopy image of mouse cartilage tissue, showing chondrocytes embedded in specialized extracellular matrix. Hematoxylin and Eosin staining.



Invasive breast cancer cells migrating. The migration has been quantified using a tracking plugin TrackMate in Fiji.

What is it for?

Widefield microscopy is an imaging technique where the whole sample is simultaneously illuminated with transmitted light or a light of a specific wavelength. The transmitted or emitted light is then visualized through the eyepiece or captured

by a camera, creating a 2D representation of the sample. Widefield microscopy is usually used for the identification and visualization of cells, cell morphology and behavior, proteins and cell components. The most common samples for widefield microscopy are fixed cells or tissue sections that either express fluorescent reporters or have been labeled post-fixation, autofluorescent and histologically stained samples. It is also possible to perform multiwell screening or live-cell imaging experiments using a widefield microscope if temperature, oxygen controls and automated stage controls are available. One major limitation in this technique is that light also from above and below the focal plane is included in the final image causing image degradation and a decrease in the signal-to-noise ratio. When imaging with transmitted light, additional contrasting methods, such as differential interference contrast (DIC), Hoffman modulation contrast (HMC) and phase-contrast can be used to improve image quality.

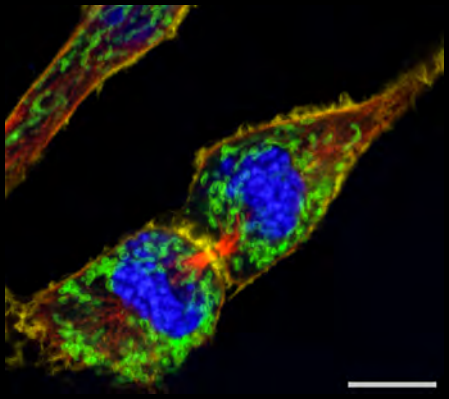
How does it work?

In widefield microscopy, the whole field of view in the sample is illuminated simultaneously. The source of light is usually a mercury lamp producing high intensity light with a broad spectrum of wavelengths. In fluorescence microscopy, optical filters are used in order to select the wavelength of excitation light that is directed to the sample via a dichroic mirror. The fluorescent light is usually detected with a CCD camera or by eye. Multi-color images of several types of fluorophores can be composed by combining several single-color images or by using dual filter blocks. In brightfield microscopy, transmitted light can be simultaneously detected by attaching a black and white (b/w) or a color camera. Fluorescence and brightfield images can then be overlaid.

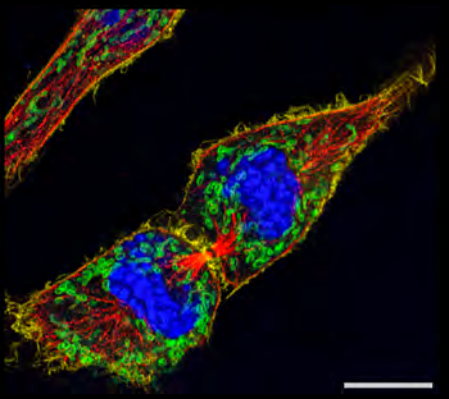
- **Optical microscope for fluorescent and brightfield imaging.**
- **Ideal to study fixed and living cells, or thin tissue samples.**

Contact: microscopy@bioscience.fi

Laser scanning confocal microscopy



Conventional confocal image, with a pin-hole size of 1.25 Airy units, of fixed HeLa cells stained for DAPI (blue), Tyrosinated a-Tubulin (red), Tom20 (green), and F-actin with Rhodamine-Phalloidin (yellow).



Airyscan Super-Resolution (SR) image of same cells. Scale bars = 10 µm. Images acquired on a Zeiss 880 laser scanning confocal microscope that includes an Airyscan detector and which is available for use at the CIC.

What is it for?

Laser Scanning Confocal Microscopy (LSCM) is a commonly used technique to study the 3D distribution of bio-components in fixed, and live cells and tissues.

Four color imaging is standard while more colors require careful calibrations with single color control samples.

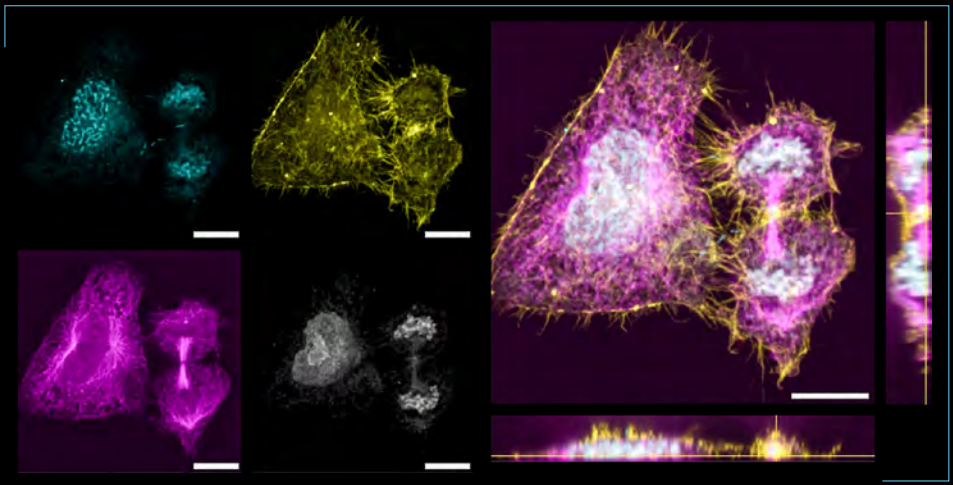
How does it work?

LSCM implements an adjustable pinhole that is placed in a conjugate optical plane in front of a single point photo-detector. Image formation in LSCM consists of raster point-by-point scanning with a pair of high-speed mirrors that scan a focused laser beam across the specimen along the x and y-axes, respectively. This makes it possible to collect sharp optical sections that contain only the fluorescence signal that is emitted from the focal plane, where point scanning of the specimen in several focal planes combines to form a 3D-image stack. The traditional compromise in LSCM for ensuring image sharpness, while also retaining a good signal-to-noise ratio, is to adjust the size of the pinhole to ≈1 Airy Unit (AU). In contrast, in the limit of imaging with a larger pinhole setting, the image quality approaches that of a wide-field image that combines in-focus and out-of-focus signal. For optimum imaging, it is also important to adjust the projected pixel size to satisfy the Nyquist sampling criteria such that the size is ≈3x smaller than the lateral resolution of the imaging conditions (i.e. accounting for the NA of objective, and λ of excitation). A caveat of LSCM, however, is that while image quality is excellent, image acquisition speed can be quite slow as a consequence of the raster point-by-point scanning approach. Confocal imaging on the Airyscan detector combines classical point scanning with a 32-channel hexagonally packed array detector, pixel-reassignment, and deconvolution. The Airyscan detector enables imaging with either ≈1.7x improved spatial resolution (Airyscan SR mode), or 4x faster imaging (Airyscan FAST mode) than by conventional LSCM.

- **Instrument for accurate and optimized 3D and 4D imaging.**
- **The Airyscan detector enables confocal imaging with either improved resolution, or speed.**

Contact: microscopy@bioscience.fi

Spinning disk confocal microscopy



Spinning disc confocal image set of fixed HeLa cells stained for DAPI (cyan), F-actin with Alexa Fluor 488-Phalloidin (yellow), Tyrosinated α-Tubulin (magenta), and Ki-67 (white). Shown are single color images from a single z-plane, and super-imposed 4-colur images in a single z plane (front view), and z-projected images (side view) showing respectively the xz and yz planes. Scale bars = 10 µm.

What is it for?

Spinning disk confocal microscope (SDCM) is a fast confocal microscope that combines laser excitation with high sensitivity camera detection. SDCM offers high imaging speed (up to 200 frames/s) with low phototoxic effects, which is ideal for live-cell imaging. The system is also a practical tool for all cell biology experiments, where

fast single, or multi-color 3D imaging is needed: multi-positions, tile imaging, optical sections of thick samples, etc.

How does it work?

SDCM is based on a microlens enhanced dual Nipkow disc scanner unit that consists of two simultaneously spinning disks, 1) a disk with thousands of microlenses, and 2) a disk with thousands of small pinholes, with a typical fixed diameter of 50 µm. These disks are perfectly aligned and rotate in unison. Collectively these disks produce thousands of excitation beams that are swept across the specimen as the disk spins. Thus, a whole field of view is illuminated very fast. The resulting emission signal from the sample is transmitted through the spinning disc that contains the pinholes and onto a high sensitivity camera. In this context, cameras gain several benefits to other photodetectors: high signal-to-noise ratio, high sensitivity (high quantum efficiency), wide detection spectrum and fast image capture of a full frame with a high resolution. While SDCM are excellent for fast, high-sensitivity, and gentle confocal imaging applications, it is important to appreciate that the fixed size of the pinholes (50 µm) is designed to match the requirements for confocal imaging with 1 AU pinhole setting with a 100X 1.40 NA oil objective. When using a SDCM for imaging with a lower magnification (and lower NA objective), this pinhole size is too large to enable 1 AU equivalent confocal imaging such that the lower the magnification (and the NA), the closer the image approaches the equivalent of a standard widefield image.

- **Fast 3D and 4D multi-color confocal imaging with excellent image quality.**
- **Photo-manipulation available.**

Contact: microscopy@bioscience.fi

Total internal reflection fluorescence microscopy

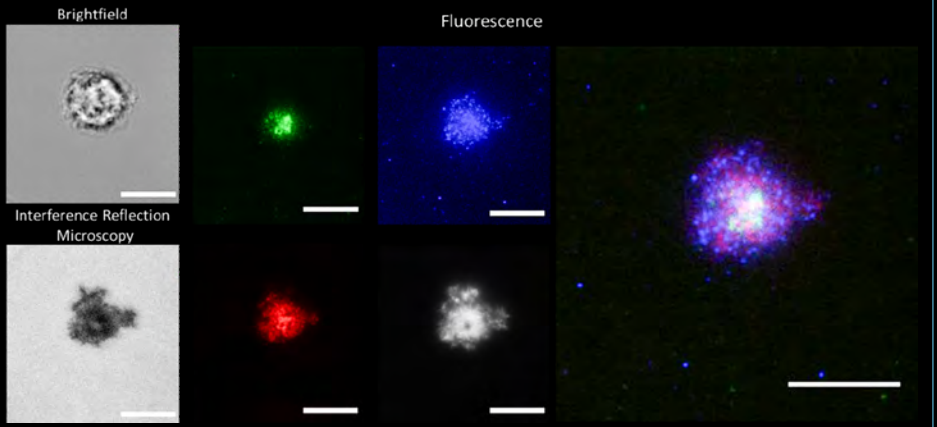


Image 1 legend: Multi-modal imaging of T-cell immunological synapse combining brightfield imaging, interference reflection microscopy, and four color TIRF imaging. Scale bars = 10 µm.

What is it for?

Total Internal Reflection Fluorescence Microscope (TIRFM) is a tool to image structures and molecular events at the cell membrane with a high axial resolution - usually less than 200 nm. Typical applications are focal adhesions, ligand binding, and endosomal trafficking studies of fixed and live cell samples. With the photomanipulation module, TIRFM can applied to study molecular dynamics. An

essential feature of TIRF imaging is a very high signal-to-noise ratio, which makes TIRF ideal for fast live cell imaging and single-molecule applications albeit with a requirement that the studied biology occurs at or very near the basal membrane.

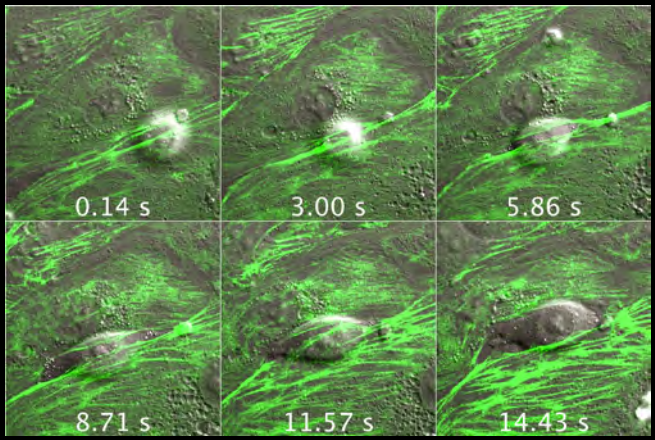
How does it work?

In a TIRF microscope, an excitation laser is directed to a sample from a specific angle, so that instead of penetrating the sample, the laser beam exhibits a total reflection at the interface of a cover glass and sample medium. This is possible only in the case of high NA objectives (NA>1.45) and a sufficient difference in refractive indices of the two materials at the interface (i.e. cover glass/water). Although the laser beam is fully reflected at the cover glass-sample interface, a small proportion of the light travels parallel along the cover glass, which creates an electromagnetic phenomenon called an evanescent field in a very restricted volume in aqueous imaging medium. The evanescent field intensity decays exponentially with its penetration distance from the interface, and only the fluorophores near the cover-glass are excited resulting in a z-resolution of 70-300 nm. The later resolution of TIRFM is equal to common widefield and confocal microscopes, but powerful setups can be utilized also for localization-based super-resolution methods, such as PALM, dSTORM and DNA-PAINT, which can enhance resolution up to 10-20nm in XY.

- **High axial resolution at cell membrane facing the cover-glass (70-300nm).**
- **Enables fast single-molecule imaging and localization-based super-resolution methods.**

Contact: microscopy@bioscience.fi

Live cell imaging



Invasive breast cancer cells pushing between two endothelial cells (green) during intravasation. DIC contrasting was used for the transmitted light. Image was captured with Nikon A1 confocal microscope.

What is it for?

Live-cell microscopy is a versatile group of techniques allowing imaging of a living specimen. Live-cell imaging is a preferred technique when the research question requires information about different phases of the cell life span rather than endpoint information. Applications where live-cell imaging is necessary, can be for example studies of cellular behavior and processes, such as cell migration, endocytosis, apoptosis, and cell division. With modern techniques such as fluorescence recovery after photobleaching (FRAP), fluorescence loss in photobleaching (FLIP), Förster resonance energy transfer (FRET) or photoactivation, it is possible to study fluorescent protein behavior, for example protein diffusion and translocations, within a cell. Additionally, effects of abnormal conditions, such as hypoxia or high or low temperatures can also be studied.

IncuCyte instrument inside an incubator, specifically designed for long term live cell imaging experiments.

How does it work?

Living cells are very sensitive to their surrounding environments, and if the conditions are not optimal, the cells' biological functions can be inhibited, or a cell can even become apoptotic. Therefore, strict control of the environmental factors is crucial for successful live-cell imaging experiments. The primary requirement for live-cell imaging is the establishment of suitable conditions for the cells (CO_2 level, humidity, and temperature) to protect normal cell function during image acquisition. Additionally, cells should be grown in a suitable dish for live-cell imaging. Cell culture media should preferably not contain a pH indicator and, if the used instrument does not have a CO_2 controller, it should be CO_2 buffered. All conditions from the concentration of fluorescent reporters in the cell, exposure times and frame rates should be properly optimized for each experiment to minimize phototoxicity. Live-cell imaging is always a compromise between achieving the best image quality and preserving the health of the cell.

- **Live-cell imaging enables the study of dynamic processes in living cells.**
- **Living cells are sensitive to surrounding conditions and therefore experiments need careful planning.**

Contact: microscopy@bioscience.fi

Stereo microscopy with microinjection and Apotome

Mouse embryo imaged with Apotome structured illumination mode.

What is it for?

A stereo microscope is a tool for visualization of large samples with low magnifications. The optical system is stereoscopic: it provides three-dimensional visualization of the sample and accurate sense of axial distances. This feature is crucial e.g. in surgery, dissection and microinjection operations. The stereo microscope is suitable

for studying several kinds of samples, for example cell cultures, animal and plant tissues, whole plants, zebrafish, eggs (CAM model), insects, and cleared organs. The stereo microscope at CIC is equipped with a color camera and a sensitive grayscale CMOS camera for fluorescence imaging. It has two objectives with different working distances: 0.5x/0.125, WD 114mm and 1.0x/0.125, WD 56mm. These objectives offer a magnification range of 3.5x-112x. Microinjection can be done with a Drummond Scientific Nanoject II semi-automatic microinjection device or manual Eppendorf CellTram Vario injector, permitting microinjection of any material into various samples. The most frequently injected materials are DNA, proteins, tracers, and chemicals with or without attached dyes. Furthermore, the microscope has the Apotome to perform optical sectioning of thick samples.

How does it work?

Stereo microscopes use two separate optical paths with two objectives and eyepieces to provide slightly different viewing angles to both eyes. This creates an exact three-dimensional visualization of the specimen. Naturally, the image acquisition has one light path for one camera, producing 2D images only. A 3D image can be constructed from an image set, when multiple image planes are captured through the specimen. A motorized stereo microscope can be easily used to collect 3D image stacks, but the scattered out-of-focus light cause strong background haze and blurriness to images, especially in case of thick samples. The Apotome is a method to cut the out-of-focus light and perform optical sectioning. The Apotome utilizes a grid based structured illumination, which creates illumination stripes over the region of interest. Three images are captured fast with different grid positions, and following calculations construct one high quality image with improved contrast and axial resolution.

- **Large samples imaged with bright light or epifluorescence, and optical sectioning is possible.**
- **Microinjectors available.**

Contact: microscopy@bioscience.fi

Laser capture microdissection

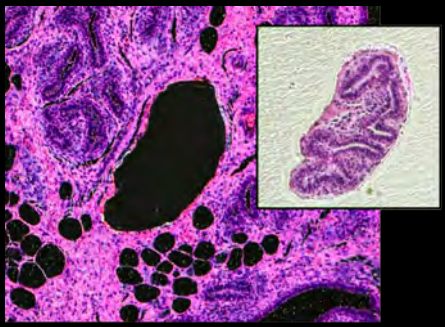
Acculift laser capture microdissection device by Targeted Bioscience. Areas for microdissection are drawn on live microscope image and cut by UV laser.

What is it for?

Laser capture microdissection (LCM) enables precisely cutting and collecting areas of interest from histological tissue sections for RNA, DNA, proteomics, or other molecular analyses. Formalin-fixed paraffin-embedded (FFPE) and frozen sections can be used.

How does it work?

The LCM device is an inverted microscope with added lasers for cutting and collecting areas of interest from whole tissue sections. Samples are similar to conventional histological sections used in microscopy. Samples can be examined on the LCM microscope with brightfield and fluorescence imaging modes for identification of the areas for microdissection. Areas for capture are drawn on a live microscope image in the LCM software and are automatically cut by ultraviolet (UV) laser, attached to a special collection cap, and lifted up from the section. Several tissue types can be collected from the same section.



An area of human mammary gland epithelium captured from a tissue section.

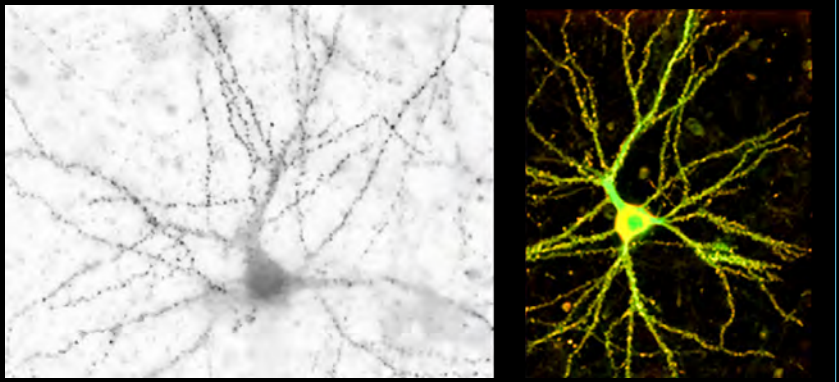
Sections for LCM are typically cut on special membrane slides, but microdissection can also be done on e.g. archived slides on normal glass slides using IR capture method. The device also enables cutting cells from membrane bottom cell culture dishes.

- **Precisely cut areas of interest from tissue section slides for molecular analyses.**
- **Area detection possible by bright-field of fluorescence stains, capture by UV cutting or IR capture.**

Contact: tbi-office@bioimaging.fi

10.HIGH CONTENT TECHNIQUES

High content microscopy



Single cell analysis.

What is it for?

High-Content Microscopy (HCM) extracts multiple features from each object detected in microscopy fields. A high-content microscope automatically and systematically captures images from multiple independent samples exposed to different conditions. Datasets may include multiple channels, z-planes, and time-points.

Imager, plate handler and acoustic dispenser.

High-content imaging applications range from basic research to chemical biology and early-stage drug discovery. Diverse features captured can describe cell morphology, cell-cell communication, proliferation, migration, protein translocation, cell signaling dynamics, responsivity, pathway kinetic constants, cell-matrix interactions, protein-protein interactions, and other parameters.

How does it work?

The samples can be cell lines, primary cells, differentiated from human iPS lines, organotypic cultures and organoids, or small animal models such as worms or fish embryos. Samples are labeled, for example with fluorescent probes and actuators, in a multiplexed fashion. Samples can be exposed, either before or during imaging, to perturbagens such as libraries of compounds for phenotyping, drug repurposing or the first stages of drug discovery. Moreover, optogenetic switches, RNAis and CRISPR-based libraries can be applied. The essence of high-content is extracting more information from smaller samples, usually miniaturized in one or more 96, 384 or 1536 well plates.

In living cells, dynamic changes in reporter intensity and localization, migration of cells, organelle trafficking and redistribution of individual protein species can be measured, over seconds or days. Fixed cells labeled with multiple affinity reagents like antibodies show single time-

points. Cell heterogeneity, ideally in living samples, can be addressed with unsupervised or supervised machine learning and related techniques. Data analysis is performed using instrument-specific software, user-defined analysis pipelines, and/or custom scripts. Analyzed data can provide signatures of perturbagens, genetic modifications or disease-states. These signatures can then be targeted by high-content compound screening.

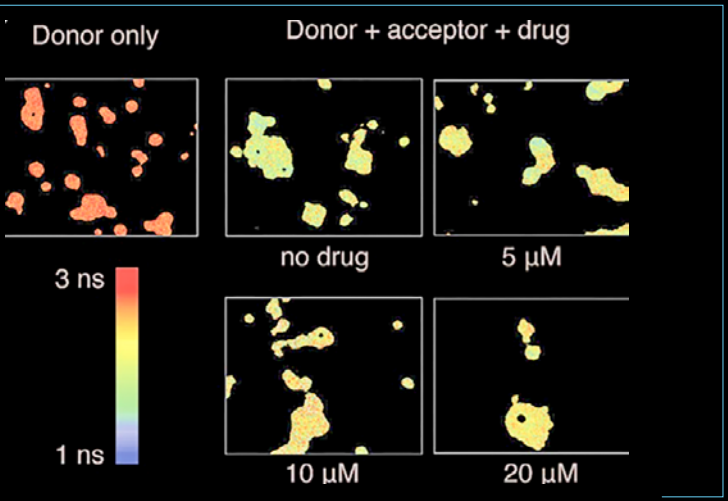
- **High content microscopy can capture and describe many different parameters within one sample.**
- **Less sample volumes - more information.**

Contact: screening@utu.fi

FLIM-FRET microscopy

What is it for?

The automated high-throughput FLIM-FRET system enables high-content FRET measurements in a fast and precise way, representing an ideal method for drug discovery and target validation. Fluorescence lifetime imaging microscopy (FLIM) is a sensitive and precise technique to create microscope images based on the differences in the fluorescence lifetime of a fluorophore, or in other words, based on changes in the exponential decay rate of fluorescence from a fluorescent sample. Given that the fluorescence lifetime of a molecule changes depending on environmental factors, like pH, temperature, or fluorescence resonance energy transfer (FRET), FLIM can be used as a precise method to detect changes in such environmental factors. In particular, detecting FRET, an energy transfer phenomenon caused by the close proximity of another fluorophore (typically less



Sample lifetime images showing changes in dynamics occurring due to FRET under different conditions, e.g. in the absence of protein-protein interaction (donor only / no FRET) or in the presence of protein-protein interactions (donor + acceptor + drug at different concentrations).

than 10 nm away) can be done precisely by FLIM. FLIM-FRET is useful to report on protein conformation changes and on protein-protein, protein-nucleic acid, and protein-small molecule interactions.

How does it work?

FLIM-FRET measurements are performed on a conventional inverted microscope with a frequency domain FLIM-FRET attachment that serves to excite the donor fluorophore and detect its fluorescent signal. The LI-FLIM software connected

A1	2	3	4	5	6	7	8	9	10	11	A12
B	2,563	2,245	2,250	2,256	2,277	2,296	2,323	2,338	2,370	2,371	B
C	2,553	2,250	2,251	2,263	2,266	2,290	2,313	2,345	2,368	2,366	C
D	2,565	2,248	2,259	2,263	2,266	2,283	2,319	2,335	2,359	2,364	D
E	2,556	2,243	2,248	2,251	2,282	2,297	2,321	2,362	2,365	2,373	E
F	2,564	2,232	2,251	2,278	2,279	2,293	2,323	2,343	2,367	2,369	F
G	2,557	2,239	2,258	2,275	2,277	2,304	2,328	2,341	2,374	2,370	G
H1	2	3	4	5	6	7	8	9	10	11	H12

Min	50%	Max
2,2317	2,3983	2,565

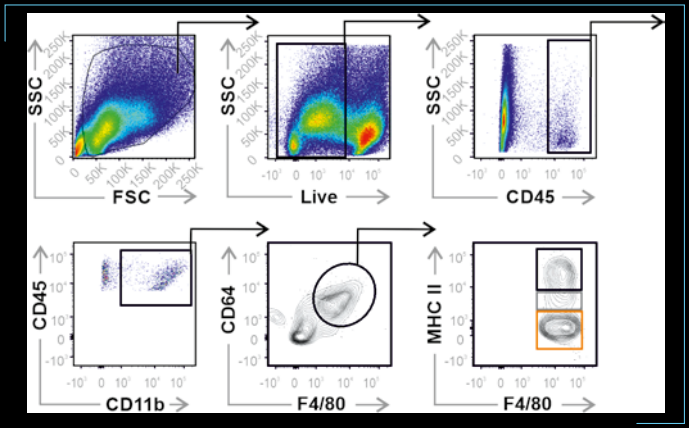
Color-coded table displaying the fluorescence lifetimes [ns] values obtained in a 96-well plate where each column corresponds to six repeats of the same condition and each well represents an average of four images taken in the same well.

to the system then calculates the fluorescence lifetimes for each of the pixels in the image. For high-content applications, the FLIM-FRET system is equipped with an automated stage and focus drive that move and position the sample according to the specified locations.

- **Ideal method for drug discovery and target validation.**
- **Precise in detecting changes in environmental factors.**

Contact: microscopy@bioscience.fi

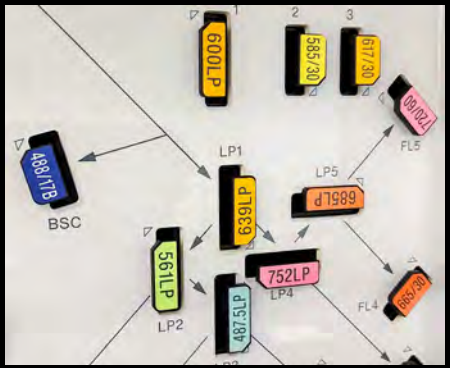
Flow cytometry and cell sorting



Flow cytometry detection of mouse ovarian macrophages (CD64+F4/80+ cells) and their subdivision to MHC II low/negative, MHC II intermediate and MHC II high macrophages.

What is it for?

Flow cytometry is a laser-based technology for the characterization of single particles, usually cells. Flow cytometry has many applications in basic research and clinical practice. It is routinely used in diagnosing hematological disorders and malignancies. In addition, flow cytometry is used for sorting specific cell populations. Flow cytometric cell sorting is an efficient way to quickly enrich cell populations with high purity. For example, performing single-cell sorting into 384-well plates is possible.



Part of filter setup .

How does it work?

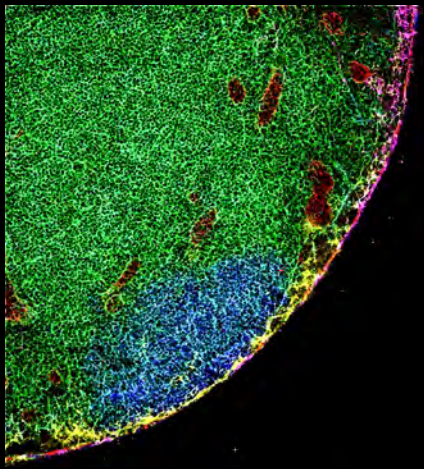
The sample is pressurized and the particles are suspended in a sheath fluid stream. Particles pass a laser in a queue, advancing at great speed (up to 40000 events/s). When the particle passes the laser, its size, granularity, and fluorescent properties are measured. In cell sorting, the stream is converted to droplets by a vibrating nozzle. Each droplet optimally contains only a single cell or no cell at all. If one wants to collect a specific droplet containing a cell of interest, it will be given an electric charge. Then, high voltage deflection plates will guide the droplet(s) into the collection tube(s) or a multiwell plate.

The flow cytometry results can be analyzed with e.g. FlowJo, FCS Express or locally made Flowing Software, and analysis yields information that is unattainable by other methods.

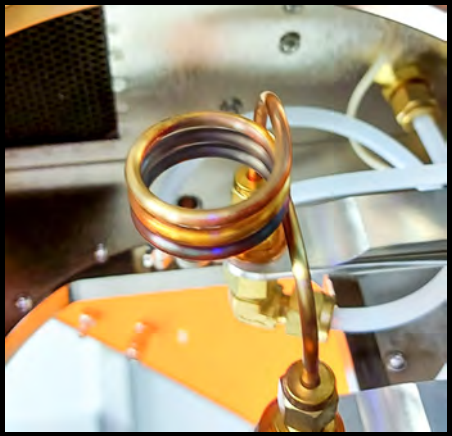
- **High speed for rare population analysis.**
- **Isolate your cells of interest.**

Contact: cytometry@bioscience.fi

Imaging mass cytometry



Mouse lymph node section stained for smooth muscle actin (alphaSMA; red), CD45 (lime), CD220 (CD45R; blue), CD8a (cyan) and CD206 (magenta).



Radio-frequency coil for the plasma.

What is it for?

Imaging mass cytometry (IMC) is a single-cell technology, which allows the analysis of up-to 40 protein markers at subcellular resolution in fixed tissue sections or cell smears. This highly multiplexed capacity can give the researcher more extensive spatial information on e.g. tissue immune landscape or tumor microenvironment architecture.

How does it work?

The samples, formalin-fixed or frozen, are labeled with metal-conjugated antibodies, each metal isotope having a distinctive mass. The labeled sample is placed in Hyperion, an IMC instrument, where a 213nm laser ablates the tissue a 1 µm2 spot (pixel) at the time in the speed of 200 µm/s.

The scanned tissue spots are vaporized into plumes, which are individually carried within the carrier gas to the Helios mass cytometer. Mass-tagging enables separation of signals based on the differences in mass, resulting in distinct signals for each marker without the need for compensation associated with fluorometric techniques. Isotopes associated with each plume are measured, and the tissue is digitally reconstructed from the 1 µm2 spots, a size which allows subcellular resolution.

Due to the high number of channels, staining panel preparation and antibody selection require careful planning. As IMC detects individual atoms, special attention has to be taken in all steps from sample collection planning to sample preparation.

The IMC technology is relatively new. Therefore, there does not exist a single software package which could process the IMC results from raw data to the final format, whether it is neighborhood analysis, dimensionality reduction or a publication/presentation image. However, several analysis pipelines have been developed for the analysis.

- **The world of dimensions.**
- **Understand the spatial heterogeneity.**

Contact: cytometry@bioscience.fi

Microscopy slide scanners

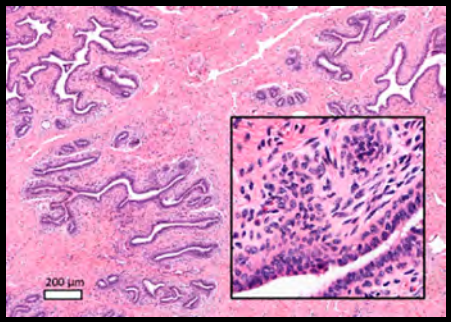
Pannoramic Midi fluorescent slide scanner in the front. Pannoramic 250 Flash visible in the back.

What is it for?

Slide scanners are used to automatically digitize entire microscope slides. Earlier, microscope-mounted cameras were used to capture histological details of interest, but modern whole slide imaging allows storage and sharing of all the histological information present on a microscope slide. In addition to convenient data sharing and evaluation, the digitized slides enable automated quantitative image analysis (using e.g. QuPath software) done by e.g. tissue type recognition and cell counting. Three slide scanners are available: Pannoramic P1000 and Pannoramic 250 Flash for brightfield imaging and Pannoramic Midi for fluorescence and brightfield imaging.

How does it work?

From the imaging point of view the slide scanners work in the same way as ordinary brightfield and epifluorescence microscopes. In addition, they have fully

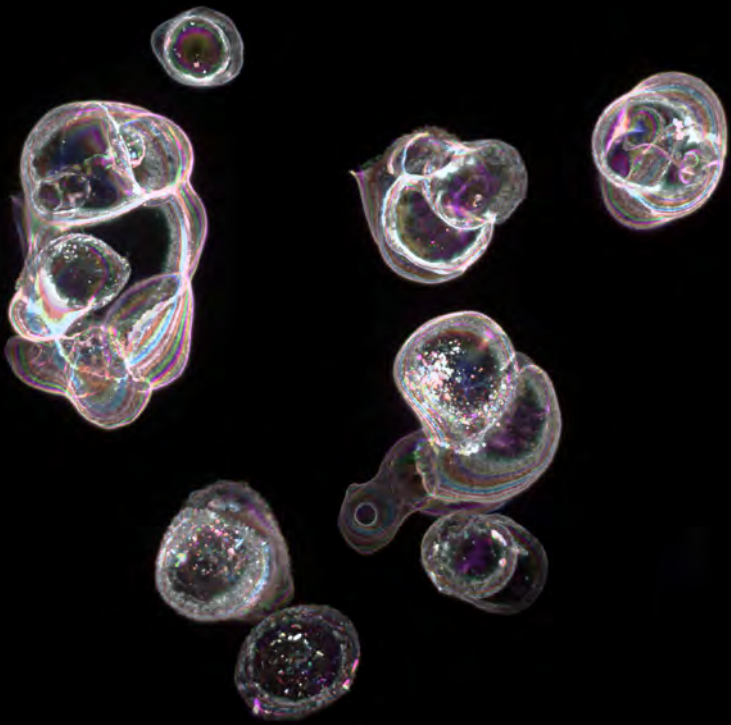


Digital slide scanned with brightfield slide scanner Pannoramic P1000.

automated scanning and focusing systems to produce high resolution images of the whole slide area. The brightfield mode can image all stains that produce contrast in ordinary brightfield imaging. Care should be taken in preparing the slides to ensure good quality scanned images. Slides must be essentially free of any flaws such as cracks, crooked coverslips, bubbles in mounting medium, etc. Feel free to contact responsible personnel for advice before preparing slides if you have any questions.

- **Slide scanners digitize whole slides of tissue samples in brightfield and fluorescence.**
- **Digitized datasets of histological sections can be evaluated and shared in a convenient way, and they enable automated quantitative image analyses of large datasets.**

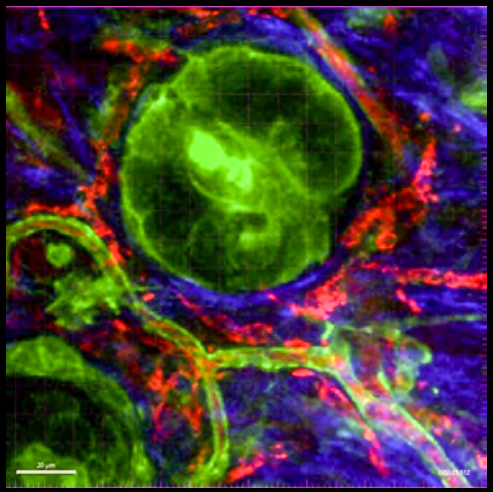
Contact: tbi-office@bioimaging.fi



Soap bubbles by Defne Dinc.

11.SMALL ANIMAL AND PRECLINICAL IMAGING

Optical in-vivo imaging



Snapshot from an intravital 2-photon microscopy time lapse of mouse ear skin showing capillaries around a hair follicle (both green), with intravenously injected tracer (red) leaking out of the vessels and ingested by tissue macrophages. Patrolling immune cell also seen in green; collagen fibers of the extracellular matrix seen in blue.

What is it for?

The IVIS optical imaging system provides quantitative fluorescence and bioluminescence imaging data from mice or rats *in vivo*. Cells expressing luciferase or labeled with a suitable fluorescent molecular species can be visualized with the IVIS Spectrum system. Macroscopic *in vivo* imaging enables, for example, phenotyping

of transgenic mice, observation of tumor growth in a living animal, follow-up of treatment responses, visualization of inflammation and infections and monitoring of nanoparticle delivery to designated targets. A principal application area is the study of oncological xenografts, in which cancer cells with bioluminescent/fluorescent reporters are inoculated into immunodeficient mice/rats. These oncology models can be used to assess anti-cancer therapies over the course of treatment *in vivo*. Non-invasive imaging of tumor growth and metastasis allows longitudinal evaluation of tumor development before, during, and after treatment, offering an excellent preclinical strategy for assessment of tumor response and recurrence.

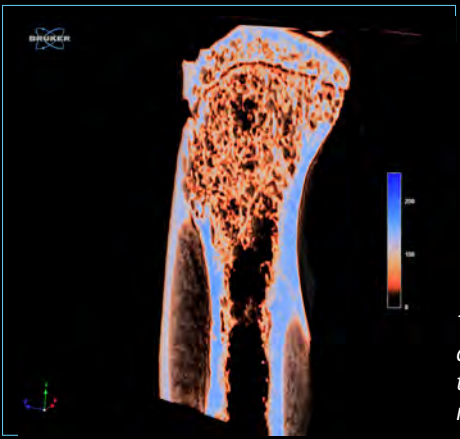
How does it work?

The system employs a light-tight imaging chamber. Inside the chamber, a heated stage with built-in anesthesia masks is available for five animals. The system has a CCD camera thermoelectrically (Peltier system) cooled to -90°C ensuring a low dark current and very little noise. The camera has high quantum efficiency over the entire visible to-near-infrared spectrum. The stage is height-adjustable, allowing for a field of view of 5-12.5 cm. LED illumination is provided for reference photography, and a halogen lamp is available for fluorescence imaging. The system has a multi-position excitation filter wheel, and replaceable filter wheels to handle emissions at various wavelengths. All of these refinements are motor-controlled via IVIS Living Image software.

- **Optical in vivo imaging is appropriate when fast or repeated imaging is required.**
- **Good for screening a large number of animals.**

Contact: tbi-office@bioimaging.fi

Micro-CT imaging



Tibia of a 3-month-old male mouse scanned and reconstituted at 5 micrometer resolution. Image generated with CTVox Image rendering program.

What is it for?

Micro-Computed Tomography (Micro-CT) is a method whereby X-ray computed tomography affords resolution on a micrometer scale. Micro-CT images can be used for volumetric analysis of scanned samples and three-dimensional image reconstruction. Mostly this instrument is used for bone structure analysis and material sciences. It can be, however, applied to e.g. studies on vasculature and soft tissues with the aid of radiocontrast agents.

The Turku Bruker-Skyscan 1272 scanner can be used for ex vivo studies only. Maximum practical size is about the size of a thumb tip. The smaller the sample, the better resolution can be achieved. The scanner is equipped with an automatic sample loader allowing unattended scans of series up to 16 samples. Further, a compression stage can be installed to study materials load stress behavior.

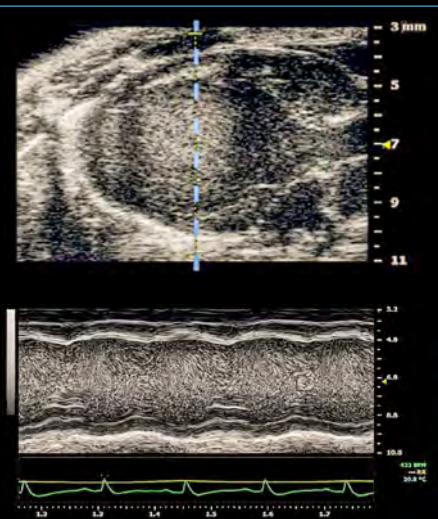
How does it work?

In micro-CT, hundreds of digital X-ray images are obtained from a single sample, but with slight variation of the rotational angle. The spatial location of every voxel (a three-dimensional pixel) can be geometrically calculated from the images. The resolution of such images is, at best, on the micrometer scale, and dependent on sample size.

- **3D resolution at 1 – 2 micrometer scale depending on sample.**
- **10 min. routine scans at 5-micrometer voxel resolution.**

Contact: jmaatta@utu.fi

Ultrasound imaging



B-mode image of a mouse heart.

M-mode image is acquired along the blue dashed line and shows the change in heart volume as it beats.

What is it for?

The high-frequency, high-resolution digital imaging platform with linear array technology and Color Doppler Mode can be used non-invasively in a variety of animal models. This setting is especially effective in investigating cardiovascular function and structure, cancer, and inflammatory-related processes.

How does it work?

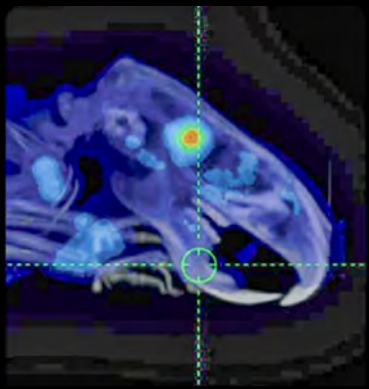
A handheld transducer with a linear array of piezoelectric elements is used to produce acoustic pulses above 20 kHz that deliver sound waves into the animal's body. Diverse tissues, organs and disease lesions absorb and reflect sound waves differently depending on their density. High-resolution grayscale images are produced when the partially reflected sound waves return to the transducer. The resulting image is instantly viewable and can be captured as a still photograph or movie. Although B-Mode, which displays a 2D cross-section of tissue, is the most common imaging mode with ultrasound, other image types can also be produced for studying physiological properties such as localization and direction of blood flow, tissue stiffness and cardiac strain, vascularity, tissue motion over time and the presence of molecules and biomarkers.

- **Ultrasound is a non-invasive technique for studying e.g. tumor xenografts and cardiovascular function and structure in animal models.**
- **Several imaging modes for different purposes exist.**

Contact: ultrasound@bioimaging.fi

PET imaging

PET methodology from radionuclide production to image analysis.



Binding of the PET tracer [18F]CFT, (a cocaine analogue) to the monoamine transporters in the rat striatum.

What is it for?

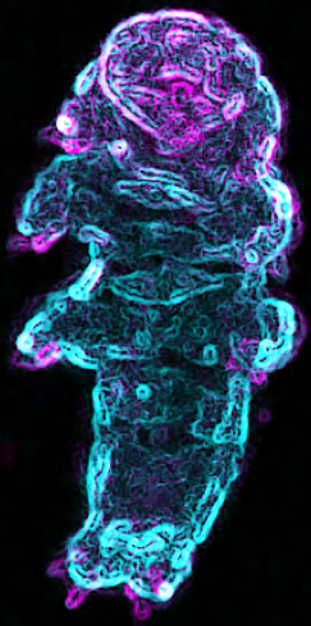
Positron Emission Tomography (PET) is a non-invasive method for imaging biochemical and physiological processes *in vivo*. Minute amounts of biologically active compounds are labeled with positron emitting radionuclides and then administered to the subjects. The temporal and spatial distribution of these tracers within the body is visualized and measured with PET. With PET it is possible to study tissue function and metabolism, the function of neurotransmitters and receptors, gene expression and drug pharmacokinetic/pharmacodynamics profiles.

How does it work?

Positron emitting radionuclides are usually produced with cyclotrons. Short-lived (T½= 2-110 min) radionuclides are then incorporated into molecules of interest using sophisticated radiochemical syntheses. Due to the short half-life of the positron emitters, these syntheses have to be performed in a very rapid process. The tracers are then injected into the subject and a PET scan is performed. The images are reconstructed as tomographic images by mathematical processing of the data.

- **Positron Emission Tomography (PET) is a non-invasive method for imaging biochemical and physiological processes in vivo.**
- **Full quantification of tracer kinetics is possible.**

Contact: contact.pet@tyks.fi



Edgy by Anna-Mari Haapanen-Saaristo.

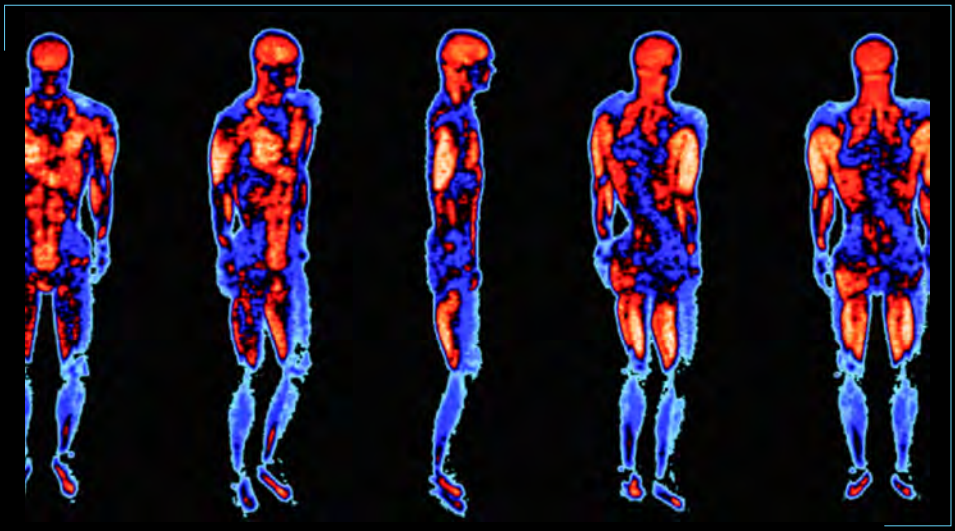
12.MEDICAL IMAGING

PET, PET/CT and PET/MRI

State-of-the-art total body PET-CT scanner at Turku PET Centre covers the body from head to thigh, delivering a full-body image at one go. This remarkable feature enables studying interaction of all organs simultaneously which is not possible with traditional PET scanners.

What is it for?

Positron Emission Tomography (PET) is an unsurpassed method for imaging biochemical and physiological processes *in vivo*. Combined with Magnetic Resonance Imaging (MRI) or Computed Tomography (CT), PET findings are localized anatomically. PET is used in patients with cancer and in cardiovascular, neurological and inflammatory diseases in clinical medicine. PET combined with tracer kinetic models measures blood flow, membrane transport, metabolism, and ligand-receptor interactions noninvasively and quantitatively. In drug development, PET characterizes drug candidates in the early stages of development, including studies for pharmacological mechanism of action, pharmacokinetics, therapeutic dose range, subject selection, and stratification.



[^{18}F]fluorodeoxyglucose ([^{18}F]FDG) is commonly used to measure tissue glucose consumption in vivo. Here, it reveals burning muscles after physical exercise.

How does it work?

Minute amounts of biologically active compounds are labeled with positron-emitting radionuclides (e.g. 11C, 15O, 18F, 68Ga) and administered to subjects. The temporal and spatial distribution of the tracers within the body is measured with PET cameras. The data is reconstructed as tomographic images by mathematical processing. CT or MRI images are overlaid with PET images for anatomical reference. Data is analyzed mathematically and visually. For the full use of the data, imaging, modelling, and analyses should be carefully planned with PET experts. While Turku

PET Centre offers dozens of different PET tracers for human use, the availability of a suitable PET tracer needs to be verified well in advance. Setting up a new tracer requires a strictly regulated process and validation for human use (GMP). Note that PET involves radiation; therefore, Ethics Committees require calculations of radiation burden to subjects.

- **A quantitative, non-invasive method for imaging physiological processes in humans.**
- **Cost-effective data for drug development.**

Contact: contact.pet@tyks.fi

PET tracer development

Production of the radiotracers is performed according GMP regulations in c-class clean room.

What is it for?

PET tracer development is a pre-designed and documented package of validated work stages that leads to a radiotracer to be used as a diagnostic tool in PET. Radiotracers are labeled with short-lived positron emitting radionuclides such as 11C, 15O, 18F and 68Ga. The goal is to develop a robust and reproducible production process of the radiotracer with high quality, the characteristics of which can be reliably analyzed and can be safely used in both preclinical and clinical studies.

CC 18/9 Cyclotron for radionuclide production.

How does it work?

The following methods are developed and optimized during radiotracer development:

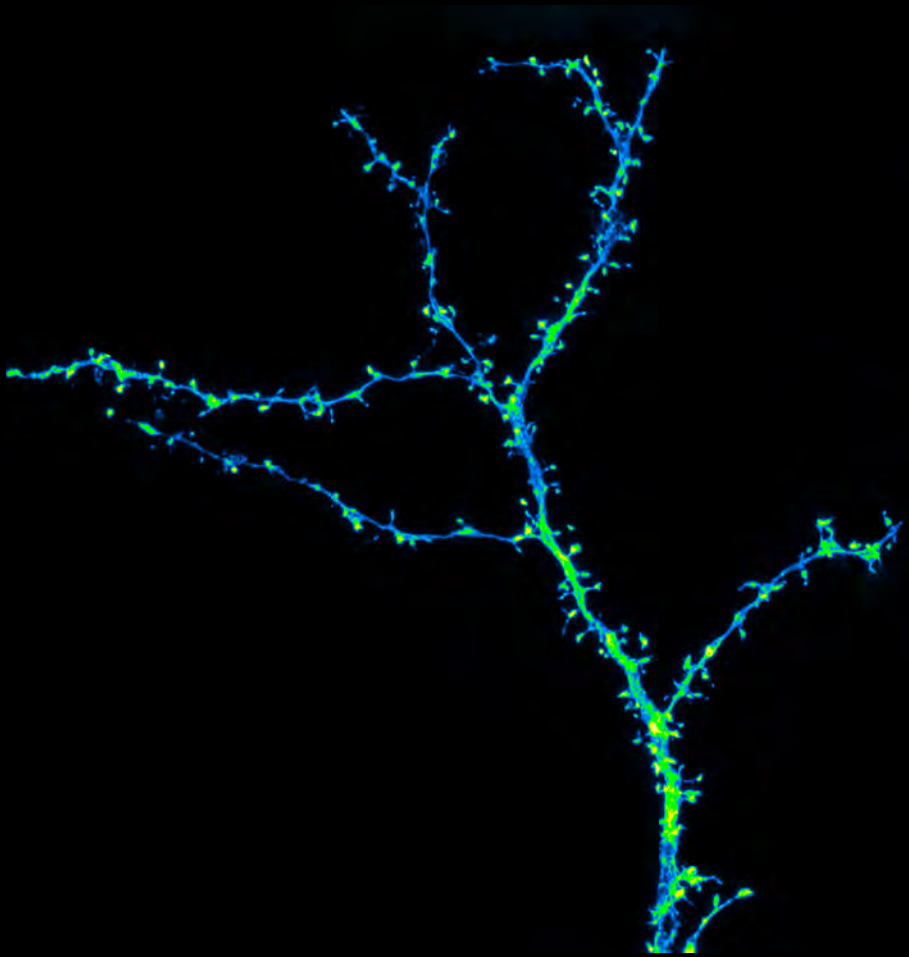
- Production of the radionuclide with a cyclotron using an appropriate nuclear reaction or a radionuclide generator
- The chemical reactions to attach the radionuclide to the unlabeled molecule in order to obtain the radiotracer
- Procedures to isolate/purify the radiotracer
- Formulation of the radiotracer, applicable for i.v. injection
- Sterilization of the radiotracer
- Automation of the production process
- Quality assurance of the radiotracer according to pre-set specifications.

The entire development process is validated through a Process Verification procedure; a series of three consecutive production runs with full quality control. EU guidelines of GMP (adequate facilities, qualification of devices, validation of methods, and training of personnel) and radiation hygiene have to be applied throughout the PET tracer development.

Radiotracers are administrated as "trace" amounts, typically less than 1 µg, that do not induce any pharmacological effects. Hence, the molar activity (MA, proportion of radioactivity to the tracer mass) is very high. A good radiotracer binds to its intended biological target with good selectivity and specificity and has a suitable metabolic profile for the study in question.

- **PET tracer development requires a tightly monitored workflow in order to deliver the desired product and comply with radiation safety rules.**
- **Appropriate PET tracers allow for non-invasive quantification of biological processes in vivo with immense specificity.**

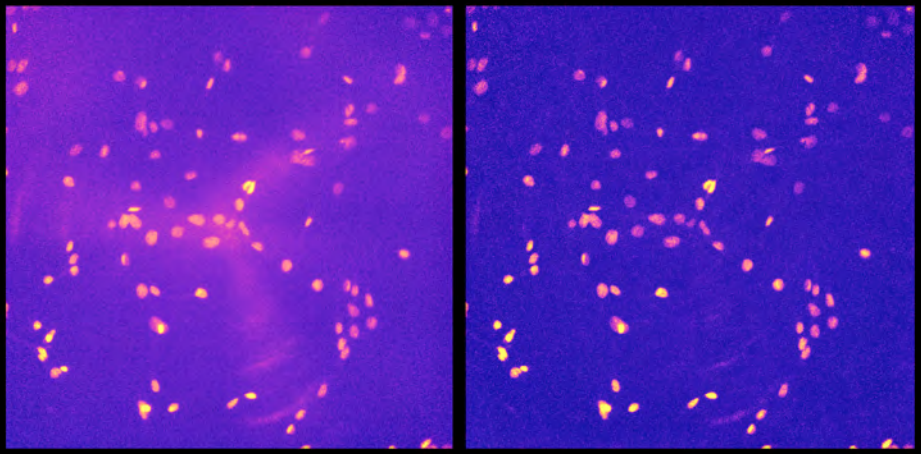
Contact: contact.pet@tyks.fi



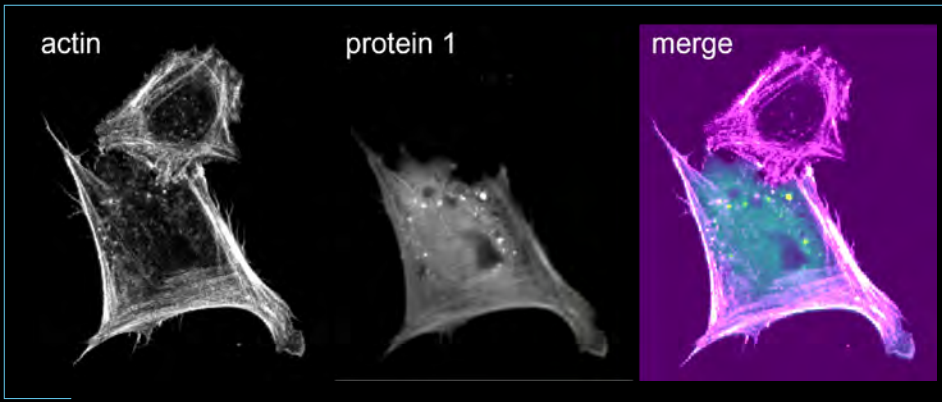
Digital tree by Pierre Heemeryck.

13.IMAGE DATA HANDLING AND ANALYSIS

Image processing



Uneven illumination removed from the image using background subtraction.



Cell expressing two proteins of interest, that can be visualized as one image using pseudocoloring.

What is it for?

Bioimaging devices often produce images that are plagued with noise, unwanted movement, focus drift or out-of-focus haze. With image processing, it is possible to improve the quality of such images. Image processing can consist for example of drift and shading correction, denoising, specific filtering methods (e.g. sharpness, high pass, low pass, etc.), as well as arithmetic operations (e.g. addition, multiplication, logical operators). Image processing also covers areas such as reconstructing 3D datasets from tomographic data or using deconvolution to improve image quality. Additionally, image processing entails basic adjustments such as brightness and contrast, inverting images or changing their pseudo-color palette, making it easier to visualize multiple channels simultaneously. Image processing is often needed before the image data can be used for its final intended purpose, such as quantitative analysis or visualizations.

How does it work?

Image processing is usually performed with specialized software created for this sole purpose. Usage of programming languages in addition to such software is becoming more popular. It is good practice to keep image processing to a minimum, especially before quantitative image analysis, as often seemingly inconsequential details in the implementation of image processing can have dramatic effects on the final image analysis outcome. Therefore, when image processing is needed, it is important to test and document the used processing algorithms to ensure the image processing pipeline produces appropriate results and is reproducible. The same final quantification should also be tested both without and with the processing, and with different types of processing and its settings. Often, image processing should be done by experts only, or ordered as a service. Overlooking these aspects may lead to the publishing of mis- or under-reported scientific discoveries.

- **Image processing should be kept to a minimum, especially before quantitative analyses.**
- **Image processing cannot "create" new resolution or data, but it can distort it and introduce errors.**

Contact: image-data@bioimaging.fi

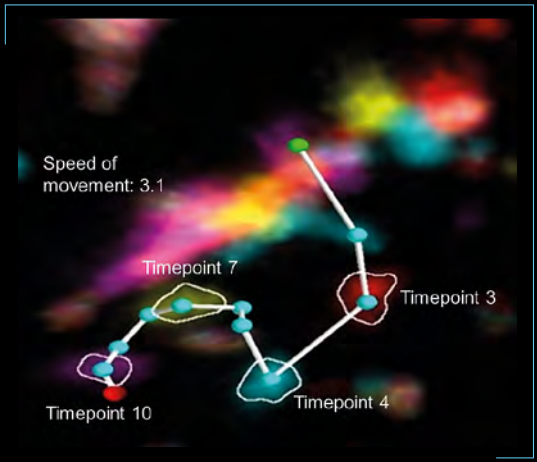
Image analysis

In segmentation-based analysis the image is divided into identifiable objects that can be quantified.

What is it for?

Today, displaying bioimages is not enough for reliable scientific conclusions or publications - quantification of images is required. Bioimaging has transformed from a qualitative to a quantitative science. Without image analysis, images are only data, not yet information. Image analysis is needed to convert the data into usable information. In recent years, artificial intelligence and deep learning have become a powerful tool for image analysis, enabling more complex analyses than before. Image analysis can be divided into two main approaches. In conventional approaches, images are analyzed either pixel by pixel, for instance to quantify colocalization between two different markers, or based on segmentation. In segmentation-based analyses the image data is first segmented, meaning that it is divided into objects that the computer can identify. After segmentation, numerous parameters such as number, size, shape and distribution of the objects can be quantified. The other main approach is machine learning-based methods. These can be used to for instance recognize objects such as cancer cells, or segment complex objects that would be difficult to segment using conventional approaches. In these methods, the computer has to be trained first with a large amount of training data. Before image analysis, image processing (see previous section) is often needed.

Motion tracking is one of the most complex image analysis procedures, requiring identification of segmented objects in successive time points.



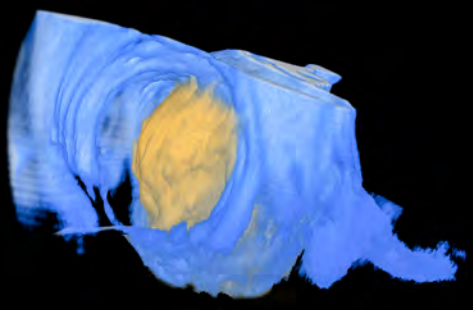
How does it work?

Biomedical image analysis requires specialized software. The desired software is first identified, and then the appropriate workflows are determined (intermediate steps, algorithms and their settings, statistical analyses, etc.). In some cases, tailored modifications and programming are required. With deep learning methods, training data and its (manual) annotations are often needed first. Image analysis can also be obtained as a service, guaranteeing fast and reliable results but enabling scientists to be involved as much as they want to be.

- **Image analysis offers endless possibilities and is revolutionizing bioimaging.**
- **The planned image analysis often needs to be considered already during image acquisition.**

Contact: image-data@bioimaging.fi

Image visualization



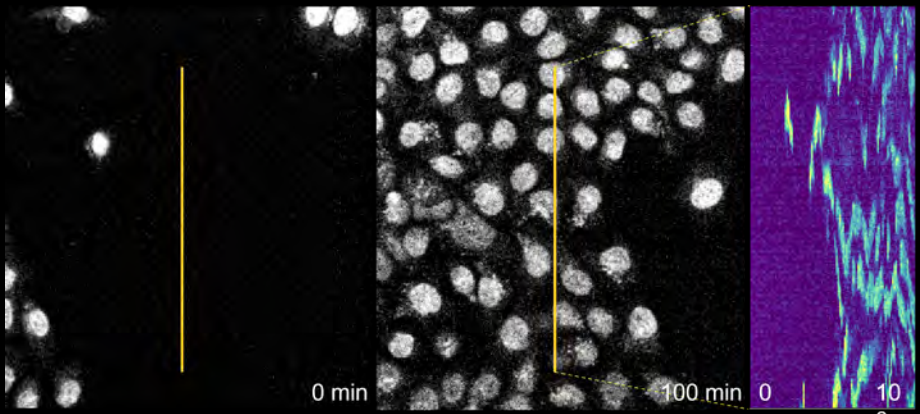
3D rendering of a cancer cell trapped inside a blood vessel.

What is it for?

While quantitative analyses nowadays produce the actual numerical results from bioimage data (see previous section), the generation of intuitive and efficient visual representations illustrating the quantitative results is often needed for publications, presentations, and data navigation. Visualizations are also frequently used for quality control when designing image processing and analysis workflows and for evaluating their settings and reliability. Compared to image processing and analysis, there is more freedom in image visualization, as visualizations are generally not used for scientific conclusions, nor should they be used for such.

How does it work?

2D data can usually be visualized using common image analysis and processing tools. Multidimensional images are often observed as a collection of separate images, as projections (e.g. maximum intensity), or for example as kymographs. Data from high-throughput microscopy screens can be visualized for example as image thumbnails or heatmaps. 3D image data can also be transformed into 3D renderings (e.g. volume or surface rendering) using special software, allowing a more realistic visualization. Stereo/3D images and movies can also be created, and they are often the best method to convey 3D structural information. The 4th dimension,



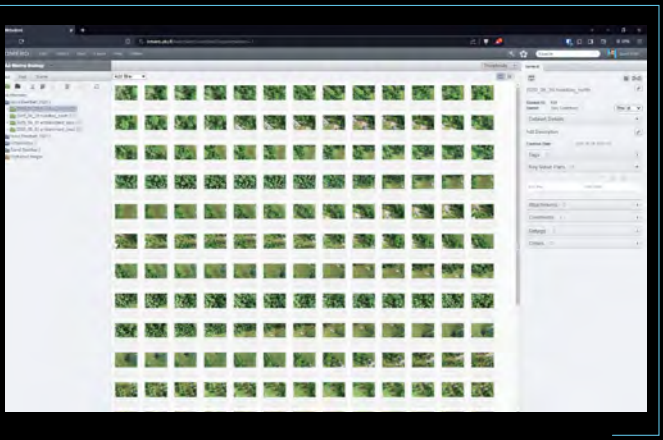
Kymograph of cell migration in a line selection.

time, can also be added if the original data is 4D. It is also possible to combine various visualization approaches with virtual reality environments to allow seamless navigation through the data and intuitive interaction with the visualized objects.

- **Consider color blind people when creating superimposed images.**
- **Quantitative analyses must be done on original image data, never on visualizations such as projections or 3D renderings.**

Contact: image-data@bioimaging.fi

Data management



Using OMERO system to easily store and manage large datasets.

What is it for?

Biological and medical imaging devices have the capacity to generate large amounts of image data, spanning up to tens and even hundreds of gigabytes, or more. Image data commonly spans three or more spatial dimensions, with varying image characteristics and metadata schema. Reliable and redundant physical storage of these image datasets may be a challenge due to the large sizes and varying file formats. Furthermore, image analysis pipelines can be complex and require consistency in the raw data in order to be predictable. The ability to share the same image data between researchers and organizations is a driving force for transparency and reproducibility.

Data management solutions specifically designed for image data are used to store, manage, and browse original image data and its metadata, as well as various intermediate versions of the data, such as those that have been created as part of processing and analysis workflows. Data management also entails sharing the

final data with the scientific community in conjunction with publication, which is increasingly required by funders and scientific journals. This sharing is typically done through public databases according to FAIR principles (data must be Findable, Accessible, Interoperable and Re-usable), and this may also involve metadata harmonization and human curation.

How does it work?

The Open Microscopy Environment (OME) is a consortium of academic and industrial organizations that produce open source software and format standards for biomedical image data. The main products are the OMERO server for managing, visualizing, and analyzing microscopy images, also for publications, and Bio-Formats, a cross-platform software library for reading and writing image files that supports most of the microscopy image formats being used today. Turku BioImaging offers open access to two OMERO servers, as well as guidance for public FAIR publication of data.

- **Data management is nowadays considered an area of key importance in bioimaging.**

Contact image-data@bioimaging.fi for any kind of help with image data.

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Image analysis

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Data management

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