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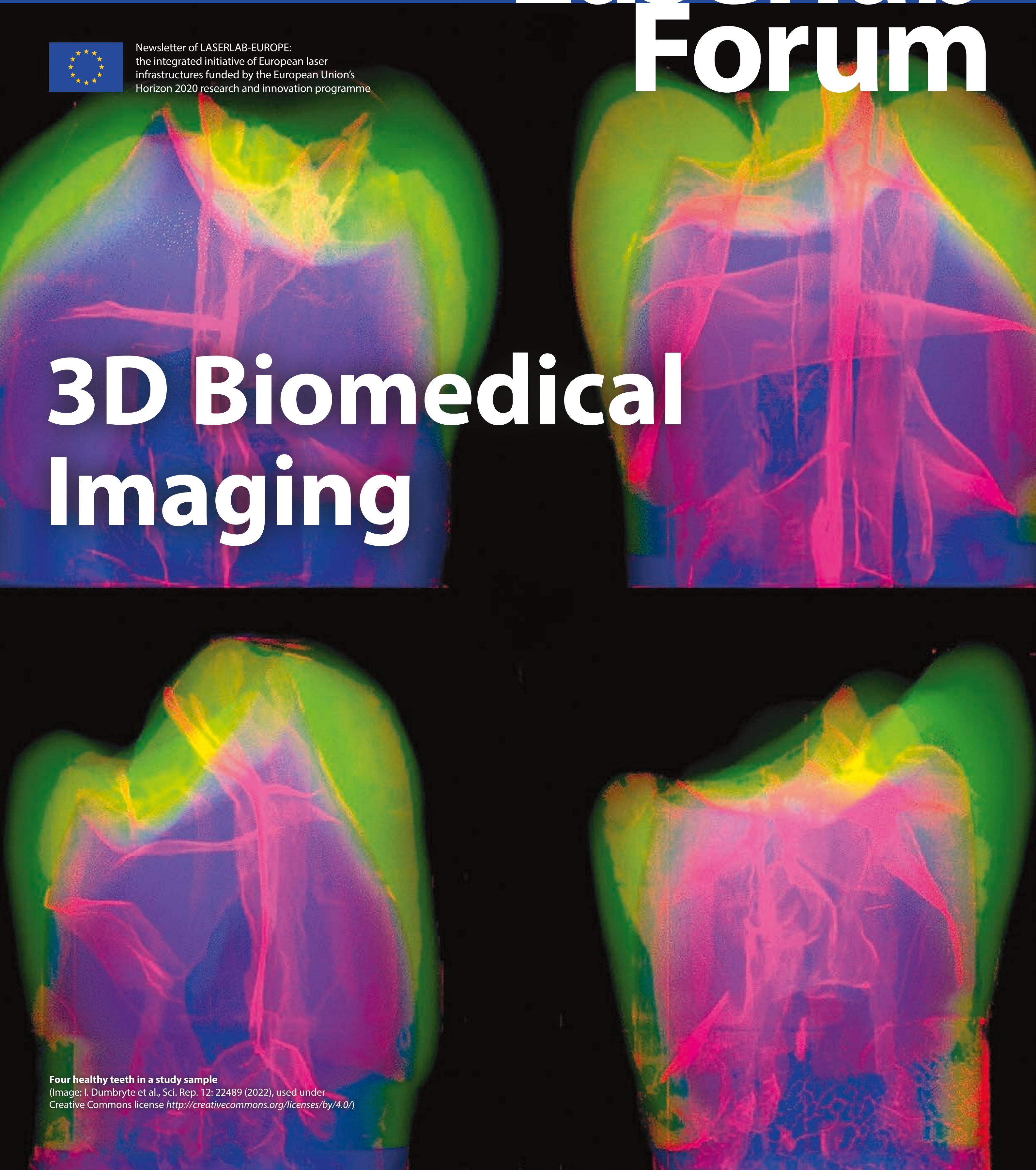
Laserlab Europe

Laserlab Forum

Newsletter of LASERLAB-EUROPE:
the integrated initiative of European laser infrastructures funded by the European Union's Horizon 2020 research and innovation programme

3D Biomedical Imaging



Four healthy teeth in a study sample
(Image: I. Dumbryte et al., Sci. Rep. 12: 22489 (2022), used under Creative Commons license *http://creativecommons.org/licenses/by/4.0/*)

In this Issue

Editorial

Sylvie Jacquemot

After exploring a subject as vast as the universe, the Laserlab Forum is going to focus on a more societal topic. Biomedical imaging has strongly evolved from the early, simple use of X-rays to diagnose bone fractures; it is now a mature technology, proven to be a key technique for healthcare, whose recent advances and new applications are presented in this issue.

Besides highlighting such developments, I would like to take the opportunity to update you on the latest news from Laserlab-Europe. Following calls closed earlier this year, funding from the European Union was acquired for three new projects: Lasers4EU, RIANA, and NanoScan. They will join the two projects launched previously, THRILL and fastMOT, in the AISBL portfolio and reinforce the consortium's sustainability. Please have in mind that the Laserlab-Europe office provides support for all our partners in searching for suitable calls, organising workshops and think-tank meetings on dedicated topics, and coordinating contributions to proposals. Thus, I strongly encourage you to contact us for future joint endeavors.

Enjoy reading.

Sylvie Jacquemot

News

Advancing Technology for High-Repetition Rate Intense Laser Laboratories

THRILL
TECHNOLOGY FOR HIGH-REPETITION-RATE INTENSE LASER LABORATORIES

The project THRILL, which has been granted more than ten million euro of funding by the European Union, aims at providing new designs and high-performance components for high-energy high-repetition-rate lasers, enabling the technical readiness level required to specify and build the needed devices. The project is focused on three enabling technologies: laser amplification at both high-energy and high-repetition-rate, the transport of high-energy laser beams over long distances, and the resilience of optical coating for large optics.

The major activity within THRILL will be organized around producing several prototypes demonstrating a high level of technical readiness, and proposing concrete steps to increase the performances and effectiveness of the industrial community through the co-development of advanced technologies up to prototyping in operational environments. The project, which is coordinated by GSI, is also offering an outstanding opportunity to train a qualified work force for research institutions and industry. Laserlab-Europe AISBL is one of nine companies and research institutes participating in THRILL's efforts.

fastMOT: Innovative light sensing solution for non-invasive imaging of deep organ structures

fastMOT

Traditionally, organ monitoring and deep-body functional imaging are performed using ultrasound, X-ray (including CT), PET or MRI. However, these techniques allow only very limited measurements of functionality and are usually combined with exogenous and radioactive agents. To overcome this limitation, six partners, including Laserlab-Europe AISBL, ICFO and POLIMI, have joined forces to develop an ultra-high performance light sensor in different imaging techniques to radically improve the performance of microscopy and imaging.

With its new sensor, the fastMOT project will enable deep body imaging with diffuse optics. Implemented in the new Multifunctional Optical Tomograph (MOT), the light sensor will achieve a

100x improvement of signal-to-noise ratio compared to using existing light sensors. The fastMOT project, which started in April, will receive a total of 3 million euro in funding: 2.49 million euro from the European Innovation Council programme and 525,000 euro from the UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee.

New Integrated Infrastructure Initiative in Photonic and Quantum Sciences

I-PHOQS
INTEGRATED INFRASTRUCTURE INITIATIVE IN PHOTONIC AND QUANTUM SCIENCES

I-PHOQS will be the largest Italian facility network of leading research infrastructures (RIs), offering full access to national and international users from academia and industry, conceived to foster inter-disciplinary research in most domains of science. Funded by the European Union – Next Generation EU, through the Italian Ministry of University and Research (MUR), I-PHOQS is developing and will make available a considerable number of experimental set-ups and instrumentations well beyond the current state of the art. The project is jointly realised by the National Research Council (CNR) and the Politecnico di Milano; the RIs LENS and CUSBO (Laserlab-Europe partners) participate in I-PHOQS together with ELI-Italy and Beyond-Nano.

New D100X Laser for simulation of extremely high temperatures and pressures

Scientists at the Central Laser Facility (CLF), institution of the Science and Technology Facilities Council, developed a powerful laser system, called DiPOLE100X (D100X), capable of simulating extreme conditions found on distant exoplanets. The laser, used in an experiment at the European XFEL in Germany, can replicate temperatures of up to 10,000 degrees Celsius and pressures equivalent to the core of the Earth. By subjecting various materials to shock compression, researchers aim to understand how these substances transform under high-pressure environments. The D100X has

HZDR

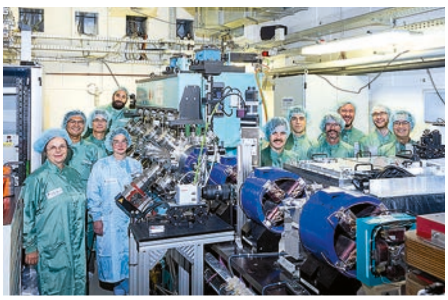
already exceeded expectations by delivering intense pressures and generating unprecedented amounts of data. Future studies using the laser system will focus on carbon-based materials, like diamond, and their transitions between solid and liquid states. The successful experiment marks a significant advancement in laboratory astrophysics and the study of matter under extreme conditions.

What is Laserlab-Europe?

Laserlab-Europe, the Integrated Initiative of European Laser Research Infrastructures, understands itself as the central place in Europe where new developments in laser research take place in a flexible and co-ordinated fashion beyond the potential of a national scale. The Consortium currently brings together 35 leading organisations in laser-based inter-disciplinary research from 18 countries. Additional partners and countries join in the activities through the association Laserlab-Europe AISBL. Its main objectives are to maintain a sustainable inter-disciplinary network of European national laboratories; to strengthen the European leading role in laser research through Joint Research Activities; and to offer access to state-of-the-art laser research facilities to researchers from all fields of science and from any laboratory in order to perform world-class research.

Breakthrough in compact and affordable free-electron laser technology

Extremely intense light pulses generated by free-electron lasers (FELs) are versatile tools in research. Particularly in the X-ray range, they can be deployed to analyse the details of atomic structures of a wide variety of materials and



HZDR/Sylvio Dittrich

to follow fundamental ultrafast processes with great precision. Until now, FELs such as the European XFEL in Germany are based on conventional electron accelerators, which make them long and expensive. An international team led by Synchrotron SOLEIL, France, and Helmholtz-Zentrum Dresden-Rossendorf (HZDR), Germany, has now achieved a breakthrough on the way to an affordable alternative solution: they were able to demonstrate seeded FEL lasing in the ultraviolet regime based on a still young technology – laser-plasma acceleration. In the future, this might allow building more compact systems, which would considerably expand the possible applications of FELs.

New X-ray technique to image phase transitions of quantum materials

Patricia Bondia

Although in the last two decades scientists have explained light-induced phase transitions in materials by invoking nanoscale dynamics, real space images have not yet been produced and, thus, no one has seen them. An international team of researchers, including scientists from ICFO – the Institute of Photonic Sciences and the Max Born Institute (MBI) among others, has recently developed a new imaging technique that allows the capture of the light-induced phase transition in vanadium oxide (VO_2) with high spatial and temporal resolution. The new method is based on coherent X-ray hyperspectral imaging at a free electron laser, which has allowed them to visualise and better understand, at the nanoscale, the insulator-to-metal phase transition in this very well-known quantum material.

ERC Grants

The European Research Council (ERC) promotes frontier research by awarding prestigious grants to outstanding researchers for projects of ground-breaking nature. Laserlab-Europe researchers have again been successful in the ERC's highly competitive selection process. Congratulations to the fifteen scientists who were recently awarded ERC grants for a period of five years, nine receiving a Starting Grant (up to € 1.5 million), three receiving a Consolidator Grant (up to € 2 million), and three receiving an Advanced Grant (up to € 2.5 million).

Pelayo Garcia de Arquer (ICFO): Nanoscale advance of CO_2 electroreduction

Pelayo García de Arquer, leader of the CO_2 Mitigation Accelerated by Photons group at ICFO, has been awarded an ERC Starting Grant to pursue the project "Nanoscale advance of CO_2 electroreduction" (NASCENT). The project seeks to advance the understanding of electrochemical interfaces using a novel combination of operando spectroscopies and, using this information, programme them using atomically designed materials to bring CO_2 electroreduction closer to viability.

Samuel Beaulieu (CELIA): Ultrafast topological engineering of quantum materials

In his ERC Starting Grant project UTOPIQ, Samuel Beaulieu aims to develop new techniques allowing the measurement of electron topology in quantum materials. These new methods will be articulated around the in-depth study of the photoelectric effect, explained by Einstein more than a century ago, which consists of removing electrons from matter with light. In addition to measuring the energy and the ejection angle of the electrons, the typical quantities measured in photoemission experiments, the effect of the rotation of the polarization of light during the photoelectric effect will be taken into account. These measurements promise to reveal new information on the topology of electrons within solids. Subsequently, new mechanisms to control the topology of electrons within matter, using ultrafast light pulses, will be developed and investigated in detail.

Marcus Ossiander (IEP-TU Graz): Extreme ultraviolet meta-optics for attosecond microscopy

Marcus Ossiander received an ERC Starting Grant for his project "Extreme ultraviolet meta-optics for attosecond microscopy" (EUVORAM). According to Ossiander, ultrafast physics opens up many possibilities. "We can use it to study solar cells, improve catalysis and other chemical reactions, or even analyse how fast digital communication can be in the first place." In the project, flat nanostructures are designed to mimic the function of a lens and to focus extreme ultraviolet light. The short wavelength then makes it possible to observe the smallest electronic movements with time resolutions in the range of attoseconds.

Adrien Leblanc (LOA): Experimental signatures of quantum electrodynamics in the strong field regime

Theory of quantum electrodynamics (QED) unifies electromagnetism and quantum physics for the description of the interaction between light and matter. In the so-called "strong field regime", i.e. when the light intensity is sufficient for the QED effects to have a nonlinear response and become preponderant thus producing strong signatures in the laboratory, this theory remains barely explored experimentally and is currently carried out theoretically by perturbative methods. In his ERC Starting Grant project EXAFIELD, Adrien Leblanc aims to create sufficient light intensities to reach conditions beyond the perturbative regime and thus detect stronger QED effects to improve our understanding of the strong field regime of QED physics.

Hugo Marroux (LIDYL): Solution attosecond chemistry

Hugo Marroux' research consists of studying the behaviour of molecules following x-ray irradiation on the attosecond (10^{-18} seconds) timescale, characteristic to the electrons' movement. To access this limit of the time domain, he develops state-of-the-art laser technology producing attosecond bursts of x-ray radiations. In his ERC Starting Grant for his project SATTOC, Hugo Marroux will use these new laser technologies to study similar events in the liquid phase where the surrounding molecules participate to the fast electron transfers. The liquid environment not only allows studying these fundamental solute solvent electron transfers, but it also opens these investigations to a variety of biorelevant systems.

Margherita Maiuri (POLIMI): Manipulation of photoinduced processes by reshaping transition states via transient strong coupling

With her ERC Starting Grant project ULYSSES, Margherita Maiuri proposes a new paradigm for controlling physicochemical processes activated by light to improve their efficiency. The project will develop a novel platform that exploits optical nanostructures and ultrashort laser light pulses for real-time manipulation of molecular reactions, with applications ranging from photovoltaics to photocatalysis.

Andrea Trabattoni (DESY): Multi-messenger soft-field spectroscopy of molecular electronics at interfaces

Helmholtz junior research group leader Andrea Trabattoni was awarded an ERC Starting Grant for his project SoftMeter. Using a novel approach combining a series of ultrashort, yet weak field laser pulses, the project aims at resolving ultrafast processes occurring at the interfaces of two different materials that are in the gas phase. Within a perturbative approach based on the concept of electron self-diffraction, SoftMeter will circumvent the drawbacks of strong-field spectroscopic techniques. The outcomes could have significant impacts for catalytic and solar harvesting technologies exploiting aerosols interfaces for instance.

Matz Liebel (LLAMS): Phototransient microscope

In his ERC Starting Grant project, photonics researcher Matz Liebel will develop a phototransient microscope (PIROscope): an innovative biomedical imaging platform that will provide chemically resolved images of biological materials such as cells, bacteria or tissue. He hopes to visualize molecular details of breast cancer tissue at high resolution and the metabolic activity of bacteria following antibiotics treatment. Routine diagnostics in hospitals often rely on dyes to stain and visualise key cellular building blocks. The PIROscope identifies these structures based on their vibrational or chemical fingerprint. This approach eliminates complex, costly and often error-prone sample preparation steps and further allows measuring the mass of the individual components.

Sérgio Domingos (CLL): Microwave fingerprinting artificial molecular motors in virtual isolation

With his recently awarded ERC Starting Grant, Sérgio Domingos is exploring new experimental strategies to bring the promise of rotationally resolved spectroscopy to the realm of molecular nanotechnology. The ERC-funded project, MiCRoARTiS, aims to demonstrate the harnessing of conformational dynamics of artificial molecular motors in the gas phase. This class of highly functional molecules can undergo structural changes in a controlled manner when triggered by light or heat.

Thomas Bocklitz (Leibnitz-IPHT): Non-invasive computational immunohistochemical staining based on deep learning and multimodal imaging

In order to distinguish between healthy and diseased tissue in tumour diagnostics, conventional methods involve staining tissue samples and then having them examined by pathologists. These steps are labour-intensive and require a great amount of time and money. Researchers in the ERC Consolidator Grant project STAIN-IT want to develop a faster and gentler procedure. In the transdisciplinary project, Thomas Bocklitz, head of the research department "Photonic Data Science" at the Leibniz IPHT, and his team are researching and developing a digital staining method. Their goal is to use multimodal imaging techniques in a non-invasive way. To do this, image data is analysed using artificial intelligence to mimic immunohistochemical staining.

Ioachim Pupeza (Leibniz-IPHT):Laser-based infrared vibrational electric-field fingerprinting

The major goal of the ERC Consolidator Grant project LIVE (Laser-based infrared vibrational electric-field fingerprinting), led by Ioachim Pupeza, is to research and develop novel light sources as well as innovative IR technologies and instruments and to open up application potentials for the diagnostic analysis of biomedical samples. The process is expected to significantly increase both the throughput rate of procedures and shorten the time required for a single analysis, which is an important factor for the clinical setting.

Costanza Toninelli (LENS): Quantum interfaces with single molecules

Costanza Toninelli has received an ERC Consolidator Grant for her project "Quantum interfaces with single molecules" (QUINTESSEnCE) project. The challenge is to exploit quantum effects in systems of increasing complexity such as molecules in the solid state, with the possibility of miniaturisation and portability typical of integrated photonic devices. QUINTESSEnCE takes up the challenge, combining the extreme flexibility of molecular chemistry, which allows the creation of molecules with customised energy states, with the most advanced nanophotonic techniques.

Niek van Hulst (ICFO): Photons and electrons on the move

Niek van Hulst received his third ERC Advanced Grant for his project entitled "FastTrack: Photons and electrons on the move". In this new project, he will investigate the dynamic organisation of the natural light-harvesting membrane architecture, its packing order, diffusion, and reorganisation in response to light stress. The research will address questions related to which pathways are taken to charge separation and the role of fluctuations, coherences, input-spectra and vibrations.

Morgan Mitchell (ICFO): Field sensors with exceptional energy resolution

Morgan Mitchell has recently been awarded an ERC Advanced Grant for the project "Field-SEER: Field Sensors with Exceptional Energy Resolution". In this project, he will develop magnetic sensors with combined spatial, temporal, and field resolution beyond what is possible with existing sensing approaches. Ultra-high-coherence media, including Bose-Einstein condensates and optically-addressed nuclear spin ensembles, will be developed as sensors for application in fundamental physics and biomagnetism.

Majed Chergui (FERMI): X-ray spectroscopy of molecular chirality in solutions

Majed Chergui, founder of the LACUS centre at EPFL, has recently won an ERC Advanced Grant for his project "CHIRAX: X-ray spectroscopy of molecular chirality in solutions", which aims at implementing steady-state and time-resolved X-ray circular dichroism to resolve molecular structures and their evolution with element specificity. The research will in addition further develop new tools using the orbital angular momentum of X-ray light to perform helical dichroism studies.

3D Biomedical Imaging

Biomedical imaging plays an important role in health and life sciences, with 3D biomedical imaging now opening new possibilities from basic research to clinical diagnostics and treatment. The articles in this focus showcase examples of possible applications and tools with a transformative impact.

X-ray tomography and machine learning for tooth microcrack analysis (VULRC, Lithuania)

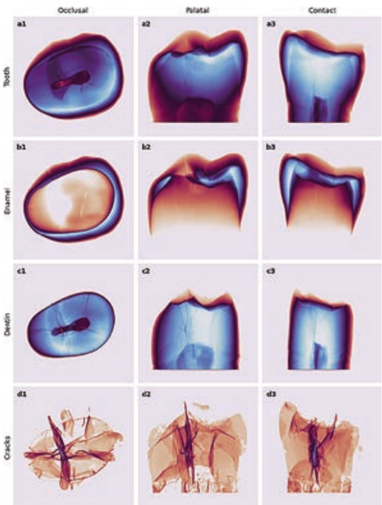


Figure 1: X-ray µCT data-cube projected density maps along three major axes indicate CNN-segmented voxels belonging to the tooth, enamel, dentine, and cracks

The combination of X-ray micro-computed tomography (µCT) with convolutional neural network (CNN) assisted voxel classification and volume segmentation has, for the first time, made it possible to take a look at the network of microcracks (MCs) inside a tooth and reveal a 3D image without destroying the sample.

This experimental work was performed by an interdisciplinary team including a dentist, an astronomer, and a laser physicist from Vilnius University, together with colleagues from Stanford and Swinburne Universities.

Four extracted, undamaged human premolars were scanned using a µCT instrument and segmented with a newly trained CNN image segmentation model to identify enamel, dentine and cracks. This technique allowed 3D characterisation of all the MCs in a tooth, regardless of where in the tooth they began and extended (Figure 1), along with evaluation of the arrangement of cracks and their structural features (Figure 2). Moreover, the morphological characteristics of the different tooth surfaces, such as the degree of convexity, surface roughness and enamel layer width, did not interfere with the MC assessment procedure.

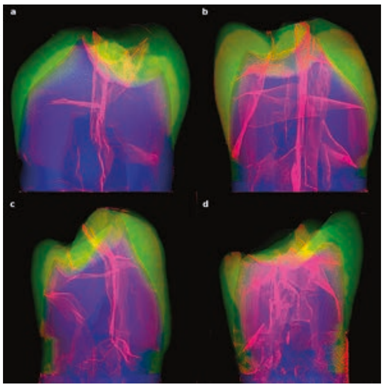


Figure 2: X-ray µCT data-cube projected density maps of CNN-segmented enamel (green), dentine (blue), and cracks (red) reveal an intricate inner structure in the four healthy teeth used in the study

The work revealed an intricate star-shaped network of MCs covering most of the inner tooth, suggesting that MCs could be considered as structural and possibly functional elements of the tooth, offering a protective role (by redistributing forces), rather than a damaging one.

From a clinical point of view, there is a need to revise the definition of MCs, to re-evaluate their role and impact on tooth integrity and longevity, and to develop new algorithms for the monitoring and treatment of teeth with MCs in daily clinical practice. More widely, this detailed volumetric imaging will expand understanding of the cracking pattern in natural hard materials, and provide a greater insight into how to design biologically-inspired solid structures and predict the propagation of cracks within them.

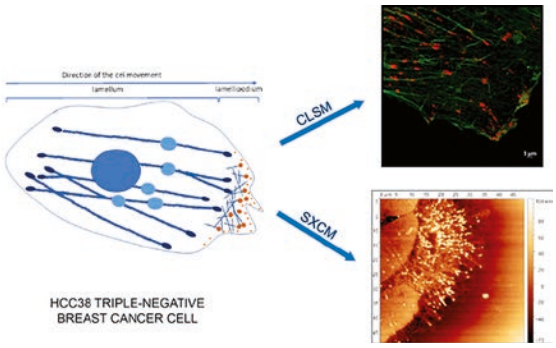
Irma Dumbrytė, Donatas Narbutis and Mangirdas Malinauskas (VU, Lithuania)

I. Dumbryte et al., Sci. Rep. 12: 22489 (2022)

Imaging of cancer cell adhesion using combined soft X-ray contact microscopy and confocal laser scanning microscopy (MUT-IOE, Poland)

High-resolution monitoring of cell adhesion structures is essential for the study of cell movement mechanisms. It determines the metastasis of cancer cells, which is of clinical importance in determining treatment. A soft X-ray contact microscopy (SXCM) technique was used by biologists at the Centre of Biomedical Engineering (CIBIO) at the Military University of Technology (MUT) in Warsaw, Poland, to study the metastasis of breast cancer cells.

A team at the Institute of Optoelectronics at MUT (MUT-IOE) developed a compact SXCM system, based on a laser plasma soft X-ray source with a gas puff target. This was then combined with a commercially available confocal laser scanning microscope, which allowed the structures of Focal Adhesion (FA) complexes responsible for cell attachment to the substrate to be uncovered.



Imaging of breast cancer cell adhesion structures using soft X-ray contact microscopy (SXCM) and confocal laser scanning microscopy (CLSM) techniques. Focal adhesion structures are visible.

Observing FA structures and their reorganisation in living cancer cells, without additional modifications, enabled scientists to elaborate on cell cancer movement. The figure illustrates cell adhesive structures (FAs and actin fibres) seen under the confocal laser scanning microscope, and the recorded image of the cell's lamellipodium imprint on the photoresist surface using SXCM. Photoresist PMMA may be degraded during exposure, depending on the efficiency of radiation passage through cellular structures. After removing the cell residue and degraded fragments of the PMMA, atomic force microscopy (AFM) was used to scan the imprint of the cells. AFM 3D images represent surface features of imprints with nanometre resolution.

SXCM, performed with a table-top system, helped to obtain a resolution showing the substructure of the FA protein complex without a cell fixation step, with the technique used revealing the size, area and cross-sectional plots of FA inside HCC38 breast cancer cells. The detailed knowledge of cell adhesion and native FA structures could bring about new therapeutic options to combat cancer.

Paulina Osuchowska and Elżbieta Trafny (MUT-IOE)

P.N. Osuchowska et al., Int. J. Mol. Sci. 22: 7279 (2021)

XPulse laser plasma X-ray source for phase contrast mammography (CELIA, France)

left: XPulse 3D mammography Prototype, right: Laser plasma X-ray conversion system

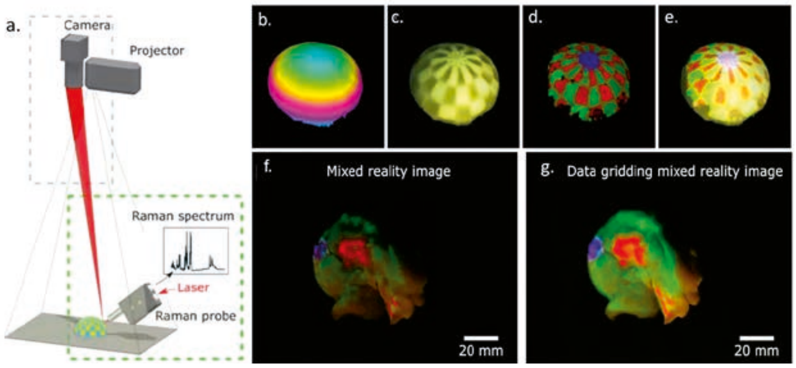
Mammography is the most widely used imaging technique for breast cancer screening and diagnosis. Although studies have been conducted on its effectiveness for the detection of breast cancer and the reduction of associated mortality, the technology is still constantly evolving, in particular to improve the generation and detection of X-rays, and to exploit new methods and techniques of image acquisition and reconstruction.

The XPulse project – led by ALPhANOV, Amplitude Laser Group, CELIA Laboratory, Imagine Optic and Institut Bergonié and funded by the Region Nouvelle Aquitaine and FEDER – aims to develop an innovative X-ray phase contrast mammographic system, based on the use of a laser plasma X ray source. This system will improve the contrast and resolution of the images, reduce the deposited dose, and improve the patient's comfort by realising 3D full tomographic images without breast compression.

Phase contrast breast imaging applications often require the use of high power and high brightness sources. While such conditions are easily available on synchrotron sources, laboratory-scale sources remain a technological challenge. Laser-driven x-ray sources represent a promising solution, since they are mostly limited by the available power from short pulse laser systems: with rapidly evolving laser technology, available power is increasing each year. For mammographic applications, the laser driver will need to be a kW-class, short pulse (ps or sub-ps) laser system. The XPulse collaboration has prototyped a laser plasma conversion system combined with a kHz, 100 W-class laser driver. This system will soon be integrated into the phase contrast mammography imaging prototype and used for preclinical tests on breast phantoms and biological samples.

Fabien Dorchies (CELIA)

Real-time molecular imaging of near-surface tissue using Raman spectroscopy (Leibniz IPHT, Germany)



Adapted from W. Yang et al., Light-Sci. Appl. 11: 90 (2022)

a. Raman-based system for the acquisition of MVR images
b. Data accessing the topology of a hemisphere phantom
c. Brightfield information mapped on the topology information
d. Molecular information combined with AR and the topological information and
e. information directly projected on the sample
f and g. Visualisation of pharmaceutical and lipid-rich compounds on a brain tissue sample

Current medical imaging techniques mostly provide information based on morphological or anatomical differences in the tissue, disregarding the underlying molecular composition. Raman spectroscopy has the technological potential to provide the intrinsic molecular fingerprint of a sample label-free, non-invasively, and non-destructively. Such molecular sensitive methods could be used for clinical in vivo diagnostics, to detect, and potentially delineate, cancer from healthy tissues; however, current fibre optic probe systems do not support image acquisition or provide instantaneous data analysis. To overcome these challenges, a team of scientists has been working to develop a fibre optic probe-based imaging system that can exploit the whole potential of Raman spectroscopy. [1]

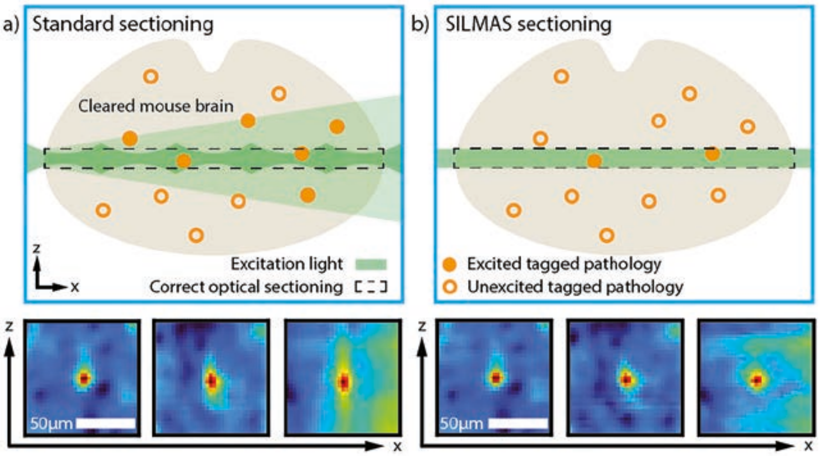
The proposed system enables handheld imaging acquisition using a fibre optic probe, as well as real-time data processing and reconstruction of molecular information. It combines Raman spectra measurements, simultaneous computer vision-based positional tracking with real-time data processing, and real-time formation of molecular virtual reality (MVR) images. These images can be observed as augmented chemical reality (AR) on a computer screen or can be projected onto the tissue itself, creating mixed reality (MR) information that can be viewed in real-time with the naked eye. Sample topologies can be added to the acquired data, enabling mapping of the molecular information onto a 3D sample surface.

The proposed system will facilitate real-time molecularly specific clinical diagnostics and molecular boundary demarcation, with smart and intuitive visualisation of the data using AR and MR, opening future clinical applications. It offers easy, direct access to the patient site and can provide biochemical distributions from the region of interest, for disease tissue differentiation during surgical resection. With a spatial resolution of 0.5 mm in the transverse plane, a topology resolution of 0.6 mm, and a spectral sampling frequency of 10 Hz, large tissue areas can be sampled in a few minutes, making the system highly suitable for clinical tissue-boundary demarcation. It also has non-medical applications, for example in manufacturing and quality control.

Wei Yang, Florian Knorr, Ines Latka, Matthias Vogt, Gunther O. Hofmann, Jürgen Popp and Iwan W. Schie (Leibniz IPHT, Germany)

[1] W. Yang et al., Light-Sci. Appl. 11: 90 (2022)

Adapted from D. Frantz et al., Biomed. Opt. Express 13: 4907 (2022)



Comparison between standard sectioning in a) and SILMAS sectioning in b). Below are examples of fluorescent pathology at different penetration depths in cleared tissue. In a) the z-resolution is deteriorating with depth, while in b) the z-resolution is uniform throughout.

SILMAS – 3D microscopy for the quantification of pathology in whole mouse brains (LLC, Sweden)

Structured Illumination Light-sheet Microscopy with Axial Sweeping (SILMAS) is a volumetric imaging method for cleared tissue being developed by laser diagnostics researchers and neuroscientists at Lund University, Sweden.

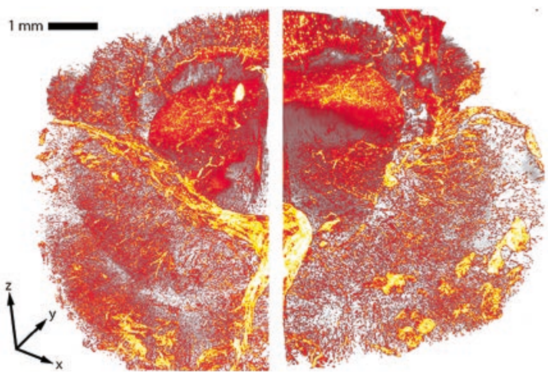
Tissue clearing has become increasingly popular with the neuroimaging community over the last decade, as it allows researchers to image uncut brain tissue and visualise fluorescently-tagged neural structures using visible light. SILMAS is specifically designed to image such samples at a high, uniform, and isotropic resolution, offering improved contrast and more quantitative intensity values than standard light-sheet microscopy.

Light-sheet volumetric imaging is performed by stacking optically-sectioned 2D planes into 3D volumes. Despite tissue clearing, the sectioning quality inevitably deteriorates with penetration depth, due to light scattering. Additionally, most microscope designs have limited field-of-view (FOV), so multiple images are stitched together into one plane to achieve a larger FOV. As a result, the optical resolution suffers in the third dimension, and is non-uniform within each plane.

In SILMAS, a structured light-sheet is used to reject of out-of-plane signals from the scattered light that is deteriorating the image. The light-sheet has a high numerical aperture and is swept across the FOV to obtain thin and uniform optical sectioning. As a result, the method can reach uniform volumetric resolutions down to 1 µm^3 in whole mouse brains. By rejecting out-of-plane signals a quantitative intensity signal, attenuated with tissue depth, is obtained at high contrast. This attenuation can be compensated for, which allows for accurate visualisation. These characteristics make SILMAS data uniquely fitted to the quantification of fluorescently-tagged pathology throughout whole brains from mouse models.

In an ongoing study, a neural network is being developed for the quantification of Lewy pathology, which is key in the development of Parkinson's disease. The study aims to determine to what extent the improved data uniformity can optimise the training of a neural network, thereby reducing the need for manually labelled data. This would significantly streamline the workflow for data processing in neuroscience, and contribute to more rapid progress in the field.

Lund University



3D volume of a whole cleared mouse brain captured with a prototype SILMAS instrument at 2 µm isotropic resolution

David Frantz and Edouard Berrocal (Lund University)

D. Frantz et al., Biomed. Opt. Express 13: 4907 (2022)

Introducing a modulated excitation to localise single molecules (ISMO, France)

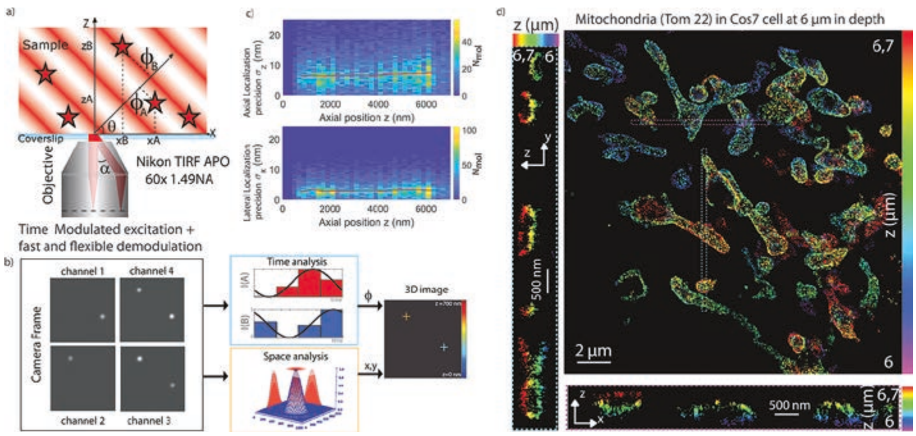
Recent developments in fluorescence microscopy have enabled imaging beyond the diffraction limit, reaching previously inaccessible observation scales in biological samples. Single molecule localisation microscopy (SMLM) techniques (PALM, (d)STORM, PAINT, etc.) can achieve lateral localisation precisions of a few nanometres, but improvement in the axial direction remains a major challenge to the development of a nanoscope with isotropic 3D resolution, capable of imaging at several tens of microns depth.

In SMLM, the position of the fluorescent emitters is usually obtained by fitting the point spread function (PSF). Spatially-based localisation precision thus strongly relies on the PSF shape, which is degraded by defocusing or aberrations, and strongly affects 3D imaging. Researchers from ISMO, in collaboration with Institut Langevin, recently proposed a new localisation strategy, Modulated Localisation (ModLoc) [1,2], based on a time signature to retrieve the fluorophores' position over the whole field-of-view.

With this strategy, wide-field uniform excitation of the sample is replaced with a shifting structured excitation, typically a moving fringe pattern (cf Figure a). This induces a time-modulated emission of the illuminated fluorophores, where the phase holds its position. The short *on*-time of a single molecule in dSTORM means that modulation frequencies typically over 500 Hz are required, which is too fast for sequential image demodulation for most cameras. An optical assembly, based on a Pockels cell or galvanometric mirrors, steers the photons in four sub-images that are then acquired in a single camera frame (cf Figure b), achieving demodulation without photon loss.

Results to date show an improvement in localisation precision by a factor of 2.4, and the unique capability to achieve uniform, sub 7 nm precision for in-depth imaging (cf Figures c, d). Furthermore, because it is resistant to

S. Lévêque-Fort, ISMO/CNRS



a) Introduction of a tilted, structured illumination pattern to encode axial information; b) modulated fluorescence is sampled at ~kHz on four sub-arrays on the camera to retrieve the phase; c) lateral and axial precision within the first 7 µm; d) 3D imaging of mitochondria in COS7 in dSTORM (Alexa Fluor 647)

optical aberrations, ModLoc allows imaging of complex samples, such as tissues or organoids, up to several tens of microns in depth.

Work is ongoing to apply the ModLoc technique to identify multiple dyes associated with various proteins, with further developments planned within the framework of the EIC Pathfinder Open project *RT-SuperES* beginning in July 2023, which aims to deliver a multiscale nanoscope.

Abigail Illand, Pierre Jouchet (ISMO, Université Paris Saclay), Emmanuel Fort (Institut Langevin), Sandrine Lévêque-Fort (ISMO)

[1] P. Jouchet et al., Nature Photonics 15(4): 1–8 (2021)
[2] P. Jouchet et al., Phil. Trans. R. Soc. A. 380: 20200299 (2022)

Adaptive optics fluorescence microscopy for high resolution in vivo imaging (ISMO, France)

Light-sheet fluorescence microscopy and two-photon excited fluorescence microscopy are popular techniques for 3D imaging of living samples, offering low phototoxicity, sectioning capability, and good spatio-temporal resolution. They are widely used in embryonic development imaging, cell tracking and vasculature studies, and have played a key role in deciphering brain functions in neuroimaging. However, the refractive index inhomogeneity of biological tissues produces optical aberrations when targeting high-resolution, in-depth imaging using high numerical aperture objectives, significantly reducing contrast and resolution.

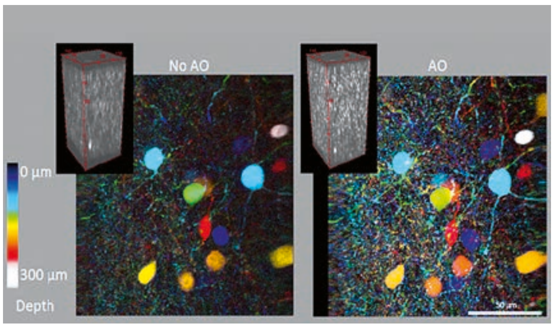
A novel adaptive optics (AO) method has been proposed to compensate for such aberrations and increase the image quality, based on direct wavefront sensing from an extended scene Shack-Hartmann wavefront sensor (SHWFS). This approach delivers fast, efficient and easier correction [1], as it neither requires the iterative algorithms used in sensorless AO setups, nor the complex and/or expensive use of fluorescent beads or a pulsed laser to generate a guide star.

The benefit of the extended scene SHWFS has been demonstrated for scattering samples, delivering improved accuracy at large depths in low signal-to-background ratio conditions [2]. The sensor was implemented in an AO two-photon fluorescence microscopy (AO-TPFM) setup, with a dual-colour labelling strategy: the wavefront was measured using red anatomical labelling, thus preserving the photon budget of the green labelling of interest. The figure shows the ability to correct aberrations up to 350 microns deep inside a fixed brain tissue, resulting in a large gain in intensity and resolution. Since the scattering length in fixed brain tissue is two-times smaller than in intact tissue, the technique promises deep in vivo imaging at depths reaching 700 microns, with contrast typically increased by a factor of five for small structures.

The sensor was also implemented in an AO light-sheet fluorescence microscope (AO-LSFM) for in vivo imaging of densely labelled samples [3]. Combined with an approach based on axially swept LSFM, the novel AO strategy enabled coverage of a large field of view (typically 400 microns), whilst maintaining a high 3D resolution (typically 0.4 x 0.4 x 1 micron) and increased signal deep inside a zebrafish larva. The setup delivered enhanced 3D in vivo images down to 300 µm deep in various areas, such as the heart and brain, demonstrating its performance capabilities.

Alexandra Fragola (ISMO, Université Paris Saclay) and Fabrice Harms (Imagine Optic)

[1] A. Hubert et al., Opt. Lett. 44: 2514-2517 (2019)
[2] S. Imperato et al., Opt. Express 30: 15250-15265 (2022)
[3] A. Hubert et al., http://biorxiv.org/lookup/doi/10.1101/2023.01.06.522997 (2023)



AO-TPFM for closed-loop correction in fixed brain slices. 2D maximal intensity projection of a stack of images in cortical brain slices of GAD-GFP mice without (left) and with (right) AO correction. Cell depths are colour-coded. Inserts: original Zstacks (S. Imperato, ESPCI and L. Bourdieu, IBENS)

Triggering proton-boron fusion reactions using a 10 GW tabletop laser

Fusion reactions are literally a "hot" topic, requiring temperatures in excess of 100 million degrees Celsius. They hold the promise of providing near limitless, clean, baseload energy, but the amazing benefits of their potential use remain balanced against the extremely challenging realisation of the fusion schemes.

Conventional fusion approaches mostly utilise the deuterium-tritium reaction (yielding one alpha particle and one neutron), as it has a relatively low minimum temperature. A class of advanced fusion schemes may, however, prove more attractive in the context of energy gain and safety. For example, the fusion reaction between a proton and the boron-11 isotope gives off three alpha particles, and the reactants involved are all abundant and stable isotopes. Moreover, the reaction is aneutronic, i.e. almost no neutrons are generated, strongly reducing such effects as radiation damage and radioactive contamination of surrounding materials. Unfortunately, proton-boron (pB) fusion is not currently achievable with conventional methods, because the reaction requires a temperature approximately ten times higher than that for deuterium-tritium fusion. Thankfully, advancements in laser technology over the last few decades offer a different approach to triggering the pB fusion reaction, under plasma conditions far from thermodynamic equilibrium. This possible approach has renewed the interest of the scientific community in this matter. As well as potentially facilitating controlled fusion energy generation (with advantageous electricity conversion), the pB reaction generates a high yield of alpha particles with an energy range of several MeV, which have multidisciplinary applications.

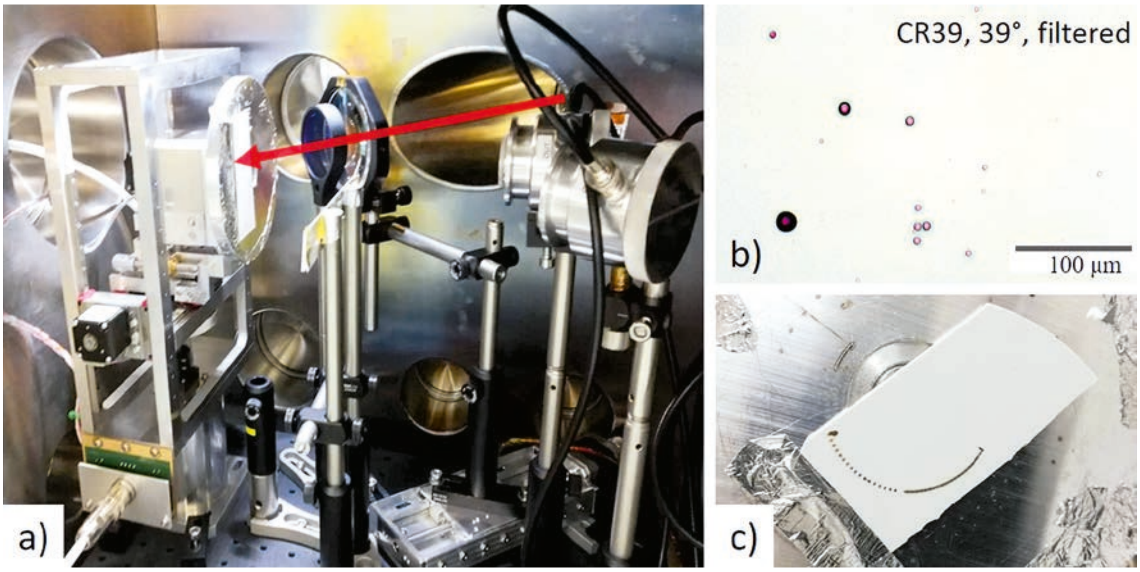
In the last 15 years, a number of research teams have carried out various experiments focused on triggering laser-driven pB fusion, with results showing a steady increase in the emitted alpha yield. A team from ELI Beamlines has also contributed to the progress in this field, using the high-energy TW-level PALS (Prague Asterix Laser System) in Prague, Czech Republic, for several experiments supported by Laserlab-Europe [1, 2]. High-power lasers have been used to accelerate protons from different hydrogen-rich targets to energies around 600 keV and above, in order to reach the main resonance in the pB reaction cross-section. Such energetic protons can interact with boron either inside the laser-plasma if the target contains both hydrogen and boron elements (so-called "in-target" scheme), or using the beam-plasma approach, where protons collide with boron plasma (so-called "pitcher-catcher" scheme).

So far, the maximum measured alpha particle yield from laser-driven pB fusion has reached 10^{11} particles/sr/shot [2]. Such numbers are, in principle, sufficient for some applications; for example, production of medical isotopes. However, despite this relatively high yield, there remained a couple of disadvantages with the high-power laser systems being used for triggering the pB reaction. Firstly, the systems had to be used in single-shot mode, so only a few shots could be achieved each day, and it was not possible to produce a continuous flux. Secondly, the laser systems and their operation involved a high level of complexity, whereas many potential applications would require compact and cost-effective approaches.

To address these issues, the teams from Queen's University Belfast and ELI Beamlines came up with the idea of using the secondary resonance in the pB reaction cross-section, which has not been widely investigated in previous laser-driven experiments. Although this resonance is ten times less efficient and narrower than the main one, the corresponding proton energies are around 160 keV, some four-times lower than those of the main resonance. This would mean that less powerful laser systems could be used for the proton acceleration, provided that the repetition rate of the shots were increased, for example by using kilohertz lasers.

To test the idea, an experiment was performed at the HiLASE laser centre, with support from Laserlab-Europe("Proton Acceleration at 1 kHz for Proton-Boron Nuclear Fusion Studies" - HILASE002698) [3]. The experiment was led by Daniele Margarone from Queen's University Belfast and was realised through the participation of the ELI Beamlines team. A commercial tabletop PERLA GW-level laser system was used, which delivered ~1.5 ps long pulses at a high-repetition-rate (1 kHz, i.e. 1000 shots per second). The "in-target" approach was employed, using a double-layered target containing hydrogen atoms deposited on a boron substrate. The target was prepared specifically for this experiment by researchers from the Department of Macromolecular Physics at Charles University, Prague, using plasma-assisted vapour phase deposition.

This combination of laser and target setup made it possible to accelerate the protons to the energy region



b) adapted from V. Istokskaia et al., Commun. Phys. 6: 27 (2023)

a) Compact experimental setup inside the vacuum chamber: the laser (red arrow) is focused on the target stuck to the automated holder, and the nuclear track CR39 detectors are located in front of it, covering a large angle. b) Microscopy image of the alpha particle tracks of different energy on the surface of the CR39 stripe. c) Photo of the double-layer target containing H and B atoms with holes on it, from shots carried out at different repetition rates.

around the secondary pB reaction resonance. Filtered CR39 nuclear track detectors were used as the main diagnostic to measure the emitted alpha particles. These detectors were located inside the vacuum chamber at different angles around the target, and accumulated emissions from hundreds of shots at 1 Hz. The results indicated that the measured energy spectrum of the alpha particles was in good agreement with the expected one (in the several MeV range, peaking at around 3.5 MeV), and the yield was around 10^4 particles/sr/shot.

After the experiment, two different numerical simulations (particle-in-cell and hydrodynamic) were performed to investigate the laser-plasma interaction. These simulations confirmed the acceleration of protons within the range ~100 keV – 300 keV and suggested that the pB reaction was triggered in the plasma plume rather than inside the target, due to the presence of the relatively high prepulse.

As repetitive laser-driven alpha particle sources have never been demonstrated, an additional test was carried out to provide a proof-of-principle of the experimental generation of alpha particle beams at 1 kHz using a motorised target holder prototype designed for high-repetition-rate operation.

Overall, the experiment has demonstrated that it is possible to use a compact commercial moderate-power laser with a special hydrogen-boron target to trigger the pB fusion reaction at a high-repetition-rate operating regime and provide a continuous flux of alpha particles. By optimising the target delivery system for a kHz regime, it is possible to generate alpha particle currents exceeding 10^6 particles/s with the PERLA laser. Moreover, with new laser systems that offer higher maximum laser energy, it will be possible to accelerate protons to energies around the main resonance, which should deliver a further enhancement in the average alpha particle current (up to 10^8-10^9 particles/s expected at the 1 kHz regime). These advancements will pave the way towards future applications of multi-MeV alpha particles produced from the pB fusion reaction triggered by tabletop high-repetition-rate lasers.

Valeria Istokskaia
(ELI Beamlines Facility, ELI ERIC)

[1] A. Picciotto et al., Phys. Rev. X 4: 031030 (2014)
[2] L. Giuffrida et al., Phys. Rev. E 101: 013204 (2020)
[3] V. Istokskaia et al., Commun. Phys. 6: 27 (2023)

Joint ELI User Programme, progress of integration and new members

As the ELI Facilities transition from construction to initial user operation, commissioned equipment becomes available to the scientific user community within the framework of the Joint ELI User Programme. It is an essential step for ELI to bring its facilities together and demonstrates the readiness to perform groundbreaking science. Two calls were opened so far with the 2nd call broadening the scope of the available equipment offered resulting in a significant increase in proposal submissions, up from 44 in the 1st call to 102 proposal submissions from 23 countries in the 2nd call for all three ELI facilities. Proposals are evaluated by external experts based on scientific excellence. The Joint User Programme is expected to launch two Calls annually with the next one set for mid-September 2023.

A significant milestone was also achieved which will shape ELI for the future. The ELI Beamlines Facility became part of ELI ERIC on 1 January 2023, transferring all assets, rights, obligations, and intellectual property from the Institute of Physics (Czech Academy of Sciences) to ELI ERIC. The ELI ERIC will operate the high-power laser facilities ELI Beamlines and

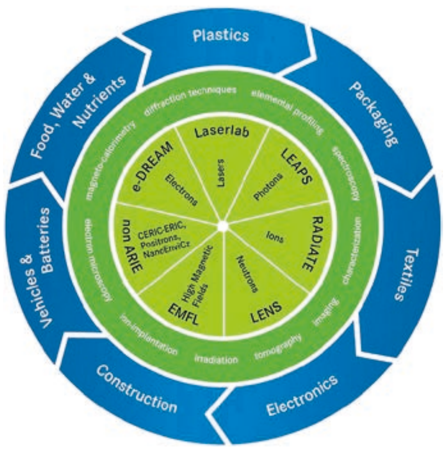

ELI ERIC

ELI ALPS as an integrated organisation, with a unified governance and single management structure. Preparations for the integration of ELI ALPS are progressing quickly with the expected integration for 1 January 2024.

The ELI ERIC will also welcome Romania as a Founding Observer from 1 January 2024. The decision opens a new chapter in the alliance, laying the groundwork for Romania's ELI NP facility to integrate into the ELI ERIC organisation over the next three years. The cooperation on the Joint ELI User Programme has been a key driver along with other scientific and technical cooperations between ELI ERIC and ELI NP within the framework of the IMPULSE Project.

Alexandra Schmidli

ReMade@ARI offers access to 48 European analytical facilities



Are you developing materials for a circular economy or are you facing a specific challenge in your circular materials research? Then Remade@ARI's calls are for you: From 30 August to 11 October 2023, the project is again accepting proposals in its second call.

ReMade-at-ARI currently opens calls for proposals twice a year for access to a broad range of instrumentation and techniques. Launched in September 2022, the project aims to support the research and development of innovative, sustainable materials as we move towards a circular economy that focuses on recycling rather than wasting materials. Its offer: Provide scientists with analytical tools to explore the properties and structure of materials right down to atomic resolution, enabling you to contribute to the much-needed shift from a linear to a circular economy.

ReMade-at-ARI also provides a comprehensive training and education programme including free monthly online seminars by research infrastructure experts highlighting specific research techniques.

The project is funded for four years by the EU with a budget of 13.8 million euros. Ten Laserlab-Europe members are part of the consortium.

https://remade-project.eu

How to apply for access

Interested researchers are invited to contact the Laserlab-Europe website at www.laserlab-europe.eu/transnational-access, where they find relevant information about the participating facilities and local contact points as well as details about the submission procedure. Applicants are encouraged to contact any of the facilities directly to obtain additional information and assistance in preparing a proposal.

Proposal submission is done fully electronically, using the Laserlab-Europe Proposal Management System. Your proposal should contain a brief description of the scientific background and rationale of your project, of its objectives and of the added value of the expected results as well as the experimental set-up, methods and diagnostics that will be used.

Incoming proposals will be examined by the infrastructure you have indicated as host institution for technical feasibility and for formal compliance with the EU regulations, and then forwarded to the Access Selection Panel (ASP) of Laserlab-Europe. The ASP sends the proposal to external referees, who will judge the scientific content of the project and report their judgement to the ASP. The ASP will then take a final decision. In case the proposal is accepted, the host institution will instruct the applicant about further procedures.

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