Euro BioImaging
Preparatory Phase II Project

D8.3 Report on potentially interesting new imaging technologies for which user need should be demonstrated

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Abstract

This document provides a report on potentially interesting new imaging technologies that are not yet part of Euro-BioImaging's technology portfolio offered by the 1st generation of EuBI Node Candidates, and for which user need should be demonstrated. These could then be further evaluated in feasibility studies and considered for future inclusion in the EuBI ERIC infrastructure, according to the procedures outlined in deliverable D8.2 "*Procedure for the identification of new technologies in the fields of biological and medical imaging*".

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1. Introduction

Biological and medical imaging is a field with a long history and also a very open future. This poses an intrinsic challenge to an infrastructure like Euro-BioImaging as the possibility of timely adaptation to new developments must be provided. This is the focus of Work Package 8 of this project. In its other deliverables, procedures were developed for the identification of new technologies, for training in them, for interoperability with existing parts of the infrastructure and also for the removal from the technology portfolio of no longer needed technologies.[1]
This report aims to provide a by no means exclusive or complete selection of technologies that could be further evaluated and handled according to the procedures outlined in the other deliverables. It is based on the collected inputs from technology developers, technology providers and scientists that would be the users of proposed methods.

2. Input formats

This report strongly depends on the community input of the biological and medical imaging fields. To this end the following steps have been taken:

- As part of the creation of the Euro-BioImaging website for interim operation, WP5 designed an online new technology report form (with input from WP8) that allows users to propose a new technology for consideration. This is operational since M5. Several technology proposals were uploaded during the past months.

- In order to organize a suitable stakeholder activity to discuss these suggestions and further potential new technologies, opportunities for creating a satellite activity at a large meeting were evaluated. Early on in the project, the 17th Meeting of the European Light Microscopy Initiative (ELMI) in May 2017 in Dubrovnik was identified as the most suitable venue even though it took place outside of the initially planned time period of the deliverable (M12). Two activities for collecting feedback were prepared and executed. These were:
  1. A presentation of the collected new technology proposals in biological imaging and a discussion of new technology implementation issues at the Core Facility Satellite Meeting preceding the ELMI2017 Meeting on May 23rd, aimed at biological imaging core facilities;
  2. A presentation of the collected new technology proposals for biological, molecular and medical imaging and of the inputs of the preceding activity. This was done as part of the Euro-BioImaging Satellite Meeting during the ELMI Meeting on May 25th, 2017.

- To prepare the two activities mentioned above, the stakeholder community as represented by the ratified node candidate sites was invited at the beginning of May to submit additional technologies through the above mentioned technology report form on the Euro-BioImaging interim website.

[1] See Deliverables D8.1, D8.2, D8.4 and D8.5

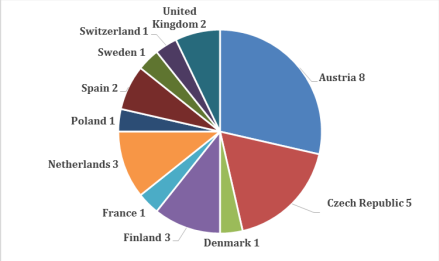
3. Report

Technology report forms

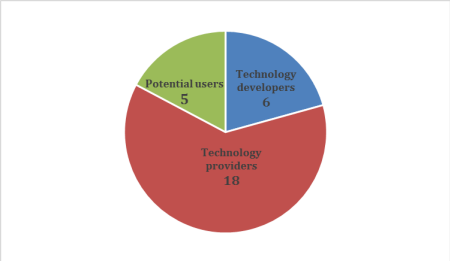
To date, a total of 29 new technology proposals have been collected through the online technology report form, 28 of which were used for the preparation of the two activities at the ELMI satellite meetings described above and were also presented there.
The 29 proposals cover 21 different technologies, with five technologies being mentioned more than once. The full list of proposed technologies can be found in Annex I of this document.

Technology submitters

The 29 proposals were submitted by people in the biological and medical fields from 11 different European countries.



The proposals were submitted by all three categories of stakeholders in the biological and medical fields that would be affected by new technologies, namely technology developers, technology providers and the potential users interested in a technology. In 27 cases, the submitters were affiliated with research institutes and universities, in two cases with technology companies.

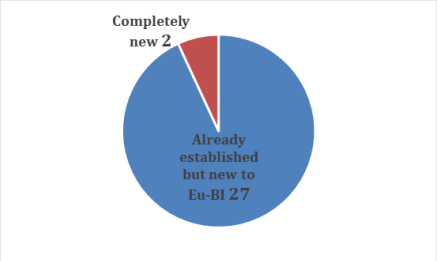


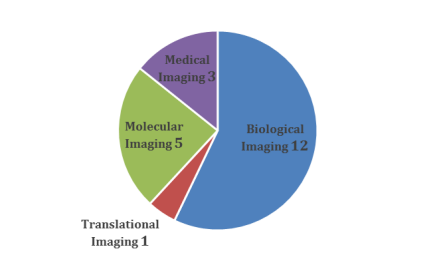
The predominance of technology providers is in line with the stakeholders and participants of the Euro-BioImaging initiative, many of whom are working in facilities and service units, but the interest in defining new technological directions extends significantly beyond, to developers on the one and potential users on the other side. This is in line with the key groups of the

technology adaption cycle[2], innovators, early adopters and the early majority that needs to be reached to bring a new technology development into the field and to cross the "chasm" that has been postulated to exist for new high technology developments and that keeps developers and users apart. This reinforces the critical role an infrastructure like Euro-BioImaging can play in technology dissemination.

Technology classification

Of the 29 proposals, 27 were categorized by the submitters as "Already established, but new to Euro-BioImaging" and two as "Completely new".
Among the 21 different proposed technologies (accounting for multiple proposals of the same technology), 12 can be associated to biological imaging, 5 to molecular and 3 to medical imaging and one covers translational imaging workflows[3].





Comment [P1]: This should be modified according to the new classification (see below)

Technology proposal presentation

The 21 proposed technologies cover all areas of Euro-BioImaging activities in the biological and medical imaging fields. Additionally, the following distinctions can be made that reveal interesting aspects for Euro-BioImaging:

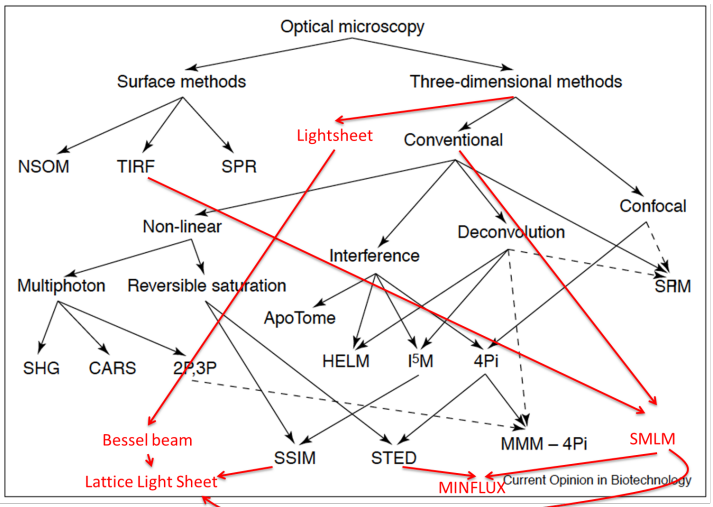
1. A majority of the proposals (11) represents new methods inside the 36 imaging technologies that were already evaluated for Euro-BioImaging and included during Preparatory Phase I of EuBI. These technologies are listed in Annex 2. In Annex 3, the submitted technology proposals are shown associated to these already recognized technology fields.
2. While most technology proposals are based on recent technology developments, at least two (Slide Imaging, Episcopic Microscopy) are based on very established optical

[2] Outlined in D8.2, see also Geoffrey Moore, "Crossing the Chasm" (1991)
[3] Listed as Biological and Molecular Imaging in Annex 1, both listed concepts are counted as one.

methods, but provide their challenge and potential in the data handling and (even more so) in the innovative analysis of the data (e.g. digital pathology).

3. The most frequently submitted proposal contains aspects of correlative multimodal imaging. Correlative approaches may combine established technologies in a great variety of new combinations and/or sample handling sequences, but they can also incorporate completely new technologies as part of their workflows. This makes their assessment different from that of single technologies.

Point 1 shows that continuous adaptation of the technology portfolio is essential to maintain the offer of cutting edge technology in an infrastructure like Euro-BioImaging. Many developments take place inside the already identified technology fields and do not require a complete de-novo assessment, but rather a reliable identification mechanism[4] and smooth procedures for technology upgrades inside the existing structure[5]. As long as user need is recognized for the general technology field, methods inside the field still need to be assessed for feasibility by proof-of-concept studies to guarantee their eligibility for open access service provision.



Adapted from: Garini et al. 2005

Figure 1: An extension of the status quo of optical microscopy of 2005, taking into account one new technology field (lightsheet imaging), developments in super-resolution imaging (single molecule localization microscopy, SMLM) and the subsequent connections inside the fields.

[4] See Deliverable 8.2
[5] Being prepared for interim operation in WP3

The dynamic of developments inside imaging fields is exemplified in Figure 1. Inclusive classifications in the existing technology fields are necessary to avoid an overly fractured representation of methods and to ensure smooth operation of the infrastructure.

Point 2 is an interesting example of application-driven instead of technology-driven developments and needs to be addressable inside the Euro-BioImaging infrastructure. Whole slide imaging is technically established, but, as stated in the submitted proposal, offers challenges in the provision of standards, training and data resources that can be addressed inside Euro-BioImaging.

Correlative and multimodal methods as mentioned in point 3 are hard to define in terms of novelty as they may consist of a combination of existing technologies that by themselves are already included in the Euro-BioImaging portfolio. They have to be additionally considered at the level of the complete workflow, both for user need demonstration and for the feasibility of open access provision. Further information about how flagship technologies are combined into multimodal pipelines is needed. This will allow to properly classify the proposed multimodal methods (as either biological or biomedical or mixed techniques), and to assess whether they can be included among the already established EuBI technologies or not.
The case of the inclusion of a new technology together with already featured technologies inside a correlative workflow needs to be considered separately. This may be the case for several new technologies mentioned below that could be offered inside a correlative or multimodal workflow. In that case user need and technical feasibility have to be demonstrated for the new technology. The value of a new technology should also be assessable as part of a correlative workflow, where it may be very beneficial, instead of only as a standalone technology where its use may be too limited to warrant inclusion in the Euro-BioImaging portfolio.

Identified new technologies

Of the 21 proposed technologies listed in Annex 1, 9 cannot be straightforwardly added to the already identified technology fields in Euro-BioImaging.

These are:

Multimodal Holographic Microscopy (MHM)
Brillouin Light Scattering Microspectroscopy (BLSM)
Photo-Acoustic Microscopy (PAM)
Micro X-Ray Fluorescence Spectroscopy
Imaging Mass Spectroscopy
Photoacoustic Imaging (PAI)
Magnetic Particle Imaging (MPI)
Magnetoencephalography (MEG)
Theranostics with radioactive probes

The proposed technologies vary significantly both in the scope of the field and in the degree of specialization.
Given the width and maturity of the fields and the proposed variations in the same technology field, imaging mass spectroscopy and photoacoustic imaging methods (for microscopy and molecular/medical imaging) should be considered for the demonstration of user need and, in case of a positive outcome, feasibility. This should be done both for standalone consideration and for inclusion in correlative workflows. In the case of Imaging Mass Spectrometry, challenges in the data-analysis provision need to be considered as part of the feasibility assessment. Micro X-Ray Fluorescence Spectroscopy would also need to be assessed in the context of data-analysis and could offer complementary information on the elements in the sample as opposed to the molecular information of mass spectroscopy (especially in a correlative workflow).

Brillouin Light Scattering Microspectroscopy is not part of the current Euro-BioImaging technology list, but given the nature of the method and the similarities to Raman spectroscopy, should be considered to be added to the field of functional imaging and assessed for user need.

Holographic microscopy methods should be considered for inclusion in the already existing multimodal advanced light microscopy methods, possibly together with other recently developed methods for quantitative phase imaging. The user need for label-free quantitative phase microscopy methods should be assessed.

Magnetic Particle Imaging and Magnetoencephalography should be assessed for user need.

Stakeholder meeting activities

Preliminary results on the collected technology proposals were shared and discussed with stakeholder communities in the two satellite activities at the ELMI Meeting 2017 described in the section “Input formats” above. During these activities, no new technology proposals were added, but the ability to accommodate and provide open access to new technology while it is still under development was seen as problematic by most imaging facilities. As a concrete and current example, it was stated that a recently developed technology like lattice light sheet imaging can only be offered if a whole staff position is dedicated to this instrument to make it accessible to users.
This highlights the problems associated with bridging the “chasm” for new technologies and how important it is to connect developers to early adopters and subsequently the early majority. This goes beyond single sites and stresses the importance of a larger infrastructure like Euro-BioImaging to provide a framework to identify new technologies, assess the need for them and the feasibility of implementation and to help them to enter the fields of biological and medical imaging.

4. Conclusions

As shown by the significant number of stakeholder-proposed new technologies, the fields of biological and medical imaging are constantly evolving and have since the last compilation of a technology list for Euro-BioImaging already undergone significant changes. It is important to be able to accommodate these in a continuous manner and procedures for technology identification (this Work Package) and for straightforward technology upgrades (WP3) will make this possible. Changes take place inside established technology fields, but also completely new technologies arise and a number of them have been identified in this report for potential further evaluation and the demonstration of user need. As the Euro-BioImaging infrastructure proceeds on its way to full operation, the technologies in this report may be the first to be identified and included, but they will be followed by many more as the imaging fields keep providing us with exciting developments.

5. ANNEX 1 – List of 29 online technology proposals
Proposals listed according to general imaging field, multiple mentions in brackets.

Biological Imaging:
Multimodal Holographic Microscopy (MHM)
Super-resolved Traction Force Microscopy (STFM)
Coherent Anti-Stokes Raman Scattering (CARS)
Brillouin Light Scattering Microspectroscopy (BLSM)
Conical Diffraction Imaging (CODIM, 2x)
Multi Foci REversible Saturable Optical Linear Fluorescence Transitions
High Resolution Episcopic Microscopy (HREM, 2x)
Phosphorescence Lifetime Imaging (PLIM)
Photo-Acoustic Microscopy (PAM)
Whole Slide Imaging/Digital Pathology
(Cryo-) Scanning Transmission Electron Microscopy (STEM) Tomography (thick specimens)
Micro X-Ray Fluorescence Spectroscopy

Biological and Molecular Imaging[6] (provisional classification):
Correlated Multimodal Imaging (CMI, 3x)
Multimodal multiscale imaging pipelines (2x)

Biomedical and Molecular Imaging:
Imaging Mass Spectroscopy (2x)
Photoacoustic Imaging (PAI, 2x)
Hyperpolarized Metabolic Magnetic Resonance
Magnetic Particle Imaging (MPI)
Magnetoencephalography (MEG)
Theranostics with radioactive probes
INDIGO-DataCloud Platform as a Service

[6] CMI and Multimodal Multiscala Imaging proposals have significant overlaps and are counted together for the total number of proposed technologies.

6. ANNEX 2 – List of 36 imaging technologies (Interim Operation)

The first generation of EuBI Node Candidates offers access to the technologies that are currently most requested in Europe and are mature and robust enough to be successfully offered to an inexperienced external user. These technologies were validated by the EuBI Proof-of-Concept Studies in Preparatory Phase I, and were evaluated in the first open call for Nodes in 2013 (see www.eurobioimaging.eu):

Biological Imaging:

- Multi-modal Advanced Light Microscopy including:
  - Spinning Disc Confocal Microscopy (SDCM)
  - Laser Scanning Confocal Microscopy (LSCM / CLSM)
  - Deconvolution widefield microscopy
  - Multiphoton microscopy systems
  - Total Internal Reflection Fluorescence Microscopy (TIRF)
  - Fourier Transform Infrared Imaging (FTIR)
- Functional Imaging: FCS, FCCS, FLIM, FRET, FRAP, Raman Spectroscopy
- Electron Microscopy (EM)
- Correlative Light Electron Microscopy (CLEM)
- High-throughput Microscopy
- Mesoscopic Imaging: OCPI, SPIM, OPT, DSLM
- Super Resolution Microscopy: STED, PALM, STORM, RESOLFT, GSD, GSDIM, 4Pi

Multi-Modal Molecular Imaging:

- (Micro)-PET
- (Micro)-SPECT
- (Micro)-MRI
- (Micro)-CT
- (Micro)-US
- Optical imaging
- Multimodal Imaging:
  - (Micro)-PET/CT
  - (Micro)-SPECT/CT
  - (Micro)-MRI/PET(SPECT)

Medical Imaging

- High-Field MRI
- Phase Contrast Imaging
- Multimodal Imaging (MRI-PET)
- Population Imaging

Challenges Framework

In addition to access to cutting-edge imaging instruments, EuBI Node Candidates provide all required resources including expert technical assistance, support for project planning, additionally required instrumentation, animal facilities, wet lab space, server space, user accommodation, etc. consultation and expertise by high-level trained experts in the field is provided during all stages of the user project.

7. ANNEX 3 – Tentative assignment of technology proposals to existing technology fields

Biological Imaging:

- Multi-modal Advanced Light Microscopy including:
  - Spinning Disc Confocal Microscopy (SDCM)
  - Laser Scanning Confocal Microscopy (LSCM / CLSM)
  - Deconvolution widefield microscopy
  - Multiphoton microscopy systems
  - Total Internal Reflection Fluorescence Microscopy (TIRF)
  - Fourier Transform Infrared Imaging (FTIR)
- Functional Imaging: FCS, FCCS, FLIM, FRET, FRAP, Raman Spectroscopy
  - Coherent Anti-Stokes Raman Scattering (CARS)
  - Phosphorescence Lifetime Imaging (PLIM)
- Electron Microscopy (EM)
  - (Cryo-) Scanning Transmission Electron Microscopy (STEM) Tomography (thick specimens)
- Correlative Light Electron Microscopy (CLEM)
- High-throughput Microscopy
  - Whole Slide Imaging/Digital Pathology
  - High Resolution Episcopic Microscopy (HREM)
- Mesoscopic Imaging: OCPI, SPIM, OPT, DSLM
- Super Resolution Microscopy: STED, PALM, STORM, RESOLFT, GSD, GSDIM, 4Pi
  - Super-resolved Traction Force Microscopy (STFM)
  - Multi Foci REversible Saturable Optical Linear Fluorescence Transitions
  - Conical Diffraction Imaging (CODIM)

Multi-Modal Molecular Imaging:

- (Micro)-PET
- (Micro)-SPECT
- (Micro)-MRI
  Hyperpolarized Metabolic Magnetic Resonance
- (Micro)-CT
- (Micro)-US
- Optical imaging
- Multimodal Imaging:

  - (Micro)-PET/CT
  - (Micro)-SPECT/CT
  - (Micro)-MRI/PET(SPECT)

  - Correlated Multimodal Imaging (CMI) (provisional)
  - Multimodal multiscala imaging pipelines (provisional)

Medical Imaging

- High-Field MRI
- Phase Contrast Imaging

- Multimodal Imaging (MRI-PET)
- Population Imaging
  - INDIGO-DataCloud Platform as a Service

Challenges Framework