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Laserlab Europe

Laserlab Forum

Newsletter of LASERLAB-EUROPE:
the integrated initiative of European laser
infrastructures funded by the Seventh Framework
Programme of the European Community

Lasers for Life

Emma Springate (CLF) operating the ARPES end-station at Artemis. © Monty Rakusen

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In this Issue

Editorial


Tom Jeltes

For most people, the term 'Lasers for Life' will bring to mind only the well-known laser eye surgery, a set of established clinical techniques that have improved the sight of countless people worldwide. Lasers are regularly applied, however, in many other areas of medical science as well. And the global medical laser systems market is growing rapidly, with a predicted size of over €6 billion by 2017.

In order to support these amazing developments, a lot of pioneering experimental work still has to be done. Several research groups from Laserlab-Europe partners are currently working on various possible medical applications of laser light that might just become as commonplace in a clinical setting as laser eye surgery is today.

On the occasion of the Laserlab Foresight Workshop entitled 'Lasers for Life', this issue of Laserlab Forum features a Focus section in which our researchers describe their promising attempts to use lasers for such different purposes as the generation of protons for radiation therapy, imaging of live brain tissue, assessment of breasts to find tumours, and real-time non-invasive monitoring of gases inside premature babies' lungs and intestines. At a more fundamental level, techniques to monitor single biomolecules are presented. And, according to another contribution, even the abovementioned laser eye surgery could perform much better if only the optimum laser wavelength were chosen.

In this issue we also present three Laserlab scientists who obtained a Consolidator Grant, a brand new grant from the European Research Council, situated right in between the familiar Starting and Advanced Grants. And we have a rather special Access Highlight contributed by Emma Springate from the UK's Central Laser Facility, which shows how their Artemis facility is used by two competing groups of scientists to reveal the intriguing and possibly very useful properties of the Nobel Prize winning material graphene.

But, to come back to the main theme of this issue of Laserlab Forum: even the news items on the following pages will give you an impression of how intimately laser science and life science have become intertwined, demonstrating the healing power of laser light.

Tom Jeltes

News

BabyLux: supporting pre-term babies

Laserlab-Europe partners ICFO (Barcelona) and CUSBO (Milan) are leading a new European project, called 'BabyLux', which aims to provide support for vulnerable babies by developing an optical device to monitor the blood and oxygen flow in critically ill newborns. The BabyLux project has a budget of €4 million and should lead to a device which will be tested already in 2014-2015.

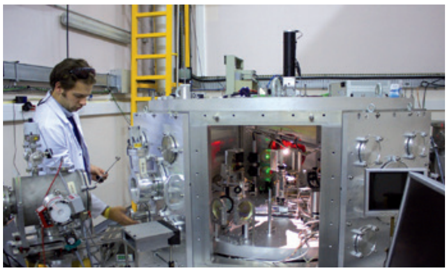
Pre-term births have risen by twenty percent in the West in the past two decades and currently account for a significant portion of children with cerebral palsy and cognitive, visual and hearing impairments. These are the result of brain damage due to lack of blood flow and oxygen delivery during the early stages of brain development. The Medical Optics Group at ICFO, led by Prof. Turgut Durduran, has already developed and tested a prototype for monitoring blood flow and oxygen levels in adult patients using lasers. This technology is being commercialised by Hemophotonics, an ICFO spin-off company also involved in the BabyLux project.

Laser system to fight cancer installed at LOA

Early 2014, a dedicated laser system for cancer radiation therapy was commissioned at Laserlab-Europe partner LOA in Palaiseau, France. The 200 TW ultrafast laser and experimental beamline is part of the French SAPHIR project in which LOA participates.

Protons generated from lasers form an alternative to the classical particle acceleration techniques that are used for cancer treatment. SAPHIR, a French project with involvement of Laserlab-Europe partners LOA and SLIC, has been launched a few years ago to determine the technical and economic viability of laser proton therapy. The final goal of the project is to realise a working prototype able to produce ions of medical interest and to prove their efficacy onto biological samples. SAPHIR is coordinated by the company Amplitude Technologies, and largely funded by the investment organisation Oséo.

During the next few months several new strategies for laser-ion acceleration will be explored and tested, with a full characterization of the beam parameters (energy, charge, diver-



Experimental chamber of the SAPHIR project used to generate protons from femtosecond intense laser systems.

What is Laserlab-Europe?

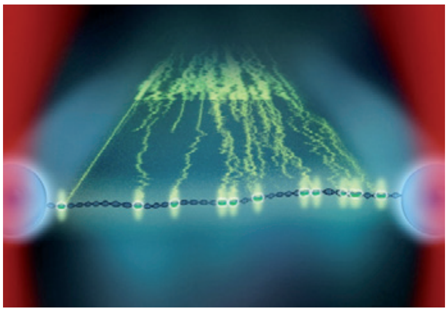
Laserlab-Europe, the Integrated Initiative of European Laser Research Infrastructures, understands itself as the central place in Europe where new developments in laser research will take place in a flexible and co-ordinated fashion beyond the potential of a national scale. The Consortium currently brings together 30 leading organisations in laser-based inter-disciplinary research from 16 countries. 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 European laboratory in order to perform world-class research.

gence). In-vitro and in-vivo experiments will be carried out in the various explored conditions, in order to observe the biological effects induced by laser particle beams, which can reach peak dose rates higher than conventional accelerators. The SAPHIR project should lead to the design of machines that are advantageous in terms of cost, weight, compactness and flexibility, and could be installed in hospitals.

Filming the crowd on DNA

Researchers of LaserLaB Amsterdam (Wuite and Peterman labs, VU University) have developed a new method to study protein dynamics on densely covered DNA *in vitro*. Their work recently featured on the cover of the journal Nature Methods.

Cellular DNA is ubiquitously covered by a high density of proteins. Such high density leads to low accessibility, which has a large impact on processes such as DNA repair and gene expression. The approach Iddo Heller and his co-workers at LaserLaB Amsterdam used to study this crowded molecular dance is based on optical tweezers, an established single-molecule technique that was used to stretch DNA and probe how its mechanical properties are affected by biomolecular processing. Concurrently, the researchers used super-resolution fluorescence microscopy to visualise protein



Artist's impression of proteins on DNA (illustration: Ivo van der Ent). The DNA is stretched between two microspheres (blue) that are held in focused trapping lasers (red). The protein trajectories (green) along the DNA are shown fading toward the background. STED nanoscopy (foreground trajectories) provides a 6-fold resolution enhancement over confocal imaging (background trajectories).

binding, diffusion, and enzymatic activity on the optically stretched DNA.

A spin-off company, LUMICKS, has now been founded to make this type of correlative optical tweezers technology available to a wide range of biological and biomedical scientists. Widespread experimental access to biologically relevant protein densities is essential for linking idealised *in vitro* experiments with the *in vivo* situation of DNA in cells. Additionally, this new technology can provide biomedically more relevant insight into (dys)functional DNA-protein interactions.

CLF spinout's airport laser scanner nominated for prestigious engineering award

© Cobalt Light Systems

The nominated team with the airport laser scanner: P. Matousek, G. Maskall, S. Bonthron, C. Tombling, P. Loeffen.

A security scanner developed by Central Laser Facility spinout Cobalt Light Systems is one of three candidates announced to be in the running to win the UK's premier engineering prize, the MacRobert Award, alongside Rolls Royce and QineticQ-owned Optasense.

The technique that lies behind Cobalt's innovation, known as Spatially Offset Raman Spectroscopy (SORS), was invented by the CLF's Professor Pavel Matousek. Using SORS, the content spectrum of a plastic bottle can be measured without knowing the bottle material or its relative signal contribution. SORS can also be applied to other systems, including biological ones, and was part of the Laserlab-Europe Joint Research Activity Optbio.

Cobalt Light Systems developed an airport security scanner that should enable airports to remove the existing hand-luggage liquid ban through phased implementation over the next few years in response to regulation. The system is now operational in 65 airports across Europe following new regulations introduced in January 2014. The fundamental science behind the device could also be used for non-invasive cancer screening, detecting counterfeit goods, and food analysis in the future.

The Royal Academy of Engineering MacRobert Award is the UK's longest running national prize for engineering. It identifies outstanding innovation with proven commercial promise and tangible societal benefit. It comprises a £50,000 cash prize and a gold medal.

L2I gets green light for roadmap

The Laboratory for Intense Lasers (L2I), located at Laserlab-Europe partner IST, Lisbon, was selected for the Portuguese Roadmap of Research Infrastructures in a recent call by FCT, the Portuguese Foundation for Science and Technology.

L2I hosts the most powerful laser in Portugal. FTC classified the facility in the top category: 'those that have demonstrated high scientific potential and are considered to have high strategic regional and/or national relevance', and it recommended the establishment of a distributed infrastructure with Coimbra Laser Lab, subcontractor of Laserlab-Europe.

Through the National Roadmap of Research Infrastructures, FCT envisages to support research infrastructures of strategic interest, to underpin scientific and technological advances and bolster the capacity of the R&D community in Portugal to be an active member of European and international projects.

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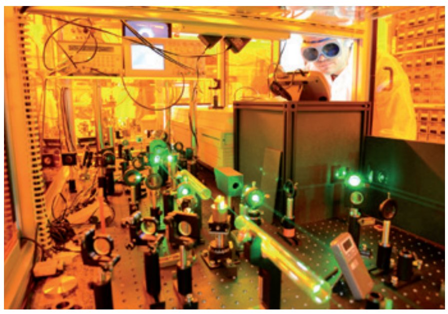


ERC Consolidator Grants

Since 2013, the European Research Council (ERC) has a new funding scheme: the Consolidator Grant. The new grant is meant for independent researchers with between 7 and 12 years experience after their PhD. The Consolidator Grant thus partially replaces the existing ERC Starting Grant, for which scientists with up to 12 years' experience were eligible. It provides funding of up to €2.75 million per grant for a maximum of 5 years. Out of 312 mid-career top researchers who have been awarded a Consolidator Grant, three are Laserlab-Europe scientists: Davide Iannuzzi from LaserLaB Amsterdam, Antonio Acín from ICFO, Barcelona, and Jens Limpert from the Friedrich Schiller University in Jena.

Davide Iannuzzi

Davide Iannuzzi: Micromachined optomechanical devices (DIDYMUS)

The project of Davide Iannuzzi, University Research Chair professor at LaserLaB Amsterdam, builds upon his 'fibre-top'-technology, which allows producing an atomic force microscope probe at the end of an optical fibre. In three ambitious research lines, he intends to combine the senses of 'sight' (optics) and 'touch' (mechanics) in three different optomechanical instruments that should allow him to tackle unanswered questions on each of the three most relevant scales in life sciences: cells, tissues, and organs.

The first project entails designing and testing a new optomechanical probe to investigate how a sustained mechanical load on a brain cell of a living animal may trigger changes in its central nervous system. In the second project, an optomechanical tactile instrument will be developed in order to assess how subsurface tissues deform in response to a mechanical stroke. The last research project aims at delivering an acousto-optical gas trace sensor, which should be so compact that it can be used inside lungs to find early signs of life threatening pulmonary diseases.

Antonio Acín

Antonio Acín: Quantum information theory with black boxes (QITBOX)

Looking for ways to exploit the extraordinary potential of quantum information, scientists are currently developing all kinds of different quantum systems. In his Consolidator Grant project, Antonio Acín, ICREA Professor at ICFO, will try to develop a theoretical framework that should allow him to understand what can and what cannot be done with these quantum systems in terms of information processing. In this framework, the quantum systems are seen as 'black boxes' – their only relevant properties are the input they receive and the output they produce.

Acín will first characterise the correlations that are possible among quantum devices. These correlations will subsequently be used to construct relevant information protocols, which will finally be applied to concrete physical setups – such as quantum-optical systems. The idea is that, based on the identified correlations, new methods can be developed to study many-body systems.

Jens Limpert

Jens Limpert: Advanced Coherent Ultrafast Laser Pulse Stacking (ACOPS)

In the future, cheap and compact particle accelerators for collider experiments and cancer treatment might be based on laser technology. In laser wake-field particle accelerators, ultra-short and high-power laser pulses are used to create electron waves in a plasma, producing electric forces by which electrons or protons are accelerated to almost the speed of light. Such laser accelerators, however, require laser systems that combine high peak power laser pulses with a large number of pulses per unit time – a high repetition rate.

In his Consolidator Grant project, Jens Limpert, Junior Professor at the Friedrich Schiller University in Jena, is planning to apply a technique called coherent pulse stacking in order to create a laser system that produces laser pulses with an energy of 32 J at a repetition rate as high as 15 kHz – numbers that are far beyond the state of the art. To this aim, he will try not only to coherently combine laser pulses from several fiber amplifiers, but he also plans to temporally store laser pulses inside optical cavities – waiting to be released as a coherent pulse train when a sufficient number of laser pulses have been built up inside.

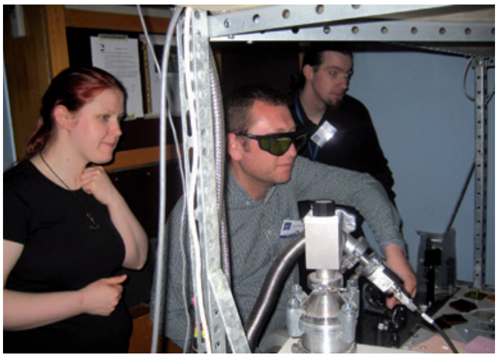
Laserlab User Training School in Riga

A Laserlab-Europe Training School for Potential Users was held in Riga, Latvia from April 9 to 12, 2014. It was organised in concert with the tenth annual Developments in Optics and Communications (DOC) conference for young scientists, sponsored by the local student chapters of the Optical Society of America (OSA) and SPIE, in order to take advantage of the synergy between the two events.

Spring had not quite reached this beautiful city on the shore of the Baltic Sea, but that did not stop a large and very international group of young scientists from attending. Sixty young scientists participated in the training school, and a total of 122 people took part in the combined event. Twenty countries were represented among the participants and speakers: Sweden, Denmark, Ireland, Canada, Bulgaria, Turkey, Poland, Israel, Latvia, Lithuania, Italy, the Netherlands, Hungary, the United Kingdom, Portugal, Finland, Spain, France, Slovakia, and Switzerland. The training school offered five laboratory exercises. The DOC conference featured 8 invited talks and over 35 contributed talks in the fields of laser physics and spectroscopy, optics in communication, optical materials and phenomena, biophotonics, and vision science. In addition, 48 posters were presented in the poster session on the last day.

The conference and training school talks took place at the Institute for Solid State Physics on the banks of the Daugava river. In the afternoons of April 10 and 11, laboratory exercises were offered at three locations. At the Institute for Solid State Physics, students had the opportunity to see pulsed lasers in action to study the fluorescence dynamics of rare earth elements, such as Erbium. This rare earth element is important in telecommunications applications where it appears in the erbium doped fibre amplifier. Time resolved luminescence spectra yield insights into the relaxation processes and luminescence mechanisms. Participants learned how to prepare samples, adjust the apparatus, and optimise the signals.

The biophotonics laboratory of the Institute of Atomic Physics and Spectroscopy offered a training session on how to measure the autofluorescence lifetime and photobleaching rate of skin. The skin was exposed to laser radiation from an optical fiber, and fluorescence light was collected. The skin could be excited with picosecond pulses (60 ps half-width) to measure autofluorescence lifetimes between 0.5 ns and 8 ns. Continuous radiation could be applied over several minutes to measure photobleaching by passing the fluorescence light through a spectrometer. These autofluorescence lifetimes and photobleaching rates can distinguish between malignant and benign skin lesions.



Finally, the Laser Centre of the University of Latvia, located at the Faculty for Physics and Mathematics, offered two sessions. In one session students learned about nitrogen vacancy centres in synthetic diamond. These have a triplet ground state, which can be manipulated by pulses of laser radiation and microwaves. The participants learned how to observe Rabi oscillations between the m_s=0 and m_s=1 states, and to measure the spin-lattice decay constant. In another session, trainees learned to work with a Ti:Sapphire laser system. They had to make the necessary adjustments to obtain the correct frequency. Then they aligned all components for a saturated absorption spectroscopy system and learned various practical skills, such as how to cut an optical fibre and couple light into it.

Thanks to the laser school and the conference, students had the chance to network with other young scientists from many countries and to learn about other fields of physics and new experimental techniques. All in all, it was a valuable experience, which we hope will be repeated soon.

Florian Gahbauer
(Laser Centre of the University of Latvia, ULLC)

Lasers for Life

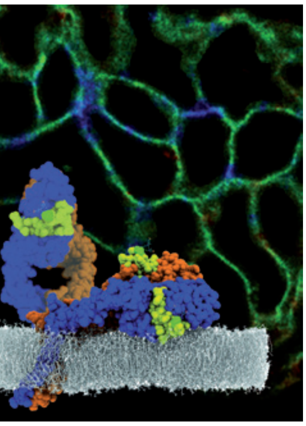
In the past decades, lasers have found many applications in the biomedical domain, ranging from fundamental research to disease diagnosis and treatment. Laserlab-Europe is active in many areas of biomedically-related laser science, and significant advances are being made across all areas. To help set out a roadmap for the field, Laserlab-Europe is holding a 'Lasers for Life' Foresight Workshop at the Royal Society, London, from the 2nd to 4th June 2014. On the following pages, Laserlab researchers provide insight into the diverse range of biomedical topics that are addressed within the consortium, starting with an overview of the UK's Central Laser Facility, organiser of the Foresight Workshop.

Aligning one of the Ultra laser systems.

CLF: Octopus, Ultra, and Astra Gemini

The Central Laser Facility (CLF) hosts an active programme of biomedical research supported by the FP7 Joint Research Activity BIOPTICHAL and its predecessor OPTBIO, in which several of CLF's laser facilities are used according to their various strengths.

Octopus is one of the world's largest facilities for laser-based optical microscopy, focussed on biological and medical research. An extensive range of imaging techniques including multiphoton microscopy, single molecule fluorescence imaging in cells, and several 'super-resolution' microscopes provide the biomedical researcher with a toolkit to investigate how biomolecular structure and dynamics in cells and tissues are responsible for the functioning of organisms in health and disease.



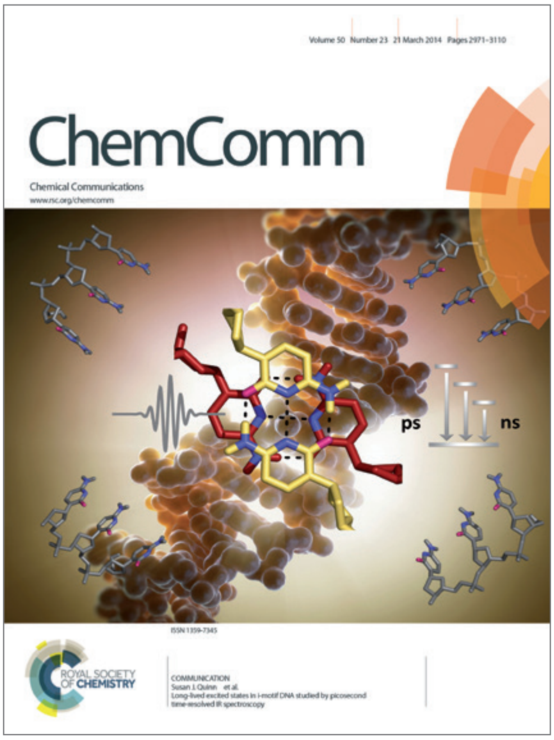
Model of epidermal growth factor receptor in cells, derived from Octopus FRET data.

For example, Marisa Martin-Fernandez from the CLF is leading a project in collaboration with cancer researchers from King's College London and a clinician from Guy's and St Thomas' Hospital, investigating the behaviour of a family of 'gatekeeper' molecules that are the targets of a number of new anti-cancer therapies. The unique combination of techniques available in *Octopus* enables the research team to study how the molecules transmit their signals to the cell, how active and inactive forms of the molecule are organised on the cell surface, and how mutations affect the signalling process. A collaboration with a drug development company is providing fluorescent derivatives of anti-cancer drugs so that their effect on the signalling molecules can be monitored. Ultimately, the goal of this research is to direct 'targeted therapeutics' by obtaining a molecular fingerprint from tumour biopsies, that can be used to ensure the patient receives the best treatment. This work is funded by the UK's Biotechnology and Biological Sciences Research Council (BBSRC).

Octopus is also in demand from European users, with Laserlab-Europe recently funding access for groups working on advanced tracking of biological molecules in cells, plant biology, and DNA damage.

The CLF's *Ultra* facility is the world's most sensitive time-resolved vibrational spectrometer, and in a similar way to *Octopus* offers multiple experimental stations linked to a suite of advanced lasers. The spectroscopic techniques offered are suitable for the study of the dynamics of molecules on timescales from femtoseconds to milliseconds. *Ultra* was partially funded by BBSRC with the specific aim of applying its unique capabilities to the investigation of biological molecules.

Laserlab-Europe has funded a number of visits to *Ultra* by Susan Quinn from University College Dublin. Dr Quinn is interested in the properties of DNA, and has used *Ultra* to investigate the photophysics of biologically relevant conformations of DNA, implicated in the mechanisms underlying photodamage. This work was recently published



Long-lived excited states in i-motif DNA studied by picosecond time-resolved IR spectroscopy.

in *Chemical* Communications, in which it featured on the front cover. She has also used *Ultra* to investigate the interaction of DNA with carbon nanotubes and nanoparticles.

The CLF's *Astra Gemini* facility is a high power, high repetition rate laser with two beams, each delivering 15 joules to target in a pulse of 30 femtoseconds (i.e. a peak power of 0.5 PW), with a repetition rate of one shot every 20 seconds. Although the facility has been targeted at ultra-high intensity physics research, it is now finding applications in biomedical imaging. The extreme acceleration of electrons in plasma to high energies (~GeV) in a short distance (~1cm) has long been a focus of intense laser research. In recent years researchers have been looking more closely at the x-ray emission that accompanies this acceleration as the electrons wiggle in the strong transverse forces in the plasma. Because of its short pulse duration (~few fs), the single shot (peak) brightness of this source is on a par with the average brightness of synchrotron sources. The spatial coherence guaranteed by the small source size of the beam (~mm) allows the acquisition of high resolution phase contrast images. An *Astra-Gemini* experiment led by the Plasma Physics group at Imperial College London has recently demonstrated the capability to image medical samples with quality comparable to the state of the art with conventional techniques.

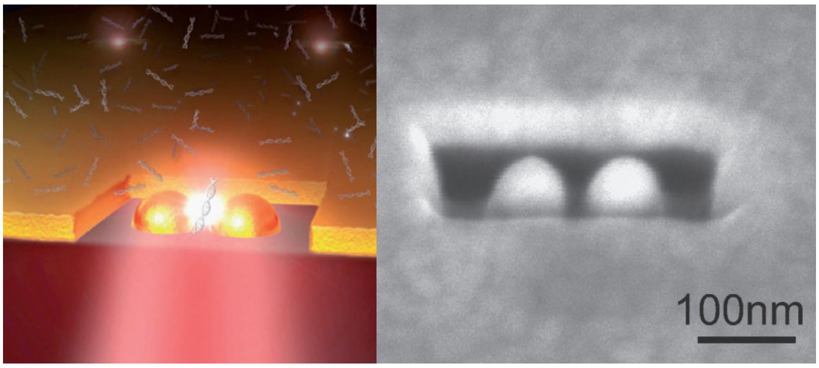
Dave Clarke (CLF)

ICFO: Biosensing of individual molecules with optical antennas

Understanding how molecules interact with each other inside the cell is key to advance our knowledge in molecular and cell biology. At ICFO, an optical device has been invented with which individual biomolecules can be detected even at the high concentrations found in living cells.

Together with the Fresnel Institute in Marseille we have conceived and fabricated the smallest optical device that can detect and sense individual biomolecules at concentrations that are similar to those found in the cellular context. The device, called 'antenna-in-a-box', consists of a tiny dimer antenna made of two gold semi-spheres and separated from each other by a gap as small as 15 nm. Light sent to this antenna is enormously amplified in the gap region, where the actual detection of the biomolecule of interest occurs. Because amplification of the light is confined to the dimensions of the gap, only molecules present in this tiny region are detected.

As an additional trick, we embed the dimer antennas inside boxes which are also of nanometric dimensions. The box screens out the unwanted contribution of millions of other surrounding molecules, reducing the background and improving the detection of individual biomolecules. When tested under different sample concentrations, this novel antenna-in-a-box device allowed for 1100-fold fluorescence brightness enhancement and detection volumes down to 58 zeptoliters (1 zL = 10^{-21}L): the smallest observation volume in the world.



Left: Artistic illustration of the antenna-in-a-box platform fabricated on gold allowing the detection of individual DNA strands at high sample concentrations. Right: Focussed ion beam image of an antenna-in-a-box as used in the experiments (© Nature Nanotechnology 8, 2013, 512-516).

Our antenna-in-a-box could be used for ultrasensitive sensing of minute amounts of molecules, becoming an exquisite early diagnosis device for biosensing of many disease markers. It could also be used as an ultra-bright optical nanosource to lighten up molecular processes in living cells and ultimately watch how individual biomolecules interact with each other, a long awaited dream of biologists.

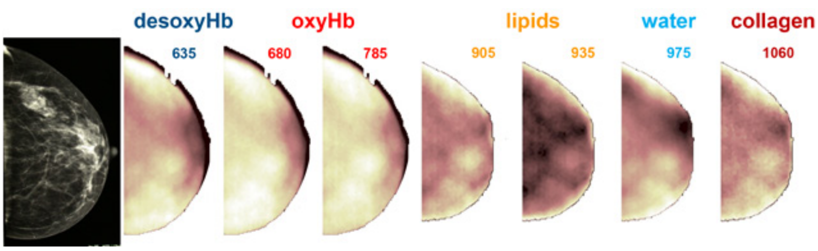
Maria Garcia-Parajo (ICFO)

CUSBO: Non-invasive optical assessment of breast density as a cancer risk factor

Breast density is well recognised as an important and independent risk factor for breast cancer. It is currently assessed through the analysis of X-ray mammographic images and is thus generally not known until the age of fifty. Within the framework of Laserlab-Europe, the CUSBO facility at Politecnico di Milano has developed a unique system for broadband time domain diffuse optical spectroscopy in the 600-1200 nm range, which can be used to measure breast density non-invasively.

Our system allows the evaluation of the average composition of biological tissues (in terms of water, lipid and collagen content) and blood parameters (total volume of hemoglobin and oxygenation level). Information is also

Left to right: x-ray mammogram and optical images at 635, 680, 785, 905, 935, 975 and 1060 nm of the left breast of a healthy subject. Above the images, the tissue constituents that mainly determine the optical behaviour at the different wavelengths are shown.



obtained on the structure of the tissue at the microscopic level. The optical measurement is completely non-invasive, painless and quick. It also provides an absolute operator-independent outcome.

A first clinical system, operated at a few discrete wavelengths yet providing also spatial information, has been developed based on the knowledge obtained by the laboratory research. The system has been used in a clinical study involving more than 200 patients, showing that optically derived parameters correlate to a high degree with both qualitative and quantitative estimates of mammographic density (i.e., BIRADS categories, typically used by clinicians, and percentage density, respectively). Recently, a dedicated portable instrument has been designed within the BIOPTICHAL Joint Research Activity and built to perform point measurements over a full spectral range (600-1200 nm).

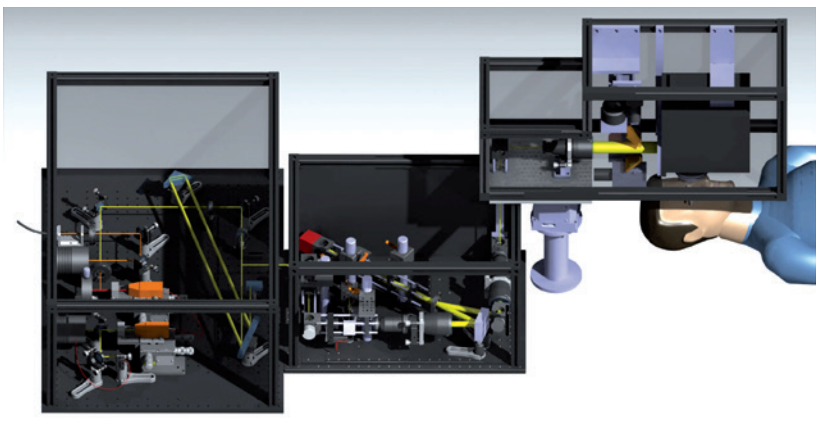
The instrumentation developed at Politecnico di Milano is unique at international level because it allows estimating the collagen content in tissue. Collagen appears to contribute fundamentally not only to breast density, but also to the origin and progression of breast cancer. Thus its estimate could provide a direct link (more direct than offered by mammographic density) with cancer risk. The impact of this pre-screening tool will be particularly significant since early diagnosis (lesion size <1cm and no lymph node involvement) leads to an impressive >90% survival rate, and great improvement in overall quality of life due to less invasive treatments.

Paola Taroni (CUSBO)

LOA: Tissue optical studies for ultra-short pulse laser surgery

The highly nonlinear and therefore strongly localised interaction process of ultra-short laser pulses with matter enables many potential clinical applications. Researchers at the Laboratoire d'Optique Appliquée (LOA) have shown that a shift of the surgical laser wavelength would lead to a significant improvement compared to current clinical laser systems.

CAD image of the demonstrator set-up of a laser surgical device for corneal grafting including a fibre laser unit (left, courtesy of Institut d'Optique Graduate School), a wavefront correction module (middle) and the beam delivery optics (right).



The first clinical ultra-short pulse laser system was commercialised with considerable commercial success in the beginning of the last decade. A number of clinical lasers are now available which provide routines for refractive and cataract surgery as well as other surgical interventions. Those systems have become increasingly widespread and produce very satisfactory results when used on transparent tissue.

However, procedures like corneal grafting need to be performed on pathological tissue, which is not perfectly transparent. In healthy cornea, the very regular arrangement of the collagen fibrils within the lamellae constituting the volume of the tissue as well as the absence of light scattering structures with micrometric dimensions are responsible for the transparency of the tissue. The transparency is lost when the regularity of the tissue structure is perturbed by pathology.

Fortunately, the light scattering processes are strongly wavelength-dependent. Our studies show the existence of a transparency window centred at about 1.65 µm even in very pathological cornea. A shift of the surgical laser wavelength from about 1 µm – which is typically used – to that window should improve the beam quality and the penetration depth considerably.

With our project partners we have developed several compact laser sources for the required wavelength range based on fibre laser technology and nonlinear optics. Our experiments on tissue show the expected results: the laser penetration depth was typically tripled and the quality of the surgical incisions was greatly improved. Interface roughness was reduced and cuts were even possible in the otherwise opaque sclera.

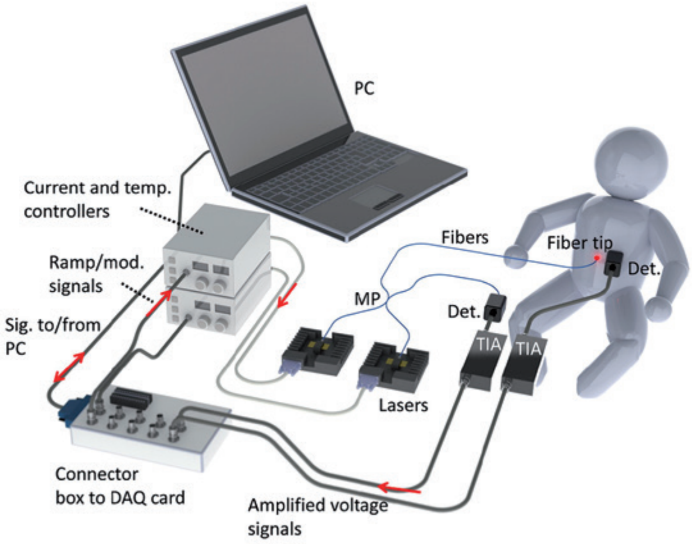
Karsten Plamann (LOA)

LLC: Optical non-invasive lung and-intestine gas monitoring in pre-term babies

Researchers at the Lund Laser Centre (LLC) are engaged in a multi-disciplinary project in which they try to measure gases inside human body cavities. The goal is to be able to continuously monitor the lung function and gas contents in the intestines of pre-term babies in a non-invasive way.

Assessing lung function is of prime importance for intensive care of pre-term children, since lack of surfactant in very premature children leads to the respiratory distress syndrome (RDS). Another severe problem for these small patients is necrotizing enterocolitis (NEC), affecting the intestines.

Following successful monitoring of gas contents in human paranasal sinuses using diode laser spectroscopy applied to scattering media (the so called GASMAS method), a feasibility study was first performed on pre-term baby thoracic phantoms. These were made up of animal lung tissue covered by gelatine layers with scattering particles and absorbing ink, mimicking the chest wall of a small child. Oxygen as well as water vapour could be detected in



Scenario for free gas monitoring in neonatal baby lungs and intestines. Single-mode diode lasers are used to observe the narrow molecular lines, which are typically 10,000 times sharper than the tissue constituent spectral features. Wavelength modulation techniques are used to isolate the gas signals. (© J. Biomed. Opt. 18, 2013, 127005)

such phantoms of realistic sizes using diode laser sources around 760 and 935 nm, respectively.

Subsequently, a pilot study on three full-term babies weighing about 4 kg demonstrated the possibility of real-world gas monitoring. An ongoing study with refined equipment on several full-term healthy babies shows promising results. Measurements on the intended target patients of weight 1-2 kg are now in planning. The hope is to develop cot-side continuous optical monitoring to replace current techniques, like occasional X-ray imaging, and to help make the start in life of these small children as good as possible.

Sune Svanberg (LLC)

LaserLaB Amsterdam: Third harmonic generation microscopy in living tissue

A major challenge in health and life science research is studying a single cell in its native three-dimensional environment of live tissue. Researchers from LaserLaB Amsterdam have demonstrated third harmonic generation (THG) to be an excellent tool for visualization of neuron morphology in living brain tissue.

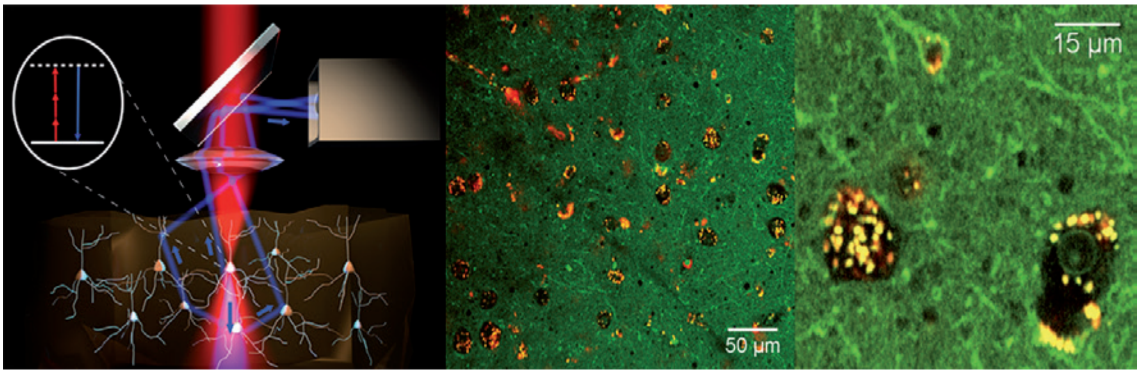
Visualization of cell dynamical processes in life tissue is of vital importance to understand the origin and progress of diseases, from the organ and tissue down to a cellular level. To enable this, tools and methods are necessary that allow observation at the sub-microscopic level, without changing or disturbing these processes. Third harmonic generation (THG) microscopy provides non-invasive, label-free contrast (that is, it needs no external contrast agents) of living tissue with sub-cellular resolution and intrinsic depth sectioning. The efficiency of THG depends mainly on the third-order susceptibility $\chi(3)$ of the medium and the phase-matching conditions.

Our group at LaserLaB Amsterdam has demonstrated THG to be an excellent tool for the label-free visualization of neuron morphology in living brain tissue. As lipids have a high $\chi(3)$ and the lipid content of the brain is high, THG is efficient. Neurons, blood vessels, astrocytes (the most abundant cells in the human brain) and axons were imaged in mouse ex-vivo brain slices, achieving near-video rate imaging of volumes of ~250x250x600 μm^3 with <0.5 μm^3 resolution.

The high-imaging speed makes THG very suitable for the study of cell dynamical processes in for example the context of neurodegenerative diseases (Alzheimer's disease, white matter diseases) or in tissue regeneration processes. Another application is in the recognition of tumour cells in the brain during a surgical resection procedure. Tissue-conserving surgery is of extreme importance in brain cancer to minimise loss of function. The major challenge of this type of surgery is the detection of tumour margins. For this purpose, a handheld THG device is now being developed at LaserLaB Amsterdam, in collaboration with the VU Medical Center.

Marloes Groot (LaserLaB Amsterdam)

Schematic representation of THG microscopy (left panel, Witte et al., PNAS 108, 2011, 5970-5975). THG images of human brain tissue, recorded at a depth 100 µm below the surface of an ex-vivo slice (middle and right panels). The neurons are visible as 'black shadows' as they produce less THG intensity than the extracellular matrix. The nucleus and nucleolus within the cells are visible. The THG signal (green) is co-collected with 2-photon fluorescence signals (red) that mainly arise from lipofuscin particles.



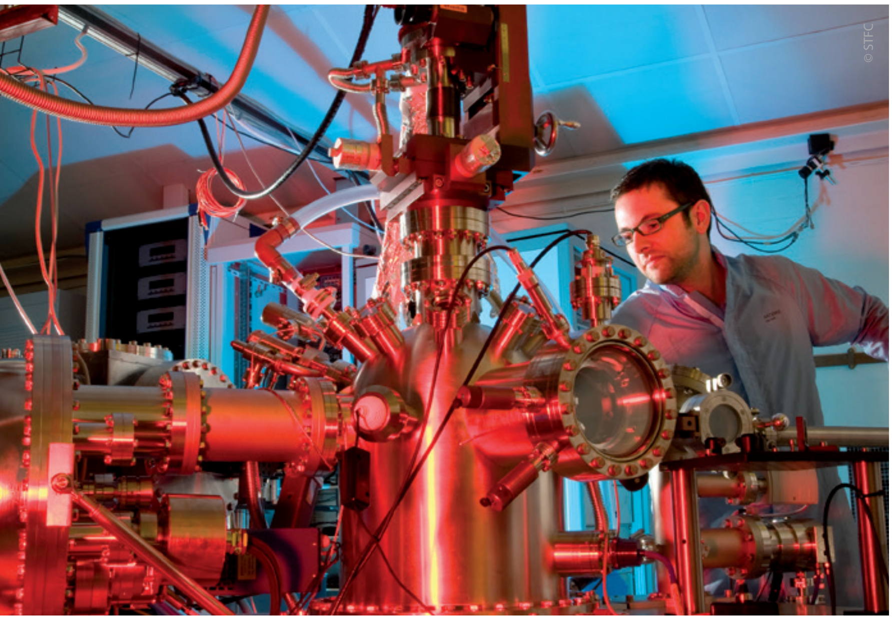
Access Highlight: Revealing the potential of graphene for solar cells, lasers and electronics

Graphene's two-dimensional honeycomb lattice is stronger than steel, lightweight, transparent and flexible, leading some to describe it as a 'miracle material' that will 'revolutionise the 21st century'. It has numerous potential applications in optoelectronic systems, such as solar cells, photodetectors and flexible displays. The key to understanding the behaviour of graphene and its suitability for these applications is to directly measure how the electrons in a graphene sheet respond to light. This has been done in two Laserlab-funded experiments at the Artemis facility that use high harmonic generation to add time-resolution to a technique commonly used on synchrotrons.

One of the palette of synchrotron techniques is angle-resolved photoemission spectroscopy (ARPES), which makes detailed static maps of electronic structure. A synchrotron beam, typically at 20-100 eV photon energy, ejects electrons from a sample using Einstein's photoelectric effect and their energies and emission angles are recorded. As the electron momentum parallel to the surface of a sample is conserved, it is possible to work back to make high-resolution maps of the electron distribution in the material.

In recent years, laser-based techniques have added time-resolution to ARPES, enabling the electronic structure to be monitored as it responds to excitation by a laser pulse. The target material is irradiated by a short laser pulse, which induces structural changes and electronic excitations. It is then probed at a series of time delays by a short wavelength pulse which generates photoelectrons that are then collected and analysed. This series of snapshots of the electron energy distribution is then sequenced into a movie of electron dynamics.

Jesse Petersen (Oxford University) operating the ARPES end-station at Artemis.



Until recently, time-resolved ARPES measurements with lasers have typically used only near UV radiation (<7 eV). The low photon energy meant that only a small subset of electrons, with certain energies and small momenta, could be ejected from the material and detected.

The Central Laser Facility's Artemis beamline at the Rutherford Appleton Laboratory is one of the first in the world to overcome this limitation. It uses extreme ultraviolet (XUV) pulses from high-order laser harmonics, with 20 eV photon energy and 30 fs time resolution. XUV high harmonic pulses are created when a short pulse laser is focused into a gas-jet and interacts with the gas, producing even shorter pulses of coherent radiation in the 10-100 eV range. The higher photon energy enables electrons with a much wider range of energies and momenta to be detected, meaning that each snapshot of electronic structure has a much wider field of view.

This turns out to be particularly important for experiments on graphene. Many of the peculiar properties of graphene are due to an electronic structure called the 'Dirac cone' – an hourglass-shaped region of electrons in momentum space. Electrons from the Dirac cone can only be ejected from graphene and detected if the photon energy is above 16 eV, making an XUV high-harmonic probe pulse essential to observe the extraordinary electron behaviour.

Laserlab-Europe provided funding for access to Artemis. Two proposals to investigate graphene on Artemis were successful at the access round. The two teams made the first direct measurements of electron dynamics in graphene and raced to write up, posting their papers on the archive within days of each other.

Direct view of hot carrier dynamics in graphene

The first experiment addressed the questions of whether graphene could be an efficient solar cell material and how the excited electrons in graphene actually decay. The team was a pan-European collaboration from five countries, led by Philip Hofmann from Aarhus University in Denmark. Two groups from EPFL in Switzerland and Aarhus University specialise in high-resolution ARPES measurements at synchrotrons. A team from three institutes in Trieste (Italy) provided expertise on time-resolved ARPES, TU Chemnitz (Germany) grew and characterised the graphene monolayers and the UK team at Artemis ran the beamlines.

The team were the first to publish their measurement of electron dynamics in graphene. They were able to directly measure the time-, energy- and momentum-resolved distributions of hot electrons in graphene after laser excitation. "The high photon energies available at the Artemis laser facility are opening a completely new perspective for studies of excited electrons", Philip Hofmann explains. "While we have seen many similar experiments on model systems to study the technique, we now have access to a wide range of fascinating materials, not only graphene but also other two-dimensional systems."

The team then looked for evidence of 'carrier multiplication' – multiple electron-hole pairs generated for every photon absorbed. Theoretical predictions have suggested this could be a way of making solar cells more efficient. The team saw that carrier multiplication was not present under these conditions, but that their measurements were consistent with theory predicting that it will happen in graphene in the conditions of weak sunshine actually relevant for solar cells.

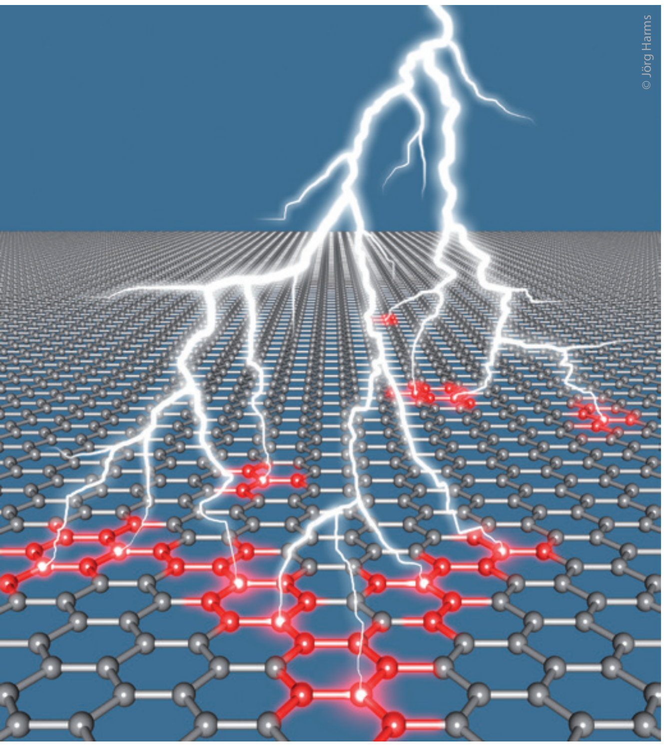
Demonstration of lasing graphene

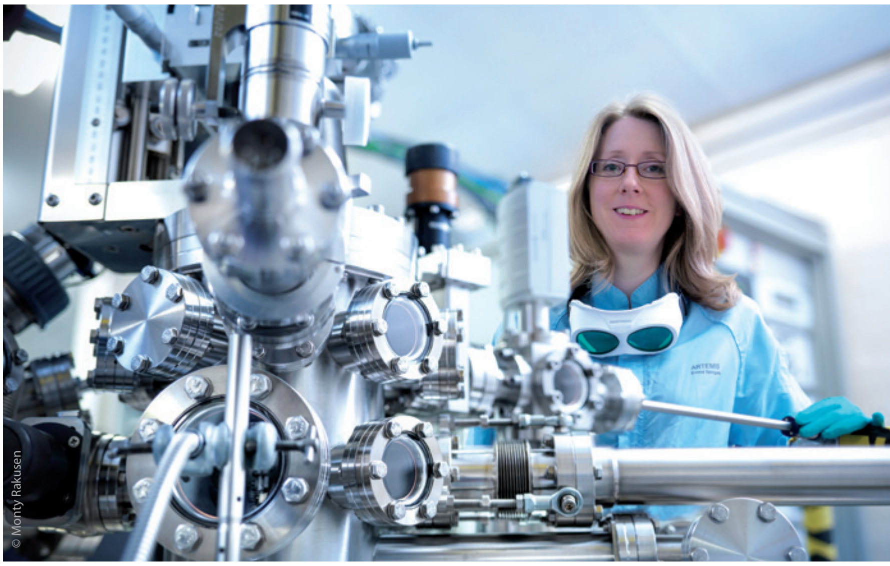
Theoretical studies and measurements of absorption have previously suggested that graphene could lase in the terahertz (the very long wavelength region of the spectrum, often used for security imaging), but there were no direct measurements.

A Laserlab experiment addressing this challenge was carried out at Artemis by the Max Planck Institute for the Structure and Dynamics of Matter in Hamburg and Oxford University, led by Isabella Gierz. A team from the Max Planck Institute for Solid State Research in Stuttgart were responsible for sample growth and characterisation.

The team used ultra-short flashes of infrared light to excite graphene and unexpectedly found that a population inversion can be produced. The discovery was sur-

Graphene, a honeycomb lattice made of carbon atoms, is a suitable material for lasers emitting ultrashort terahertz pulses.





Emma Springate (CLF) operating the ARPES end-station at Artemis.

prising because graphene lacks a classic semiconductor property long considered a prerequisite for population inversion: a band-gap. The band-gap is a region of forbidden states of energy, which separates the ground state of the electrons from an excited state with higher energy.

Because of the absence of a band-gap, the population inversion in graphene only lasts for around 100 femtoseconds. "That is why graphene cannot be used for continuous lasers, but potentially for ultrashort laser pulses", lead scientist Isabella Gierz explains. The measurements indicate that graphene could be used to amplify terahertz light which is currently only produced using inefficient nonlinear processes. A terahertz graphene laser would be particularly useful for research in condensed matter physics.

The Hamburg-based team came to a similar conclusion on the possibility of using graphene for solar cells. "According to our measurements, a single photon in graphene cannot release several electrons", Gierz says. "However, one may speculate that more favourable conditions for carrier multiplication may be met for negligible doping of the graphene layer, smaller pump fluences and higher excitation energies."

Both teams have already been back to Artemis for another round of successful experiments, and are in hot competition.

Emma Springate
(Head of Artemis, Central Laser Facility)

Publications from Laserlab experiments

Snapshots of non-equilibrium Dirac carrier distributions in Graphene, I Gierz, JC Petersen, M Mitrano, C Cacho, ICE Turcu, E Springate, A Stöhr, A Köhler, U Starke, and A Cavalleri, Nature Materials **12** 1119 (2013).

Direct view of hot carrier dynamics in graphene, JC Johannsen, S Ulstrup, F Cilento, A Crepaldi, M Zacchigna, C Cacho, ICE Turcu, E Springate, F Fromm, C Raidel, T Seyller, F Parmigiani, M Grioni, and P Hofmann, Phys Rev Lett **111** 027403 (2013).

HiPER plans for LMJ access

Academic access to beam time at the Laser MegaJoule (LMJ) and PETAL facilities, currently under construction in Bordeaux, has recently been agreed between the CEA, owners of the facilities, and the French Government. This is important for HiPER as access to LMJ opens up the possibility of demonstrating ignition, and ultimately high energy gain, which is essential for the commercial viability of power production from inertial fusion.

An EU-funded COST programme entitled 'Developing the physics & the scientific community for inertial confinement fusion at the time of NIF ignition' has recently been awarded to the University of Bordeaux. Its aim is to support the academic community in preparing bids for experimental campaigns at LMJ.

The kick-off meeting, chaired by Prof. Dimitri Batani, was held from 5th to 7th March 2014 at the University of Bordeaux in Talence. Over two hundred researchers from Europe, Russia, the United States and Japan discussed recent advances in laser-driven plasma science, including inertial confinement fusion, particle acceleration, matter in extreme conditions, and laboratory astrophysics. One of the highlights of the meeting was a visit to the LMJ facility itself.

This meeting helped the community to appreciate the scale of the task to field experiments at fusion scale, the requirements for development of precision diagnostics and the numerical simulations needed to underpin the design and analysis of experiments.

Breaking points for ELI

ELI-ALPS – and, hence, ELI as a whole – has just taken another huge step on its way towards implementation. The European Commission officially released the first and major part of the over 200 million euro EC contribution towards the construction of ELI-ALPS in the first week of May 2014.

ELI-ALPS had already been well on its way, though, and spending money for quite some time, due to a pre-financing arrangement with the Hungarian government. ELI-Beamlines in Prague received its equivalent EC funds already in 2011, and ELI-NP in Magurele in 2012. Construction at the Czech and Romanian sites is making impressive progress, as can be monitored in real time on their respective web sites.

ELI-NP recently celebrated the conclusion of a multi-ten-million euro contract for delivery of a world-wide unique gamma beam source. A contract over delivery of two 10-petawatt lasers had already been concluded earlier, similar to a contract over a 10-Hertz, diode-pumped petawatt laser to be built by Livermore for ELI-Beamlines in Prague.

The Romanian lasers will be built by a French company, while the gamma beam source will be developed by a European consortium of companies and institutions under the leadership of the Italian nuclear physics institute INFN – demonstrating the international character of ELI and its close cooperation with industry and academia during implementation.

The Hungarian Prime Minister Victor Orban (right) and Wolfgang Sandner, General Director of the ELI-DC International Association (left), laying the Foundation Stone for the ELI-ALPS facility in Szeged, Hungary, on February 6, 2014 together with Lorant Lehrner, Managing Director of ELI-ALPS.

The pan-European character of the ELI project has recently been further strengthened by the British Science and Technology Facilities Council STFC with its CEO John Womersley (also ESFRI Chair) having officially joined the ELI-DC International Association. STFC and the Central Laser Facility will jointly represent the UK in the Association.

Forthcoming events

Foresight Workshop 'Lasers for Life'
2 – 4 June 2014, London, UK

5th Target Fabrication Workshop
6 – 11 July 2014, St Andrews, Scotland

LA3NET 3rd School on Laser Applications
29 September – 3 October 2014, Salamanca, Spain

Laserlab User Meeting 2014
29 – 30 September 2014, Prague, Czech Republic

To find out more about conferences and events, visit the Laserlab online conference calendar.

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 all 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 Electronic 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 formal compliance with the EU regulations, and then forwarded to the Users Selection Panel (USP) of Laserlab-Europe. The USP sends the proposal to external referees, who will judge the scientific content of the project and report their judgement to the USP. The USP 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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