

LEAPS Meets Life Sciences Conference

WHITE PAPER

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LEAPS

League of European
Accelerator-based
Photon Sources



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EXECUTIVE SUMMARY

Research in Life Sciences on the molecular and cellular scale has seen impressive progress in recent years, not least because of the research done at LEAPS facilities. Recent technology developments in x-ray, light and electron-based technologies allowed researchers to structurally characterize and to image biological samples across multiple length scales with high temporal resolution. In addition, AI-based approaches taking advantage of the outstanding quality and wealth of the experimental data provided by LEAPS facilities, have dramatically enhanced our possibilities for in silico structure prediction of biomolecules.

For X-ray facilities, these developments provide unique opportunities to address dynamics in biological processes on a molecular scale and to explore advanced X-ray imaging capabilities of biomedical samples from the nanoscale to whole organisms.

The rapidly transforming research landscape provides therefore an excellent opportunity for LEAPS facilities to enhance their impact in the Life Sciences with the current machine and beamline upgrades, by:

- fully exploring X-ray imaging opportunities, as highly relevant complementary method to imaging approaches using visible light or electrons,
- thereby potentiating time-resolved studies, to assess dynamic processes in the complex environment of a cell or tissue to near atomic resolution, as this is an absolute requirement for a holistic understanding of any living systems,
- addressing important medical questions, regarding age-related and infectious diseases,
- understanding the structure-function relationship of disease-relevant proteins, essential for the development of diagnostics and therapies, enhancing pandemic preparedness by capitalising on the diverse expertise and infrastructure at the European level,
- fostering a better integration of complementary experimental methods and computational capabilities.
- enabling Artificial Intelligence Technologies with high-quality experimental data.

This will enable Europe to remain at the forefront of modern biology and maximise the impact of pushing boundaries in biomedical research for modern societies.



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BACKGROUND



LEAPS, the **L**eague of **E**uropean **A**ccelerator-based **P**hoton **S**ources, is the largest network of Research Infrastructures (RIs) in Europe. It is a strategic consortium representing thirteen Synchrotron (SR) and six Free Electron Laser (FEL) facilities whose primary goal is to guarantee and promote excellence in science as well as impact of fundamental, applied, and industrial research for the benefit of the European research landscape and of the whole society. To tackle the societal, scientific, and economic challenges LEAPS members are working in a coordinated manner thereby contributing to enhancing European competitiveness, integration, and global outreach.

LEAPS facilities play a fundamental role in modern biology. Life Sciences account for about 30% of all research conducted at LEAPS facilities. The COVID-19 pandemic highlighted again the high relevance of the LEAPS network when the LEAPS facilities swiftly joined forces offering their capacities to the biomedical community, ranging from imaging patient samples to structurally analysing COVID-related proteins. Rapid access calls were opened to provide beamtime for COVID-19 related projects and new mail-in services and remote access tools and procedures were quickly implemented (see DOI: 10.5281/zenodo.3795660). In this time of crisis LEAPS significantly contributed to minimise the time from proposal to publication of scientific results and facilitated rapid sharing of new molecular insights with the biomedical and medical scientific community to speed up the development of vaccines and therapeutic approaches. LEAPS contribution to Life Sciences is of course not restricted to public health emergencies but continuously addresses fundamental research questions as well as all major public health challenges such as cancer, neuro-degenerative diseases, resistance to antibiotics, or the emergence of new infectious diseases. LEAPS was also an integral driver of the founding of the ARIE consortium (<https://arie-eu.org>), which includes all analytical research infrastructure facilities in Europe. The consortium published several position papers, including articles on the relevance of these facilities for cancer and viral and microbial threats (ref). The currently ongoing technical upgrades of the LEAPS synchrotron facilities to the 4th generation will substantially enhance the experimental possibilities in Life Sciences, as the new parameters of the machines will significantly increase the imaging and spectroscopy capabilities on different length-scales.

LEAPS organised the “LEAPS Meets Life Sciences” conference in order to exchange ideas with Life Sciences experts worldwide and start a scientifically informed dialogue on the major challenges in the field and to foster informed decisions on prioritising technological improvements for the facilities upgrades.

Biological research is at the basis of our understanding of all living systems on earth. This allows us to understand the ruling mechanism of life and to tackle many questions with relevance to human societies, from our understanding of the biosphere, to optimising agricultural systems and understanding and treating human and animal diseases.

Main drivers in biological and biomedical research are technology developments which frequently arise at the interface of different fields in biology or with other scientific disciplines. Modern molecular and cell biology technologies are fundamental in biomedical sciences and originated largely from microbiology and genetics. They were driven by technological advancements that are based on biochemical and biophysical research. Drug development is closely intertwined with chemistry, biochemistry, structural biology and imaging technologies across all length-scales that in turn have been driven by research in physics and material sciences. Mathematical analysis has always played a critical role in the analysis of data derived from biological systems, which are intrinsically extremely complex and data interpretation remains a daunting task. Each new technology development enables biologists to move closer to a comprehensive understanding of how biochemical building blocks and processes eventually functionally organise into living systems. However, the overwhelming majority of biological systems and dynamic processes in biology are still unknown or are poorly understood.

The X-ray sources provided at the LEAPS facilities were instrumental in the last decades for our understanding of the structure-function relationship of individual biomolecules and their complexes at near atomic resolution and more recently of dynamic properties of such systems. X-ray crystallography has by now provided the data for more than 205000 macromolecular structures, which have been deposited in the protein structure database PDB (<https://www.rcsb.org/>). This wealth of data informed researchers about the fundamentals of many biological processes and is key for structure-based drug discovery and drugs optimization in pharmaceutical research. It also provided most of the training set for the Artificial Intelligence-based AlphaFold software launched in 2021 (<https://www.deepmind.com/research/highlighted-research/alphafold>) which can predict protein structures of individual folded proteins or protein domains with remarkable accuracy, an extra-ordinarily success story in Artificial Intelligence.

Although X-ray crystallography is a major Life Sciences-related activity at synchrotrons and at FELs, there are many other research areas in biology that are taking advantage of the unique properties of the characteristics of accelerator-based photon sources. The short wavelength and significant penetration depth of X-rays, coupled with the brilliance and coherence of the X-ray beams produced at LEAPS facilities, provide an advantageous platform for a wide range of bioimaging techniques reaching spatial resolutions from the nanometre to the micrometre length-scales. As a result of the large range of contrast mechanisms available, synchrotron-based X-ray bioimaging techniques may be customised to address specific scientific questions and are already contributing significantly to advances in biomedical research.

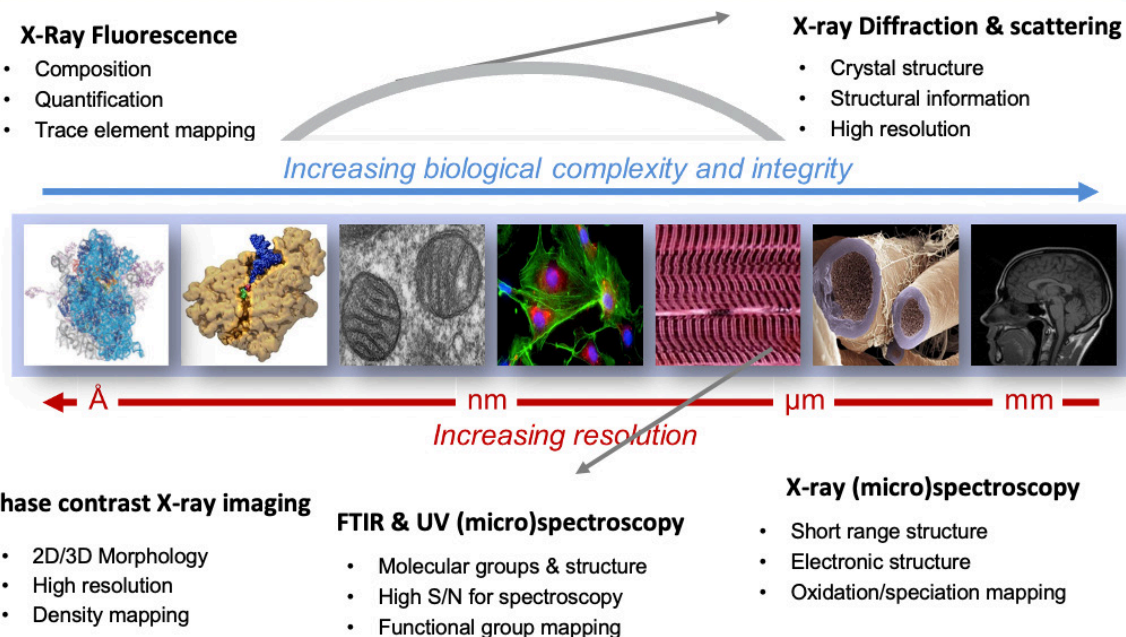
However, with an ever-growing collection of folded protein structures available in the PDB and the more recent “resolution revolution” in single particle cryo-Electron Microscopy (cryo-EM), the focus in modern biomolecular sciences is shifting towards: i) time-resolved structural analysis of proteins to capture dynamic processes at molecular level; ii) using structural biology and imaging technologies to image biomolecules, cells and tissues in physiologically complex environments spanning from atomic resolution to imaging of whole organisms in a mul-

ti-scale imaging approach; iii) studies of intrinsically disordered proteins (IDPs) and their complexes iv) high-throughput and sub-atomic resolution (1 Å or better) approaches for structural analysis.

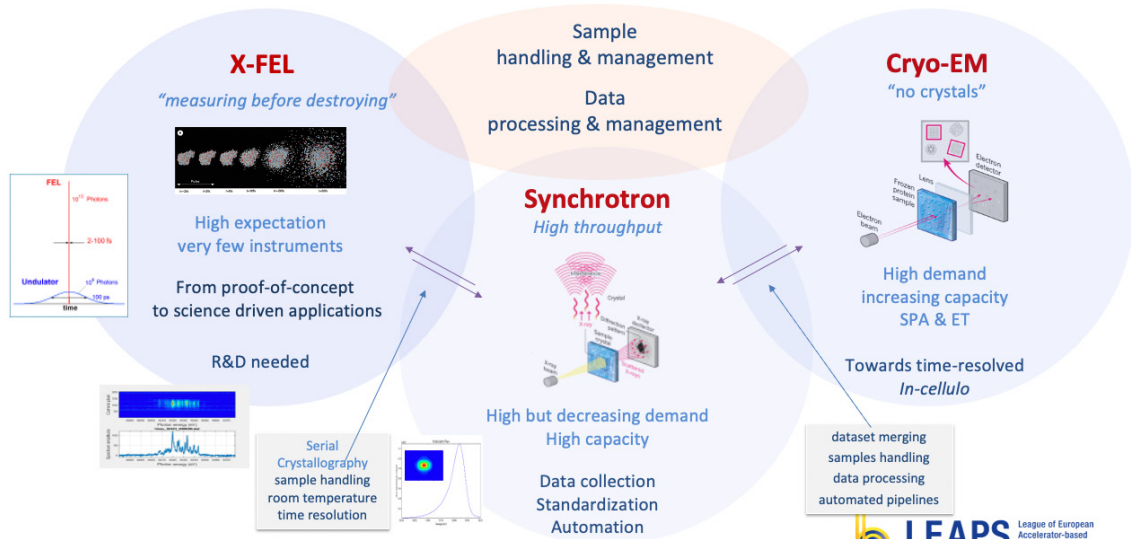
Almost all these studies are linked to technology developments which generate much higher amounts of data compared to the standard X-ray diffraction and spectroscopy applications at synchrotrons and FELs. This is especially true for recent developments in X-ray imaging technologies which require dramatically increasing IT resources. At the same time, the synchrotrons in Europe are undergoing major upgrades to 4th generation facilities and the enhanced coherence foreseen will have a substantially positive impact on X-ray imaging technologies, underscoring the relevance of an adequate computing infrastructure. These upgrades provide an excellent opportunity to support the demands of the rapidly changing scientific landscape in Life Sciences.

Topic 5 LEAPS Meets Life Sciences conference report

Towards higher spatial and temporal resolution to understand biological processes




The three pillars of Structural Biology at LEAPS facilities



The background features a dark blue gradient with numerous out-of-focus bokeh circles in shades of blue and green. Overlaid on this are thin, light blue lines forming a network or molecular structure, with small circular nodes at the intersections.

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LEAPS MEETS LIFE
SCIENCES CONFERENCE



The conference “LEAPS Meets Life Sciences” on 14th - 18th May 2023 gave an outstanding overview of recent developments in biological research with relevance for LEAPS and included the following topical sections:

- Novel Biology,
- Computational Biology,
- Modern Methods in Structural Biology and Dynamics,
- Bioimaging,
- Unmet Medical Needs
- Drug Discovery.

Emerging topics across the different sections include the increasing relevance of hybrid methods approaches, which combine diverse modalities in structural analysis of biomolecules with imaging modalities. X-ray imaging is increasingly establishing itself as a highly relevant complementary method to more traditional imaging approaches using visible light or electrons. As static structures are abundantly available but biological systems are inherently highly dynamic, time-resolved analysis of biological processes was a “fil rouge” across the conference. FEL facilities will remain at the fore-front for the analysis of structural dynamics at high spatial and time resolutions, but complementary approaches at synchrotrons and EM facilities are also emerging. All these approaches are critical for reaching a major long-standing goal in modern biology and biomedicine: assessing dynamic processes in the complex environment of a cell or tissue to near atomic resolution as this is an absolute requirement for a holistic understanding of any living systems.

The relevance of LEAPS facilities for addressing important medical questions, regarding age-related and infectious diseases was also highlighted on multiple occasions. Pandemic preparedness is globally a pressing topic and will require substantial investments, which would ideally be provided through international funding initiatives.

The dedicated strategy discussion sections following the scientific presentations regarding the positioning of LEAPS facilities in the future were centred around the following questions: How can the facilities respond to the demands of the Life Sciences community, increase their relevance, and foster scientific exchange with the Life Sciences community. Better integration with high-end computational facilities and AI-based approaches, improved on-the-fly computational capabilities as well as user-friendly, open science compatible computational workflows were identified as strategic areas for improvement. It clearly emerged from the discussions that the upgrades which many facilities undergo in the near future, will provide opportunities to strengthen imaging capabilities and bring them to the next level. On the other hand, it was noted that access, particularly to FEL facilities, remains a major bottleneck for pursuing cutting-edge high-risk biological projects. Project-oriented applications employing complementary technologies across multiple facilities in combination with improved user training and support might ease access hurdles for new users, which is likely one of the main challenges moving forward.

The background features a dark blue gradient with numerous out-of-focus bokeh circles in shades of blue and green. Overlaid on this are thin, light blue lines forming a network or web-like structure, with small circular nodes at the intersections.

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CONFERENCE SUMMARY AND OUTLOOK

Based on the presentations and strategic discussions during the conference and taking into account the limitations, which are inherent when having a selected list of speakers, the organising committee of the LEAPS Meets Life Sciences conference provides the following summary and proposes suggestions for future initiatives:

Modern methods in structural biology and dynamics

Due to the rapidly evolving technological advances and the evolving priorities in the Life Sciences community, most, if not all LEAPS facilities experience changes in the user communities and expectations. It is evident not only from this conference but also from analysis of the PDB and the literature that complementary methods, in particular cryo-EM, are of exponentially increasing relevance for the structural analysis of large biomolecules, in particular proteins and their complexes. Almost all projects in structural biology, which were presented at the conference used integrated approaches where X-ray crystallography was just one method among others to address a given biological question. Projects, which continue to rely predominantly on X-ray methods, were focusing on either time-resolved studies, high-throughput methods, pushing boundaries in resolution to detect hydrogens or analysing structural ensembles of IDPs. It also became clear that time-resolved Electron Microscopy and Electron Diffraction (not covered in the conference) have the potential to become powerful complementary methods for X-ray technologies. Regarding time-resolved studies, sample preparation, reaction triggering and delivery, as well as the ability to perform X-ray studies simultaneously with spectroscopic analysis and on-the-fly data analysis, continue to be highly relevant topics for the X-ray crystallography community in academia and industry.

Suggested actions

The scientific impact from the LEAPS facilities is strongly coupled with a strong collaboration with research units dedicated to biology in the near vicinity.

A better coordination and integration among the different LEAPS facilities and fostering methods integration by cooperation with entities such as the ERIC INSTRUCT could increase the visibility and impact of the LEAPS infrastructure in the Life Sciences community. The European Union as a transnational body with appropriate possibilities to provide funding for transnational access and integration across technologies and scientific communities is ideally suited to support new initiatives. Transnational access is still very important for researchers from countries that do not operate a LEAPS facility. It should be noted that the National Institute of Health (NIH) in the USA just recently approved a renewable 5-year funding scheme for a Life Sciences centre for user training and methods development at the US Free Electron Laser facility.

Specific challenge

The scientific community, in particular in structural biology is rapidly diversifying with respect to their technology expertise. Maintaining a user base, with expert training and knowledge to take full advantage of the X-ray facilities provided by LEAPS, becomes increasingly challenging. This is even more pertinent as the use of hybrid methods is particularly beneficial for scientific progress in biomedical sciences and it would be highly desirable to significantly expand the user base at LEAPS facilities beyond the “traditional” protein crystallography community. Also, transnational access, in particular for the European Widening countries, remains a pertinent issue.

Bioimaging

It is evident that X-ray imaging technologies including X-ray fluorescence (not covered in the conference) are the “next big thing” in X-ray technologies provided by the LEAPS facilities. Technology development in X-ray imaging is also the main area with translational potential directly into the clinics. Imaging benefits most from the enhanced capabilities in coherence and flux of the 4th generation Synchrotrons and all major LEAPS facilities are embracing technology development in this field.

Specific challenge

To maximise the impact of X-ray imaging on biomedical sciences, correlation with other imaging techniques and other data modalities (e.g. -omics data) by computational approaches is critical. This will require outreach to other biological and computational research communities and closer links to medical researchers.

Suggested actions

To best capitalise on the emerging 4th generation synchrotron facilities and to open it to new research communities, X-ray imaging processes must be streamlined, automated, robotized, and integrated with complementary imaging and structural biology techniques across multiple facilities.

Currently, national regulations in some European countries make it challenging for patient samples to be assessed at LEPS facilities. This may hamper close cooperations between the medical community and LEAPS facilities. National regulators, funding agencies as well as the EU should be made aware of these challenges and limitations to unlock the full potential of LEAPS facilities for the biomedical community.

Unmet medical needs and Drug discovery

Understanding the structure-function relationship of disease-relevant proteins is essential for the development of diagnostics and therapies, including the rational development of antibody epitopes for vaccine development, a better understanding of the pathogenicity mechanisms of infectious agents or neurodegenerative diseases, and the use of fragment-based screening to develop small molecules with therapeutic potential. In line with basic research developments, an integrated methodology approach becomes increasingly important.

Specific challenge

The tremendous relevance for human societies ability to rapidly react when exposed to a biological threat became evident during the SARS-CoV-2 pandemic in 2020 – 2022. The LEAPS facilities reacted very quickly to the SARS-CoV-2 pandemic and demonstrated the value of this consortium to tackle such a public health emergency. However, it also exposed the vulnerability of the current set-up as national and international cooperation among relevant experts with complementary scientific and complementary infrastructure needed to be organised in an ad-hoc manner.

Suggested actions

A well-established example for harvesting the translational potential of LEAPS facilities is the successful establishment of high-throughput fragment-based screening capabilities at a variety of LEAPS facilities. Similar opportunities could also be capitalised on with medical applications for bioimaging technologies. Above all, the resilience of European societies towards addressing challenges like SARS-CoV-2 should be strengthened by establishing a European level of bio preparedness capitalising on the diverse expertise and infrastructure along the lines of recently launched program of the Department of Energy in the US (<https://science.osti.gov/Initiatives/Biopreparedness>). This would require coordinated efforts between national and transnational funding agencies in Europe.

Computational Biology

All of the novel approaches in X-ray technologies are increasingly demanding with respect to computational resources. This is also true for most complementary technologies, in particular for electron- and neutron-based methods. Data analysis and access to powerful computational resources is already the main bottleneck for many experiments using X-ray sources for crystallography, in particular time-resolved crystallography, and X-ray bioimaging. In silico methods also become increasingly powerful with respect to structure prediction, as witnessed with the breakthrough achieved with AlphaFold, molecular dynamics simulators and quantum mechanics modelling.

Specific challenge

In order to foster further progress in modern biology computational approaches will be essential for maximizing the information gain from data acquisition at LEAPS facilities, for filling the resolution gaps between complementary experimental imaging modalities and for the integration of different types of biological data from different sources (e.g., bridging -omics data with imaging data).

Suggested actions

A closer integration of computational expertise and hardware in the LEAPS facilities was discussed in detail during the conference and should be followed up by the different facilities. A coordination of hardware upgrades at LEAPS facilities and their respective national supercomputing centres is highly recommended. Standardised data workflows as well as a universal understanding of the relevance of FAIR data and open software development will be fundamental for the competitiveness of European accelerator-based photon sources. European funding as follow up to the EU cluster projects on the European Open Science Cloud (EOSC), PaNOSC and ExPaNDS are essential here in further pushing the federation of computational services.

Outlook in Novel Biology

A prominent keynote presentation at the conference was an impressive reminder that our understanding of the vast majority of the biosphere is extremely limited. This is unfortunate as one repeatedly finds very valuable information about the organisation of living systems in unexpected places and several break-through discoveries or technologies started with research on rather “exotic” organisms. Hypothesis-driven research, as it is currently common in the Life Sciences, comes with the risk of fostering research on few, already well characterised biological systems.

It was emphasised repeatedly during the LEAPS Meets Life Sciences conference that the main future challenges in biology are a better understanding of native complex biological systems with high spatial and temporal resolution. For proteins, technology developments which allow tackling the structure-function relationship of intrinsically disordered proteins are also of particular importance. Fur-

ther, a better detection and understanding of the chemical space in living systems, in particular the role of lipids and sugars will become increasingly important. Computational approaches will not only be used for data analysis but also for in silico modelling will be essential for a better understanding of living systems and for efficient development of novel vaccines and therapeutics.

LEAPS and its partners



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