Euro BioImaging
Preparatory Phase II Project

D8.2 Procedure for the identification of new technologies in the fields of biological and medical imaging

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Abstract

This document describes mechanisms to identify new technologies in the biological and medical imaging fields. It proposes a procedure how to identify new technologies, assess the need for them, test the feasibility of open access and in case of a positive outcome to include them in the technology portfolio of Euro-BioImaging.

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"Prediction is very difficult, especially if it's about the future."
Nils Bohr, Nobel prize winner in Physics

1. Introduction:

Biological and medical imaging are fields that for the last decades have been characterized by continuous technological innovation. Most major technological advances in other scientific research fields (photonics, physics, chemistry, computing) find their way quickly into instrumentation or procedures applicable to biological and medical imaging. This provides exciting opportunities for biomedical advances, but also brings with it the continuous need for adaptation of new methods and new technologies. For a technology-driven research infrastructure like Euro-BioImaging (EuBI) this poses challenges in remaining at the technological front of the field while guaranteeing reliable imaging access that leads to high quality research. For this workflows are needed that A) identify new technologies early on, B) assess their relevance to the biological and medical imaging fields and the feasibility of access provision and C) regulate their inclusion into the research infrastructure. They will be the focus of this deliverable.

For the development of the procedures of this Work Package, general concepts established for technology adoption life cycles should be considered. These include the categories innovators, early adopters, the early and late majorities and laggards. A relevant modification of the general cycle is the "chasm" defined by Geoffrey Moore[1] between innovators/early adopters and the early majority for discontinuous innovations. This often applies to high technology and seems applicable for biological and medical imaging. Innovators are the initial labs and companies that develop the prototypes and the first systems based on them. Early adopters are scientific groups that can technically emulate the initial development or make the major investment into the first commercial systems. The early majority is made up of advanced imaging facilities or image-based research groups that look mainly to apply but not to technically develop the technology. They have a more pragmatic approach to equipment investments. These are the groups that will play a role for the infrastructure.
This procedure should aim to involve innovators and early adopters in the EuBI infrastructure and to help them to connect to the early majority.

2. Super-resolution light microscopy: A new technology case study

To be able to look forward, it serves to look at past instances of similar processes.
In biological imaging the recent advances in super-resolution microscopy are a good example of how a new field comes into existence, rapidly develops into a major area of activity with a range of sub-areas and is becoming a commercially available technology offer. Initial concepts for Stimulated Emission Depletion (STED), optical shelving by ground state depletion (GSD) and super-resolution by localization of sparse signals were developed theoretically in the middle of the Nineties but the proof of concept experiments could only be performed several years

[1] Geoffrey Moore: "Crossing the Chasm" (1991)

(STED) or even a decade later (localization microscopy) when all necessary components for instrumentation development and labelling became available. This is illustrated by the fact that when all factors were in place for it, localization microscopy was described separately by three groups within the same year of 2006. The time needed for the initial commercialization of super-resolution microscopy methods varied significantly depending on a range of factors including the required technical developments, IP licensing and in some cases the commercial product cycle. For localization microscopy it was three years (based on existing total internal reflection optics), six years for STED (requiring the development of a new scan module) and in the case of structured illumination microscopy (SIM) nine years as the licensing of the technology coincided with a major upgrade of the microscoscope system it was based on (Applied Precision's Deltavision => Deltavision OMX). At this point it did however include an extension to 3D SIM that was described less than two years before. After the initial commercial releases, complications arose because these products were launched into a still rapidly developing field and require frequent technology updates to follow the field. This makes investments by research institutions difficult and, similar to computing hardware, "the best day to buy a system is tomorrow". This makes the field penetration and reliable access difficult and is a challenge that needs to be met at the infrastructure level by EuBI. Figure 1 gives a graphical overview of the timelines of method developments and product releases in the field of super-resolution.

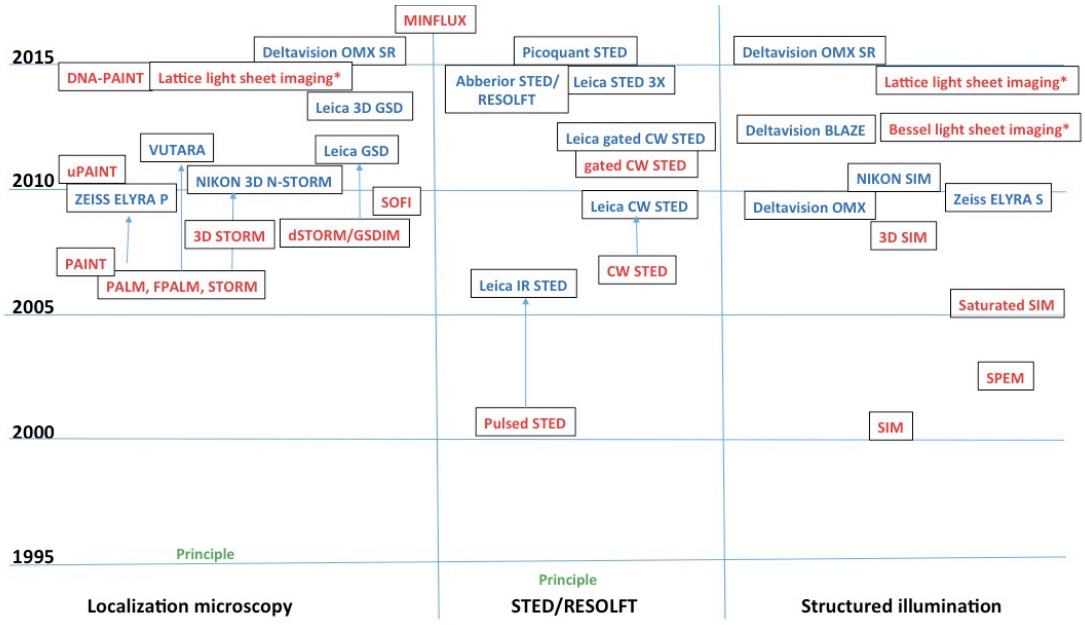

Figure 1: A very general timeline of the field of super-resolution light microscopy. Method principles are highlighted in green, the main (not all!) method implementations in red and commercial developments in blue. Arrows connect methods to their initial commercial releases. Asterisks (*) indicate light-sheet based methods that have been applied to super-resolution imaging and connect to another still developing technology development. Method acronyms used in the figure are listed in appendix I.

As we have the benefit to be able to look at the past and present in this field we can assess where the field of super-resolution stands more than twenty years after its theoretical conception and more or less a decade after it came into its own:
For super-resolution methods, the number of innovator labs was naturally very low and the number of early adopters that could take on the technologies as well. Early adopters in this case were labs that could replicate the technology or make a major investment into early commercial systems. Technology replication was easier for localization microscopy methods than for stimulated emission depletion instruments as one is less hardware based than the other. Due to the size of the required investment and the expertise required for operation, the numbers of placed first generation commercial systems were very low. In 2009, years after their market introduction, the number of placed SIM and STED systems were both still in the single digits worldwide. The "chasm" to the early majority was mainly bridged by second-generation commercial systems (new models or upgraded variants) and this has taken place in the last years. The investment into technology streamlining by microscopy companies was therefore considerable before a relevant section of the market could be reached.
As the development in the field of super-resolution microscopy methods and instrumentation is still ongoing, innovators, early adopters and the early majority are currently co-existing. This is reflected in the EuBI interim operation that includes super-resolution as a special access technology offer but super-resolution methods are also already available in several general access advanced microscopy nodes (see Eurobioimaging Interim Web Access Portal). In the field of super-resolution imaging, advanced and more generalized node offers will have to coexist for the foreseeable future as long as the field is still developing and, as shown in figure 1, recent methods (e.g. MINFLUX, 2016 and lightsheet-based SR methods) are not yet commercialized. At the current state technology developments in that field can however be accommodated by the node technology upgrade procedure recently developed in WP3 instead of being considered a new technology.

3. Procedure for technology identification and evaluation for inclusion into EuBI

3.1. Definition of a new technology

The procedure defined in D8.2 focuses on new imaging technologies that require assessment of their maturity under open access conditions, before their inclusion into the existing EuBI portfolio of imaging technologies. This procedure needs to be seen distinct from technology upgrades at EuBI Nodes, that can be implemented on existing components of the infrastructure, or technologies that are newly offered at the Node, but have already been assessed by EuBI for access provision before (see Annex 2 for current list of technologies during EuBI Interim Operation). In summary, EuBI distinguishes

A) Inclusion of new imaging technologies, which have not been assessed and offered by EuBI Nodes before (procedure outlined here in D8.2)
B) New offer of previously assessed imaging technology from the EuBI technology list at an existing Node Candidate, which has not been offered yet by the applying Node Candidate (procedure outlined in "Update of imaging technologies at EuBI Node Candidates", currently drafted by WP3)

C) Offering an existing imaging technology on newly acquired instrumentation; or existing instrumentation is upgraded/combined with new hardware/software (e.g. detectors; light source; software upgrades; etc.) (light procedure by EuBI Hub for EuBI WAP update, as outlined in "Update of imaging technologies at EuBI Node Candidates", currently drafted by WP3);

In case A) and case B), the EuBI Technology Watch Panel (TWP) will be asked for advice by the EuBI Hub, to evaluate incoming proposals. For C), the ERIC Hub receives directly the request from the EuBI Node, to update the EuBI web access portal accordingly, so that users learn about the technology update by this Node Candidate. If unclear, the TWP supports the EuBI Hub to distinguish these three cases from each other, and guide the EuBI Hub and Nodes to the correct procedure.

3.1.2 The EuBI Technology Watch Panel

The Technology Watch Panel (TWP) is suggested as an advisory body to the EuBI Hub regarding their recommendation on new imaging technologies, technology upgrades and training activities: It has been proposed to advise on the identification of new imaging technologies (case A), and on the development of the portfolio of node technology upgrades (case B), as well as training activities in emerging technologies (see WP7, D7.3, where it was referred to as Technology Watch Board, TWB). The TWP should be highly networked with EuBI Nodes, senior experts and technology providers for highest sensitivity to new opportunities. The defined set of its advisory role, composition, appointment of panel members etc. still needs to be discussed and defined in PPII WP3 [2].

3.1.3 Overview of procedure – Identification of new technologies

D8.2 outlines the procedure for identification of new technologies (case A). The central parts of this procedure have been developed and tested during the EuBI Preparatory Phase I project and enabled the preparation of the portfolio of imaging technologies for the 1st generation of EuBI Node Candidates (see Annex 2).

[2] To be further defined in Deliverable D3.3 "Detailed description of the EuBI ERIC executive management (description of all positions, reporting lines, responsibilities and operational procedures in the EuBI ERIC)"

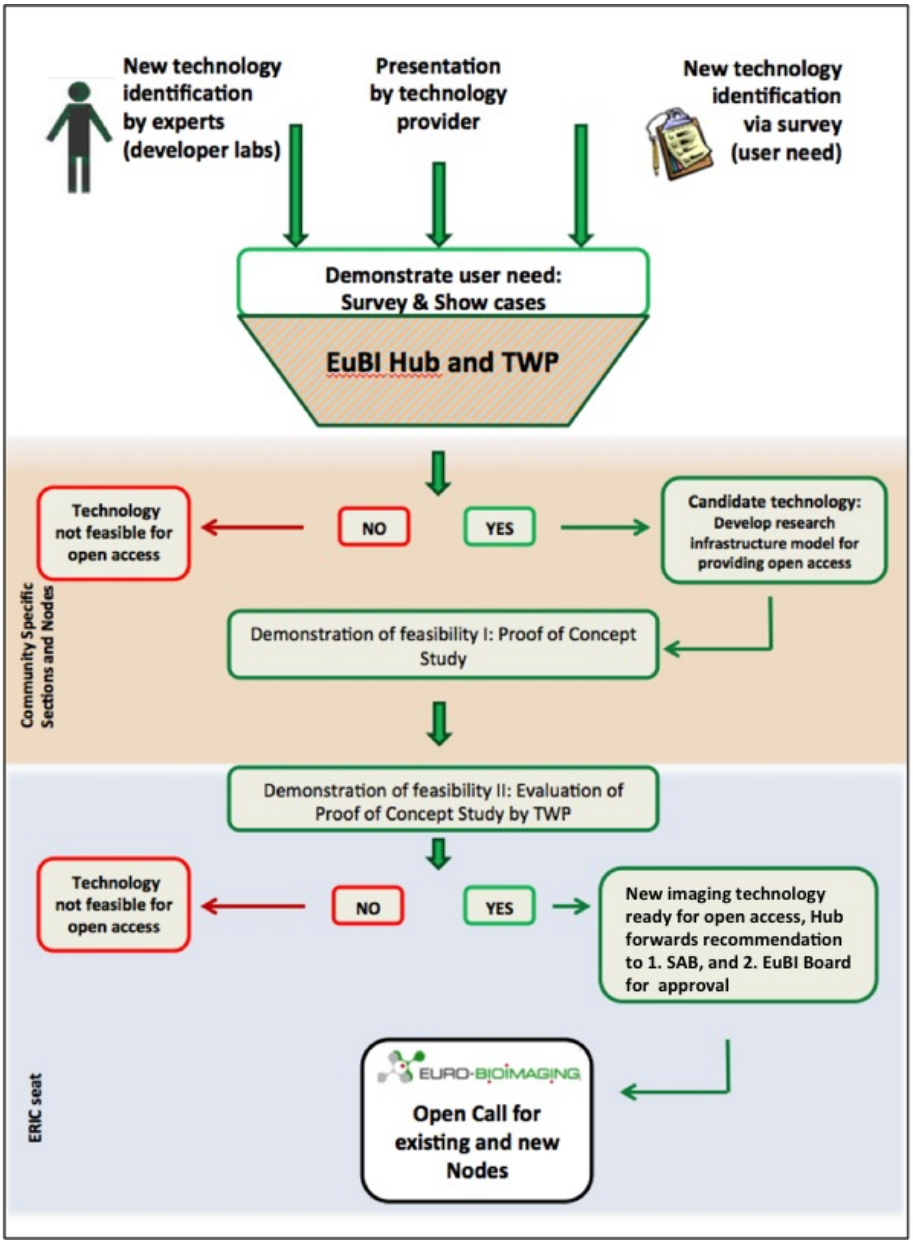

Figure 2: Overview of EuBI technology identification

In the EuBI ERIC, the identification and inclusion of new imaging technologies, that will be offered by Euro-BioImaging Nodes in open access mode, are based on

1. Identification of technology and demonstrated user needs (see below 3.2, 3.3, 3.4)
2. Development of an infrastructure model that can successfully provide open access to the technology (see below 3.5)
3. Demonstration of feasibility of open access (see below 3.6)
4. Recommendation of new technology for inclusion into EuBI by Scientific Advisory Board for approval by EuBI Board.
5. Open call for existing and new Nodes for offering this technology and independent evaluation of their applications (see below 3.7)

3.2 Collecting information on new technologies

New technologies detection will require input from different sections from the biological and medical imaging communities and needs instruments in place that can enable testing of feasibility under open access conditions. Technologies can be brought to the attention of EuBI in a continuous process that will have the following components:

- Detection based on user demand or technology pull: This will comprise periodical surveys of the stakeholder communities and as a continuously open mechanism a reporting form on the Web Access Portal (WAP) being developed in WP5.
- Detection by experts in the field or by EuBI Nodes: This can be done using the reporting form at the WAP.
- Presentation of a new technology by a technology provider (developing lab or company): This can be done through the reporting form at the WAP.

For reporting on new technologies, all potential input providers therefore will have continuous access to an online questionnaire (a reporting form on the Web Access Portal) and the regularly provided possibility to participate in a more community-targeted reporting mechanism in the form of online surveys offered through the EuBI WAP by the EuBI Hub.

3.3 Technology scope assessment

The proposed methods are forwarded by the EuBI Hub to the TWP for their assessment. This is a periodical process executed when the TWP meets and the TWP acts as an advisory panel to the Hub which recommends which procedure is applicable (see above 3.1). The assessment should cover the following points:

- Whether the technology is suitable in principle for open access
- Is this a truly new technology or an update of an existing one.
  i. If it is an update of an existing technology, a procedure currently being developed by WP3 applies (case B).
  ii. If it is a new technology, the following procedure applies (case A).

3.4 User need assessment

To demonstrate user demand, the EuBI Hub will periodically survey the needs of the biological and medical life science communities (updated online surveys every 6-12 months via the EuBI web access portal). This assessment should contain in addition to the latest field survey data, input collected by national communities, and be supplemented by an up-to-date market analysis of current availability and already existing alternative offers for a technology under consideration. Consultations on these topics should include the TWP as well as the EuBI Nodes, experts and stakeholders.
As soon as user need is demonstrated, the EuBI community-specific sections will launch a call for potential technology providers and/or identify existing EuBI Nodes with advanced expertise

in the given technology which is under evaluation, to participate in feasibility testing ("proof-of-concept study").

3.5 Formulation of a suitable infrastructure model

Upon identification of suitable technology providers or EuBI Nodes to test the technology for open user access, they will formulate an infrastructure model that should include a defined service package and the protocols for provision of access (see next point). This can to a large extent be developed from the existing guidelines for biological and medical imaging technologies that were developed in PPI[3]. The infrastructure model and service package will then be applied in the feasibility test.

3.6 Feasibility test of a new technology

For a successful infrastructure operation it is essential that the feasibility of open access and service provision to the new technology is tested with external, naïve users. This will ensure that a new technology is mature enough before inclusion into the EuBI research infrastructure.
The Proof-of-Concept Studies that were executed in EuBI PPI[4] were very successful to evaluate the initial round of technologies that were included in the first open call for nodes (Annex 2). They can serve as a template for future technology evaluations.
The main requirements to prove feasibility are:

- The technology is mature enough to be made accessible to a broad range of external, naïve users.
- The access possibility is announced in an open call and offered to the selected users based on the scientific merit of the project.
- Existence of a service package and of protocols for physical access and service provision: The offered services are clearly defined for external users and the form in which the services can be accessed and executed is established.
- Demonstration of user benefit: This is gauged by the successful execution of the proposed visitor experiment, i.e. execution within the planned timeframe, collection of relevant data that can be used for publication.

The fulfilment of these requirements will then be evaluated using a standardized questionnaire[5] provided through the EuBI WAP to be filled by the technology provider and feedback from the technology users. The feasibility test will then be evaluated by the TWP, which forwards their recommendation to the Hub.

[3] PPI/WP7-Access to innovative light microscopy technologies, WP9-Medical Imaging: Access to innovative technologies: Guidelines for Proof-of-Concept Studies (field specific)
[4] See PPI documents "Guidelines for Proof of Feasibility and Identification of Technology" and "Appendix 1: Proof of feasibility by PCS"
[5] For a suitable set of questions see PPI "Appendix 1: Proof of feasibility by PCS"

Considering the cost associated with access provision for feasibility testing, the EuBI Board will have to decide between the following options:

A. Access provision as an in-kind contribution by the technology provider (applied during the PPI proof-of-concept studies in 2012)
B. Application of access charges according to the internal procedures of the technology provider (currently applied during interim operation)
C. Support of feasibility testing by central funding of the infrastructure

Given the current finance planning for the setting up of the EuBI infrastructure option C is not part of any current budget proposal. It could only be considered for future operation budgets of the EuBI ERIC. Option B is possible, but it clashes with the idea of a feasibility test which is not service provision, but the evaluation whether a service can be realistically provided. Charging the user for being part of a test may not encourage user participation as it implies cost with possibly no benefit. Option A may therefore be the most feasible. Access provision is in the interest of the technology provider as it makes the technology eligible for future inclusion in EuBI and thus provides a potential benefit for the technology provider.

In case there are more than one technology eligible for feasibility testing within a given period, testing periods will be synchronized. In this way, the open calls can be promoted by EuBI more efficiently and more exposure is generated for the test sites. Evaluation of feasibility test results by the EuBI Hub is also facilitated by such coordination. Feasibility tests could be executed annually. This is providing sufficient agility for the EuBI infrastructure to properly evaluate developing fields and to prepare for them the inclusion in upcoming node calls.

3.7 Inclusion of a new technology

If positive, the Hub will forward the TWP advice on this technology to the EuBI Scientific Advisory Board (SAB) for their consideration. After their final evaluation, the SAB will send their recommendation to the EuBI Board for approval, for inclusion of this technology into the EuBI technology portfolio. Finally, the EuBI Hub will publish an open call for new and existing EuBI Nodes to offer this technology for open user access in the framework of the EuBI research infrastructure.
In parallel, the EuBI Hub together with the TWP and EuBI Nodes will address the training requirements for facility staff and users for the new technology and assess the potential impact of the inclusion of the new technology on other technologies in the portfolio in aspects of possible redundancy[6] and for interoperability[7] inside correlative workflows.

[6] See WP8 D8.5
[7] See WP8 D8.4

Annex 1

Method acronyms:
CW-STED: Continuous Wave Stimulated Emission Depletion
dSTORM: direct Stochastic Optical Reconstruction Microscopy
FPALM: Fluorescence Photoactivation Localization Microscopy
GSDIM: Ground State Depletion followed by Individual Molecule return
MINFLUX: MINimal emission FLUXes
PAINT: Point Accumulation for Imaging in Nanoscale Topography
PALM: PhotoActivated Localization Microscopy
RESOLFT: REversible Saturable Optical Fluorescence Transitions
SIM: Structured Illumination Microscopy
SOFI: Super-resolution optical fluctuation imaging
SPEM: Saturated Pattern Excitation Microscopy
STED: Stimulated Emission Depletion
STORM: Stochastic Optical Reconstruction Microscopy
uPAINT: universal Point Accumulation for Imaging in Nanoscale Topography

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.