

funded by the
European Commission



CONTENT

- 2 Mission and Vision
- 3 Industrial User Club
- 4 Inside
- 6 Technology Breakthroughs
- 8 Tutorials
- 10 Events



Jürgen Popp

Dear Reader,

we are pleased to present the first newsletter of the Network of Excellence for Biophotonics (PHOTONICS4LIFE). The goal of this newsletter, which will be published half-yearly, is to provide information about the field of biophotonics, in which we try to make use of the rapid progress among the various photonic technologies in biological and medical applications. But Biophotonics represents more than that. In a world facing an increasingly aging society with exploding costs for health care, we need effective and affordable techniques aiming at the prevention or early recognition of diseases, as well as individually tailored check-ups and personalized medical treatment. These challenges can be met by optical technologies, however only if we employ and internalize the paradigm change which is closely connected to Biophotonics: Away from a technology-driven towards a holistic approach exploiting close collaborations between Physicians, Biologists, Engineers, Chemists and Physicists to develop new and innovative photonic techniques and applications tailored to the users' needs to improve the quality of life.

As a field and also as a market on the rise, the importance of Biophotonics is increasingly recognized. Due to the broadness of the field it is important to bundle the forces on a multi-national level. The initiation of the Network of Excellence Photonics4Life is an important step towards this goal. Consisting of 13 European partners, each being a key player in Biophotonics, Photonics4Life represents a critical mass and acts as a nucleation agent for Biophotonics in Europe. With this newsletter we do not only want to inform you about the network and its development, but also want to attract you to join in whether you represent an academic institution or a company. Photonics4Life's portal www.photonics4Life.eu will give you detailed information about how to become a part of this project. Come along with us to explore new horizons in the field of Biophotonics!

Jürgen Popp

PHOTONICS4LIFE – Networking for better health care

Today Biophotonics is an emerging multidisciplinary research area, embracing all light-based technologies applied to the life sciences and medicine. The term Biophotonics derives from two words of Greek origin: >bios< means life and >phos< light. Its ultimate goal is to understand and to be able to manipulate life processes on the sub-cellular or even on the molecular level to comprehend the origin of diseases and either to heal or even to prevent them. Enhancing diagnosis, therapy and follow-up care, Biophotonics drives the trend towards personalized medicine and plays a crucial role in limiting health-care costs and appropriately addressing the accelerating challenges associated with population aging and the consequent increase in age-related diseases. Biophotonics is a discipline and a market on the rise, in the scientific as well as in the economic sense: Its economic and socio-political importance is reflected in double-digit annual growth rates of industries in this field.

As a Network of Excellence, PHOTONICS4LIFE aims at providing a coherent framework for the strongly fragmented field of Biophotonics in Europe. One of the challenging tasks of PHOTONICS4LIFE is therefore to structure and integrate the research and technological developments throughout the various subdisciplines of Biophotonics with their manifold interdependencies in order to overcome the widely incoherent research with strong “friction losses” and frequent “reinventions of the wheel”.

PHOTONICS4LIFE is composed of partners standing on the forefront of Biophotonics research and covering together the broadness of the field. The partners bring in local clusters or

are initiating local clustering. They will work towards a durable integration, provide a critical mass that will act as a nucleus for integrated fundamental and applied Biophotonics research across Europe and reach out to the international scene.

PHOTONICS4LIFE targets to break down barriers between different disciplines ranging from physics and chemistry via engineering to biology and medicine, e. g. by developing, introducing or supporting fresh conference concepts, interdisciplinary tutorials, journals and book projects as well as summer schools. Furthermore, with its industrial user club, PHOTONICS4LIFE aims to link the expertise of research institutes with SMEs and large companies and support start-ups in order to foster Biophotonics research and strengthen Europe's economic competitiveness and the global Biophotonics market.

With its commitment to interdisciplinarity, PHOTONICS4LIFE enables the initiation of a paradigm shift in Biophotonics research: away from a mostly linear and technology-driven towards a holistic user- and market-oriented approach. Consequently, PHOTONICS4LIFE does not only focus on individual technological developments but also puts emphasis on the needs of the physician and patient. With its objectives, PHOTONICS4LIFE is aimed directly at improving the quality of life.

Contact

Thomas Mayerhöfer and Jürgen Popp
thomas.mayerhoefer@ipht-jena.de

Biophotonics:
Photonic solutions for better health care

Understanding life processes on a cellular level | Optical systems for drug development | Optical systems for regenerative medicine | Improved environmental monitoring

Life Science Research | Food and environment

Medical diagnostics and therapy | Early diagnosis of cancer | Better understanding and diagnosis of skin diseases | Point-of-care diagnostics | Minimally invasive medicine and targeted therapies

Industrial User Club – the link to industry

Biophotonics is an emerging multidisciplinary research area, including all light based technologies applied to life science and medicine. Enhancing diagnostic methods and therapy, Biophotonics drives the trend towards personalized health care and medicine and plays a crucial role in limiting health care costs. The European Network Photonics4Life aims to structure and integrate the different research communities ranging from Physics and Engineering via Chemistry and Physical Chemistry to Biology and Medicine. As an interface between the developers of Biophotonic methods and tools, their providers and most important their users in medicine and life sciences Photonics4Life will initiate and support the development of new photonic based methods and technologies for better health care. In view of fast commercialization of newly developed methods a close link between the academics and industry is necessary.

Through it's Industrial User Club Photonics4Life will overcome the existing inno-

vation barrier by stimulating the dialogue between the research society and industry and by linking the Networks expertise and competence towards SME's, start-ups but also large companies.

Photonics4Life can rely on the full range of expertise of its 13 partners – spread all over Europe – and their associated local or national cluster in biophotonic relevant fields like:

- Photonic technologies to analyse cell processes
- Photonics for non- and minimally-invasive diagnosis and therapy
- Microfabrication of highly integrated opto-fluidic systems for biophotonic applications
- Optical micro manipulation and therapy
- Computer modelling and analysis of chemical and physical data of biological material and processes
- Clinical applications of biophotonic methods
- In joining this club companies will get amongst others:

- Access to the available technologies and methods, to the competences and to the researchers behind
- Access to the latest results of the scientific output and
- Access to information on industrial companies with activities related to biophotonics via a comprehensive data base
- Support in entrepreneurial activities in Biophotonics by dedicated intensive courses covering economic aspects and concrete project plans

Contact

IUC responsible: Jürgen Mohr

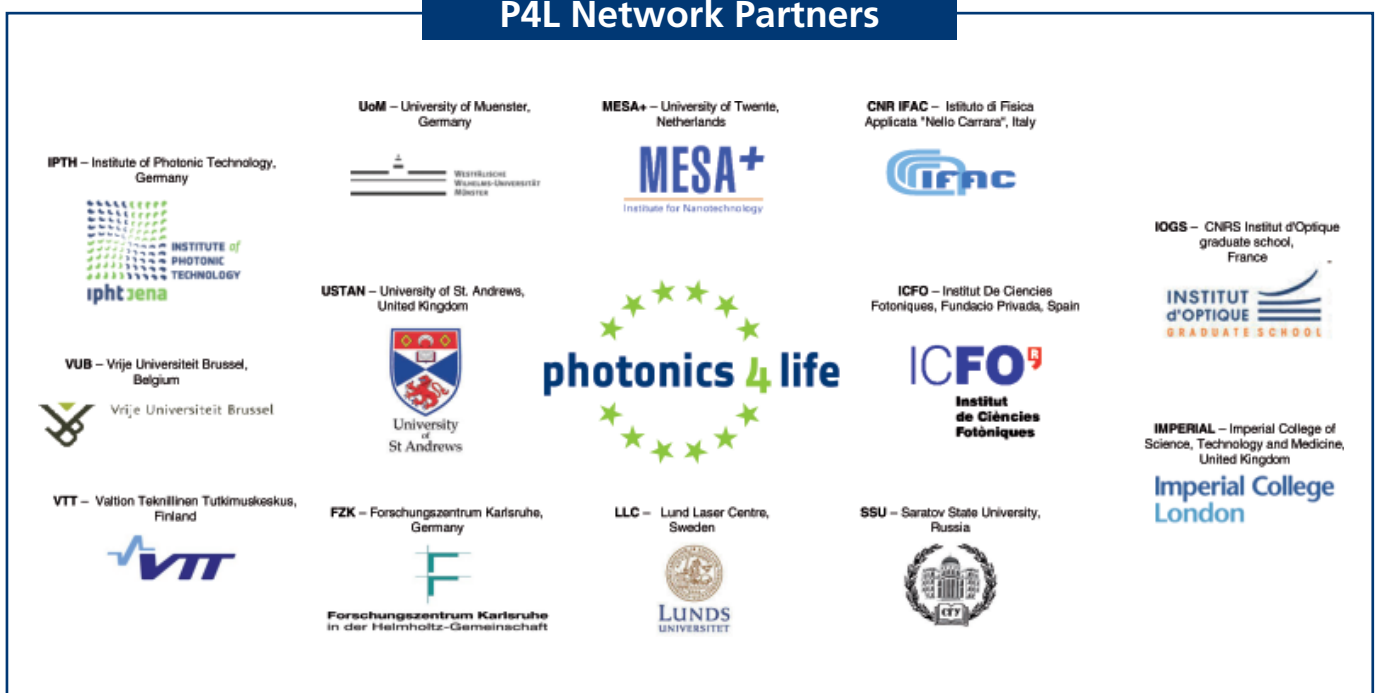
Juergen.mohr@imt.fzk.de

IUC officer: Thomas Mayerhöfer

Thomas.mayerhoefer@iphjt-jena.de

<http://www.photonics4life.eu/>

P4L Network Partners



CNRS – Institut d'Optique Graduate School

The CNRS (French National Centre for Scientific Research), with Institut d'Optique Graduate School (IOGS), jointly manages the Laboratoire Charles Fabry de l'Institut d'Optique, in association with the University Paris Sud. IOGS is constituted of three major components: Education, Technological transfer (IOTech) and Research (the Laboratoire Charles Fabry de l'Institut d'Optique, LCFIO). The school can be considered as one of top leading engineering schools in France, mainly devoted to optical science and engineering. It provides education for more than 300 students in its Master of Engineering ("ingénieur" diploma) curriculum. The school is coordinator of an Erasmus Mundus program (M.Sc. Optics in Science & Technology, OpsSciTech), and is involved into several external master curricula such as "Engineering of biomedical & medical research data" in partnership with Ecole Centrale Paris and the faculty of medicine of University Paris Sud. With the recently created innovation-entrepreneurship program, the students at IOGS have the possibility to combine engineering studies with management and innovation, through real-life startup creation projects. The mission of IOTech is to provide dedicated Research & Development solutions and to transfer the know-how and technology from LCFIO to the optics and photonic industry. IOGS has been awarded the Carnot label in 2006, for its

R&D activities within IOTech. The LCFIO laboratory is host of 6 research groups, covering aspects of optical science from lasers to atom optics. It is constituted of about 80 permanent staff, 20 invited and post-doctoral staff and 60 PhD students. The LCFIO laboratory is currently devoting extra focus on 2 transversal research priorities: "nanophotonics" and "photonics & lifesciences".

The LCFIO laboratory is currently involved into several topics linked to biophotonics such as:

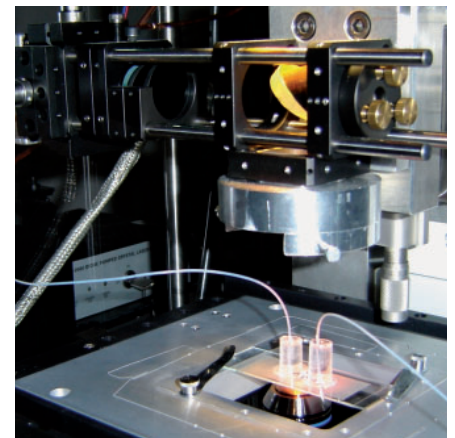
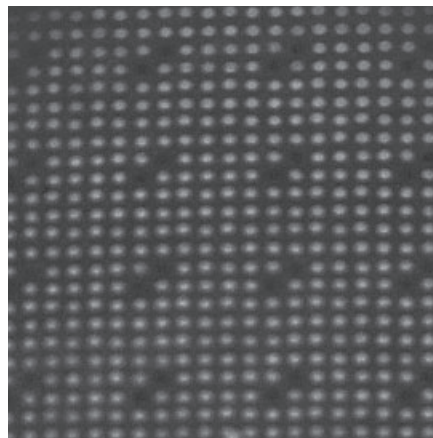
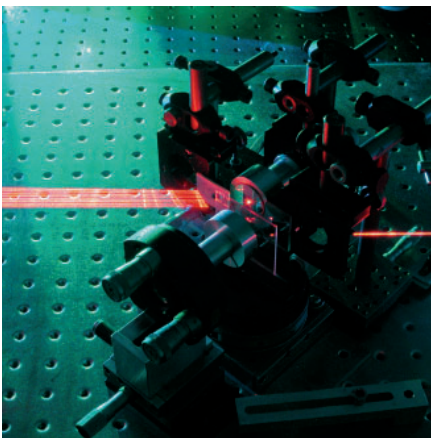
- Dynamical biochips using surface plasmon resonance imaging;
- Single-molecule fluorescence microscopy and optical trapping for detection and manipulation of single ribosomes during protein synthesis;
- Full-field optical coherence tomography;
- Ultrafast laser development for eye surgery applications;
- Pulsed laser sources for fluorescence lifetime imaging applied to prostate cancer treatment;
- Total internal reflection fluorescence lifetime imaging microscopy, and multifocal two-photon fluorescence lifetime microscopy

In this context, the LCFIO laboratory has developed numerous partnerships with hospitals (Hotel-Dieu in Paris, Henri Mondor in Creteil, Bordeaux university hospital), research centers and labora-

tories (Center for Biomedical Photonics of University Paris Sud, Applied Optics Laboratory of ENSTA/Palaiseau, CEA-LETI Grenoble, Center for Molecular Genetics and Natural substances chemistry institute in Gif-sur-Yvette). It has also drawn strong links with industry like Genoptics or Thales RT.

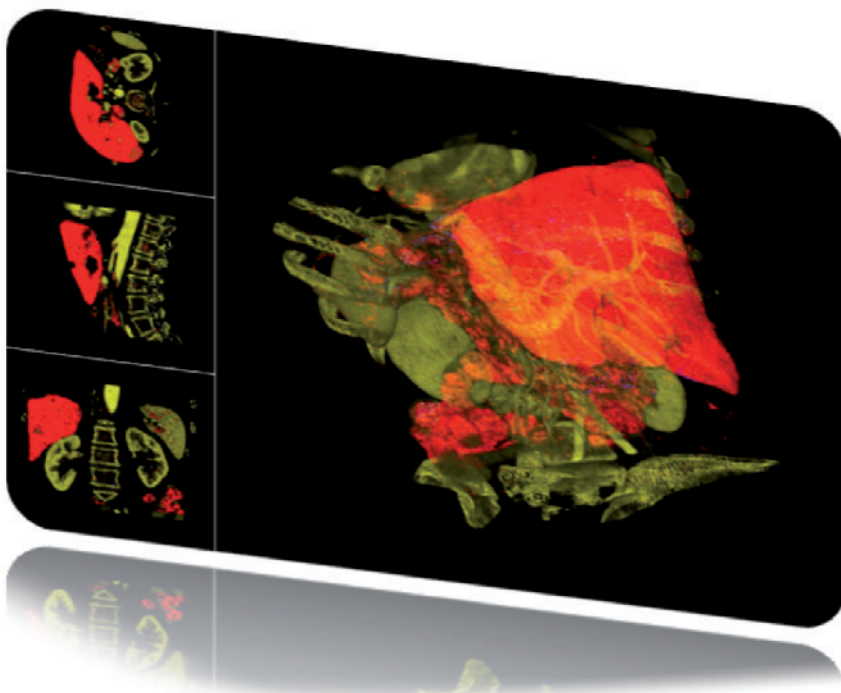
IOGS is taking part into several research and education excellence frameworks such as ParisTech (Paris Institute of Technology), UniverSud-Paris (south of Ile-de-France region). It is also member of C'nano IdF (Ile-de-France region initiative for nanosciences & nanotechnologies). All these organizations devote a specific formal effort to biophotonics, with dedicated groups. IOGS hosts the headquarters of the French Optical Society (with about 1500 members), within which about 15% are involved into biophotonics. In the recent years, IOGS has allowed several startup companies to develop within its premises, and members of IOGS have been specifically involved in the creation of two spin-offs within the focus of biophotonics: Genoptics (dynamical biochips using surface plasmon resonance imaging), and Genewave (microarray instrumentation).

» www.institutoptique.fr



VUB – Vrije Universiteit Brussel

The Vrije Universiteit Brussel (VUB) is a middle-sized but complete university that belongs to the Network of Universities of the Capitals of Europe UNICA. The Department of Applied Physics and Photonics (TONA), the Image Processing and Machine Vision Group (IRIS), and the In vivo Cellular and Molecular Imaging Center (ICMIC) are partners in Photonics4Life. The **Department of Applied Physics and Photonics (VUB-TONA)** counts 40 researchers and is internationally recognized for its basic and applied research on "micro-optics" and "micro-photonics". The group is equipped with top-quality optical modeling tools and computing infrastructure and with micro-optical measurement instrumentation housed in clean-room conditions. It can rely on a unique large-scale cyclotron facility for high-aspect ratio ion beam lithography for prototyping of "plastic 3-D micro-optical modules". VUB-TONA also has access through strategic partnership in the European Community supported Network of Excellence on Micro-Optics NEMO to complementary micro-optics technologies. One part of the young biophotonics research team aims at designing, modeling, prototyping and demonstrating low-cost manufactu-



inspired micro-optical components. The goal is to analyze and mimic the operation of compound insect eyes with in-house micro-fabrication technologies, and to synthesize micro-optical systems with novel functionalities inspired by nature's evolutionary design.

The Image Processing and Machine Vision Group (VUB-IRIS) has digital image processing and computer vision as its core research activities. It is constituted of six research clusters, including mathematical problems in imaging, humanitarian demining, remote sensing, computer/machine vision, medical imaging and multimedia communication. In the field of medical image processing, VUB-IRIS mainly works on automated image processing and analysis schemes for the extraction of bio-medical parameters in order to assess the presence or evolution of a disease in quantitative terms with the aim to aid in diagnosis and prognosis (CAD). The team continuously diversifies its research on new imaging systems and multimodal image analysis towards new modalities. In RX-mammography VUB-IRIS works on change detection both at the level of microcalcifications and at mass and architectural distortions in mammographical images of screening studies. Additionally the group analyzes in MR-brain studies the sulcal patterns at the surface of the brain by means of flat maps and look into the segmentation and analysis of the mitral valve in both cardiac US and MR images. The algorithmic approaches are robust deformable registration techniques, 4D/5D segmentation- and pattern recognition methods, probabilistic geometrical deformable models and atlases.

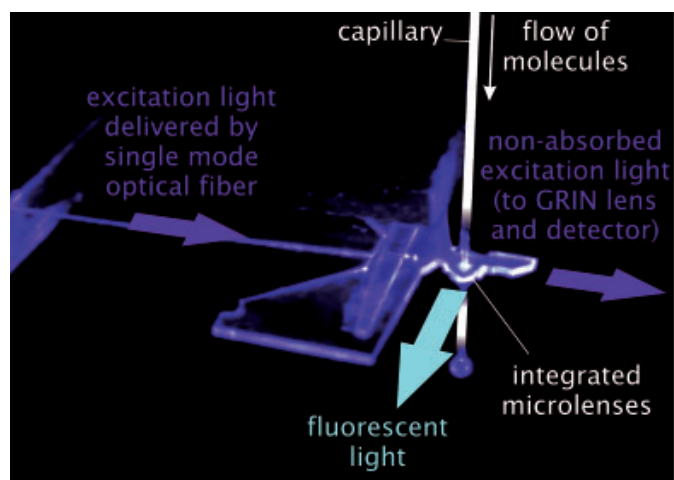
In collaboration with the Ambient Multimedia research cluster, VUB-IRIS is also active on the compression of 3D and (3D+time)



erable photonics-based systems for biochemical micro-analysis. These **optical-lab-on-a-chip** micro-systems aim at measuring the absorption spectrum and detecting the weak signal emission of fluorescence-marked molecules that flow in micro-capillary systems or in micro-fluidic channels. The other part of the group focuses on modeling, prototyping, and characterization of bio-

medical data. Recently, the group is looking into monitoring activities of elderly with a novel type of 3D camera based on the principle of time of flight.

The In Vivo Cellular and Molecular Imaging Center (ICMIC) of the Vrije Universiteit Brussel (VUB) has been founded in the beginning of 2005, and is directed by Prof. Bossuyt and Dr. Lahoutte. At the moment it hosts 5 PhD students, one technician, one master thesis student and 3 post-doctoral researchers. ICMIC has centralized multiple small animal imaging modalities including MicroSPECT, Optical imaging, MicroCT and Ultrasound together with a unit for probe development and a vivarium for



the housing of animals in one laboratory. Different research teams collaborate in an interdisciplinary research effort which encompasses the development and validation of innovative core technologies, their application in preclinical translational research and the introduction of these emerging technologies into clinical diagnostic imaging practice.

Imaging modalities such as MRI (Magnetic Resonance Imaging), PET (Positron Emission Tomography), SPECT (Single Photon Emission Computed Tomography), CT (Computed Tomography) and Echography used in the clinic have been miniaturized and are currently used to study small animals with high spatial resolution. Non invasive optical imaging technologies such as bioluminescence imaging and fluorescence imaging have been developed in small animals and contributed substantially to the development of the entire new field of 'imaging gene expression' using reporter genes. Different imaging strategies allow to probe complex biologic interactions dynamically, to study disease pathogenesis and to test the effect of therapeutic interventions in intact living systems over time. ICMIC is doing research on in vivo imaging of heart diseases, cancer and stem cells.

- » <http://www.tona.vub.ac.be>
- » <http://www.etro.vub.ac.be/Research/IRIS/iris.asp>
- » <http://www.icmic.net>

Summer school



Registration for the interdisciplinary summer school Biophotonics '09 is open. The two weeks school is organized in cooperation with P4L and P4L students will be supported by a partial coverage of the fee. Participation is also possible for students outside P4L.

- » <http://www.biop.dk/biophotonics09/School/School.asp>

P4L offers young researchers a number of different possibilities to interact within the network, to learn techniques from different labs and advance their career. Short term exchanges (STEs) of members of the research teams of network participants require merely support of the guest and a host organization

from P4L and a brief description of the aimed research activities. Upon request STEs may be extended to the network's industrial partners.

Any details on the mobility activities in the network can be found on the new "Training and Mobility" section of the P4L website.

- » http://www.photonics4life.de/index.php/plain_site/Training-and-Mobility

Contact

p4l-mobility@uni-muenster.de

PHOTONICS4LIFE – Kick-off and first General Networking Meeting

PHOTONICS4LIFE officially started with its kick-off meeting on the 6th and 7th of May 2008. The meeting took place at the Institute of Photonic Technology, Jena, Germany which is coordinating the network. More than 50 scientists from its 13 core partners as well as from cooperating institutions were gathered to start the joint work and to grow together. In the focus of the first day was on one of the most important matters for Photonics4Life, namely the inclusions of physicians into the development of photonic tools for healthcare. The second day was dedicated to the starting of the individual work packages of Photonics4Life, which include beside the development and application of Biophotonic tools also e. g. outreach to industry and organization of training courses as well as summer schools for students. The General Networking Meeting, which took place from the 2nd to the 4th of September in Brussels and had 40 participants, served the purpose to control the development of the project and to fine-tune its course.



Contact

Thomas Mayerhöfer and Jürgen Popp
thomas.mayerhoefer@ipht-jena.de

PHOTONICS4LIFE – First Scientific Meeting

More than 70 scientists of Photonics4Life were involved in the first Photonics4Life scientific meeting, which took part from at the 18th and 19th of November in Brussels. The meeting aimed at further promoting the mutual integration and the preparation of multilateral scientific projects within Photonics4Life. Networks of

Excellence (NoEs) have been introduced first into the 6th Framework Programme of the European Commission. Originally not primarily directed towards research, it has been realized that common research projects are an important measure of structuring and integration. In addition, such projects often generate excellent results, in many cases comparable to those of Specific Targeted Research Projects (STREPs) at a fraction of the costs. Photonics4Life plans to initiate a multitude of these so-called P4L-Projects to bridge gaps and white spots, which will be identified by other Photonics4Life activities, namely the mapping of the research landscape in Biophotonics. To foster the initiation of the P4L-Projects also a poster exhibition took place, which led to numerous interesting discussions.



3-D optical molecular imaging by time-resolved optical projection tomography

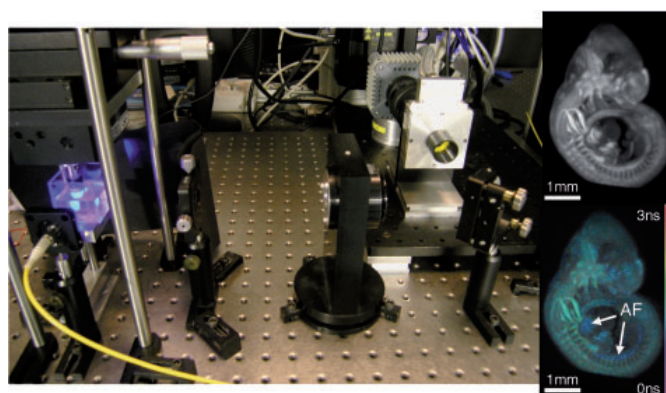
Researchers in the Photonics Group at Imperial College London have demonstrated the combination of Fluorescence Lifetime Imaging (FLIM) and Optical Projection Tomography (OPT) to realise 3-D tomographic imaging of fluorescence intensity and lifetime. FLIM is a quantitative time-resolved imaging technique that measures the characteristic decay time of fluorescence molecules and finds particular application in sensing fluorophore microenvironment, mapping protein interactions via Förster Resonance Energy Transfer (FRET) and exploiting autofluorescence signals for label-free contrast. OPT reconstructs the 3-D intensity distribution of fluorescent molecules in chemically-cleared biological samples and has been applied to imaging embryos, plants and small transparent animals. Combined with FLIM, it provides a quantitative tomographic molecular imaging technique, particularly suited for samples in the $0.1\text{-}1\text{ cm}$ range.

Using a novel set-up incorporating a supercontinuum excitation source (Fianium Ltd) and gated optical image intensifier (Kentech Instruments Ltd) technology, time-resolved intensity images were acquired, as a function of sample orientation, of a fluorescently labelled mouse embryo (supplied by James Sharpe, CRG Barcelona, the inventor of OPT). From this multi-dimensional data set, 3-D fluorescence intensity and lifetime distributions were reconstructed, with the antibody-label and autofluorescence signal being contrasted through their fluorescence lifetime.

This work demonstrates the feasibility of using fluorescence lifetime contrast with OPT to provide functional imaging for the investigation of 3-D biological samples (e.g. cell cultures, organs, embryos, etc) with the ability to exploit autofluorescence contrast and to map protein interactions using FRET. Extension of this approach from *in vitro* to *in vivo* imaging is anticipated.

Contact

Valerie Nadeau
v.nadeau@imperial.ac.uk



Picture of FLIM-OPT system, with insets of intensity and FLIM reconstructions of an anti-body labelled mouse embryo that also presents autofluorescence (AF) from the heart and dorsal aorta.

Sampling the Single Cell Proteome with Optically trapped Smart Droplet Microtools

A novel approach to extracting proteins from single cells has been developed by Mark Neil, Oscar Ces and colleagues at Imperial College London. This method is based upon the optical trapping and manipulation of $\sim 1\text{-}5\ \mu\text{m}$ sized detergent or lipid coated oil droplets (Smart droplet Microtools (SDMs)). SDMs currently come in two flavours depending on their composition; those that have

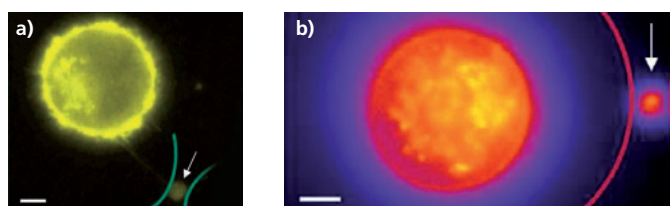


Fig 1. False colour fluorescence intensity images of SDMs after docking and removal of (a) membrane tether and (b) EGFP protein from EGFP labelled human colon cancer cell. Scale bars = $4\ \mu\text{m}$.

fusogenic lipid coatings can fuse with the cell membrane resulting in the formation of membrane tethers (Fig 1 (a)) and those with detergent coatings can be manoeuvred and docked with a target cell for effecting spatially selective uptake of proteins from the plasma membrane (Fig 1 (b)). The SDMs are stored and isolated from target cells for controlled cell-SDM experiments in an integrated, microfluidic chip platform. This single cell approach provides an exciting alternative to existing methods that rely on the analysis of large quantities of proteins from across many cells and meets the need of researchers to investigate subtle differences between single cells from within a large population or where such single cells are rare, such as stem cells or metastatic cancer cells.

Contact

Single Cell Proteomics Group
www3.imperial.ac.uk/chemicalbiologycentre/singlecellanalysis

Surface enhanced Raman spectroscopy (SERS) – a powerful tool in analytical, bioanalytical and biomedical diagnostics

Raman spectroscopy is a valuable tool in various research and application fields like surface science, electrochemistry, biology, and material science. An especially promising application field is Biophotonics. The technique yields vibrational fingerprint information from all kind of samples often without the need for extensive sample preparation. Therefore, it can not only be employed to unravel fundamental cell processes in order to understand the origin of diseases, but has also numerous practical analytical applications like e. g. the identification of bacteria, revealing the polymorphy of drugs, the quality of food or food ingredients.¹ However, Raman signals are inherently weak and therefore usually do not allow the investigation of substances at a low concentration level, e. g. residues of medic in body liquids. A solution to this problem is surface-enhanced Raman spectroscopy (SERS). Here, rough coin metal surfaces enhance the Raman signal by factors up to 10^{15} , depending on the applied method.²⁻⁴ A larger enhancement is observed when the SERS technique is coupled with

the resonance Raman enhancement. Indeed, single-molecule detection has been reported with surface-enhanced resonance Raman scattering (SERRS).⁵ Within this tutorial the SERS technique and some potential applications will be introduced. In Fig. 1 the investigation of the biomolecule adenine both with Raman and SERS spectroscopy is illustrated. As mentioned above, the Raman spectroscopy provides detailed fingerprint information, but only if the aqueous adenine solutions are comparably highly-concentrated. To decrease the detection limit, silver nanoparticles are added, which allow through the SERS effect a detection of several orders of magnitude less molecules.

Although SE(R)RS spectroscopy is widely applied, the mechanism leading to the surface enhancement is not completely understood yet. In general there are two main contributions: the electromagnetic⁶ and the chemical mechanism⁷. The electromagnetic contribution of the SERS effect is due to an electromagnetic field enhancement caused by a plasmon

excitation through the incident laser light on the metal surface. Electrons in the metal are excited to an oscillation against the metal cores, called surface plasmon resonance. In nanostructured surfaces the excited surface plasmon resonance leads to an electromagnetic field, which reaches out to the metal surface, where the analyte is located. Since the surface plasmon resonance has to be stimulated by the incident laser light, the excitation wavelength for a SERS experiment must be adapted to the surface plasmon profile of the respective metal and also to the nanostructure of the metal surface, which also has an effect on the plasmon resonance wavelength. The most widely employed metals for SERS experiments are silver and gold, having excitation wavelengths in the visible down to the NIR spectral region.⁸ However, in the last couple of years SERS substrates also for UV excitation wavelengths are developed.⁹ The chemical mechanism on the other hand is associated with a charge transfer process between the adsorbed analyte and the metal surface. Therefore, vibrations involved in the charge transfer process are enhanced, a mechanism which is similar to the resonance Raman enhancement.⁷ An especially for Biophotonics interesting application is the online monitoring of small concentrations of drugs in blood serum or contaminations in water. Also in these cases, the detection limit of the Raman spectroscopy is comparably large due to the weak Raman signals. Therefore, the SERS technique, combining high specificity and high sensitivity, is used for quantitative measurements. Unfortunately, due to the dependence of the SERS activity on the properties of the SERS substrate, the reproducibility of SERS spectra is generally rather low. Using metal colloids as SERS active substrate the reproducibility is also affected negative by the inhomogeneous

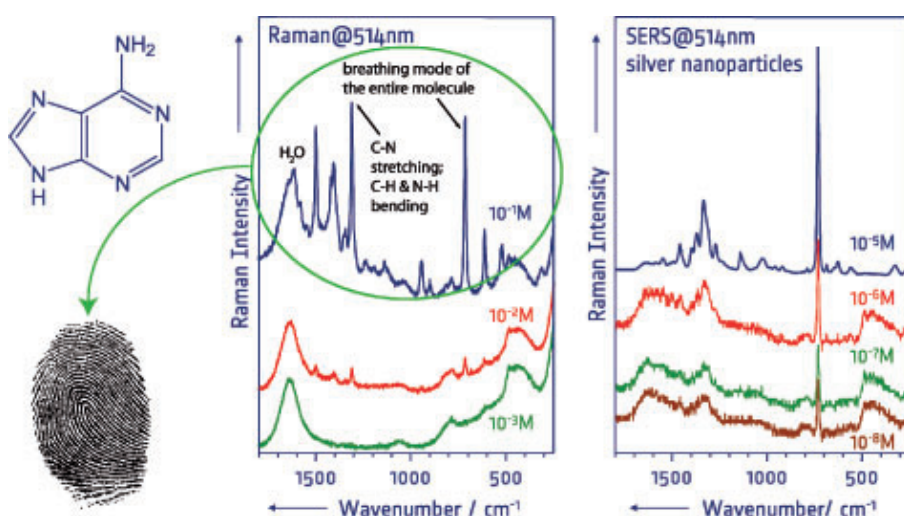


Fig. 1. Raman spectroscopic and SERS investigation of the biomolecule adenine. Applying Raman spectroscopy only high amounts of adenine can be detected. (left) To improve the detection limit of the highly specific Raman spectroscopy, silver nanoparticles are added and thanks to the SERS effect, the Raman bands are enhanced by several orders of magnitude. (right)

dispensation of the nanoparticles and the formation of 'hot spots' (Fig. 2C). By means of theoretical considerations it could be shown that in the gap between two nanoparticles an enormous high field enhancement exists (Fig. 2B). Therefore, the SERS intensity can be easily increased by the aggregation of metallic nanoparticles.^{10,11}

Applying a combination of surface enhanced Raman spectroscopy and special microfluidic devices reproducibility can be achieved (see Fig. 3). A homogenous dispensation is provided for the measurements by using a two phase liquid/liquid segmented flow in a microfluidic system. With the implementation of an internal standard it is even possible to compensate the influence of the substrate properties on the SERS spectra. With such a setup quantitative SERS measurements and even online monitoring of concentration changes are possible.^{12,13}

The above described SERS technology can be used for quantitative measurements,

as well as for qualitative detection of microorganism like bacteria and viruses. For an identification of those organisms the detection of their DNA is commonly a used way. In Fig. 4 a schematic detection of DNA is depicted. Therefore, capture DNA is immobilized on a surface, for instance a micro-chip. Since the target DNA is complementary towards the capture DNA the formation of double stranded DNA takes place. This linking can be detected by means of fluorescence dyes used as labels or label-free techniques like normal Raman spectroscopy. However the application of normal Raman spectroscopy for micro analytics is again hampered due to the weak Raman effect.

Therefore, the SERS technique can be applied for chip-based DNA detection, meaning a fast and on demand preparation of rough silver nanoparticles by using enzymatically silver deposition forming spatially well defined SERS substrates. Due to the corrugated structures of the silver nanoparticles (see Fig. 5) the substrate is highly SERS active. Furthermore

the broad absorption spectrum, which is caused by the broad distribution of the enzymatically produced silver nanoparticles in geometry and size, renders them ideal for investigations employing several

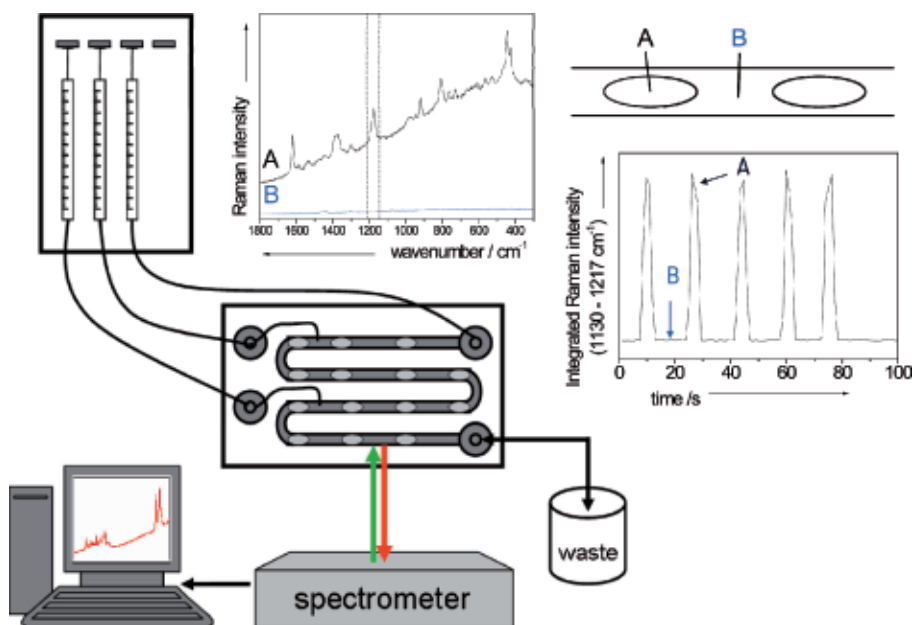


Fig. 3. Online concentration measurements by means of SERS. Small amounts of analyte solution are pumped into a microfluidic channel system via a syringe pump system. SERS spectra of single droplets including nanoparticles and analyte molecules are recorded by focusing the laser beam within the microchannel. Spectrum A is recorded in such a droplet including metal nanoparticles and the analyte crystal violet. If no droplet is in the focus no enhancement occurs and only a background signal of the separation medium is detected (spectrum B). By plotting the integrated Raman intensity of crystal violet against the measuring time, a regular alternating pattern is achieved.

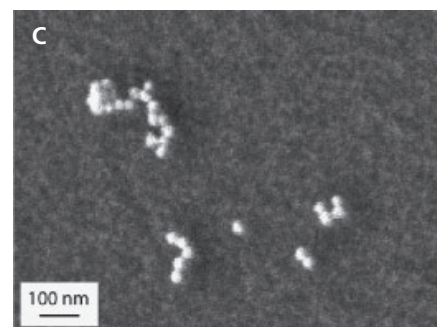
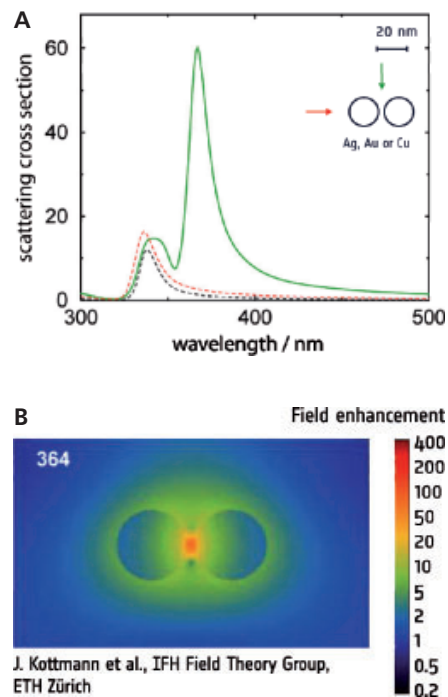


Fig. 2. Aggregation of metal nanoparticles for a more efficient enhancement of the Raman intensity. (A) For illustrating the aggregation effect by means of theoretical considerations, the scattering cross section of a nanoparticle dimer is plotted against the excitation wavelength. If the k vector is oriented perpendicular to the dimer, meaning that the electric field oscillates along the dimer axis, a strong electromagnetic field in the gap between the nanoparticles is achieved. (B) The field enhancement between two nanoparticles is pictured. Due to the aggregation of metal nanoparticles the field gets enormously enhanced. (C) SEM image of aggregated gold nanoparticles illustrating the inhomogeneous dispensation and the formation of 'hot spots'.

excitation frequencies. By preparing the SERS substrates in an array format on a glass chip many different analyte molecules can be observed simultaneously on one chip. A spatial resolution in the μm -range, which can be reached through

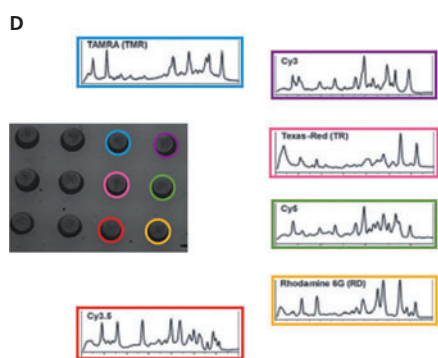
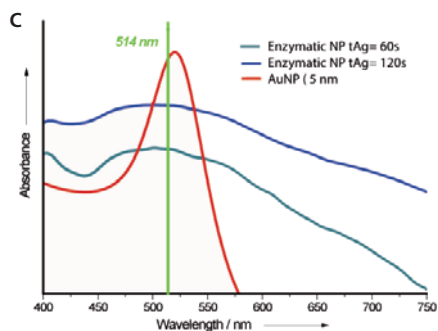
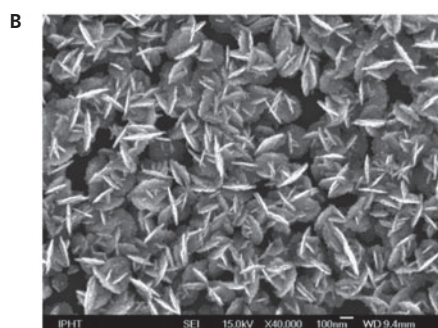
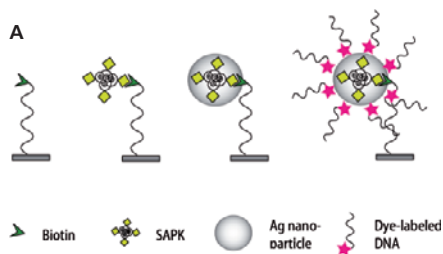


Fig. 5. (A) Principal approach for the enzyme induced silver deposition on biotin modified oligonucleotides, (B) SEM image and (C) UV/VIS absorption spectra of the enzymatic silver nanoparticles, (D) possible appearance of a multiplex DNA array (spectra adapted from the literature¹⁵).

a microscope, provides optimal conditions for multiplex detection with a variety of different molecules.¹⁴

Another approach for chip-based analytics is, instead of using freshly and on demand prepared metallic nanoparticles, the application of regular patterned SERS substrates prepared by electron beam lithography.^{16,17} In Fig. 6A the preparation of a rhomb-shaped SERS array in a two step process by means of electron beam lithography is illustrated. A SEM image of the resulting pattern shows the reproducibility of these nanostructures across a large measuring area (Fig. 6B). For determination of the enhancement factor, the SERS array was coated with nearly monolayered crystal violet and the enhancement factor was estimated to be in the range of 6 to 9×10^3 . These results show the great capability of this array for bioanalytical and analytical devices.

Within this tutorial an approach for quantitative SERS analytics using microfluidic devices was introduced. This technique can be used for pharmaceutical applications in the future. Furthermore new SERS substrates, on demand prepared silver nanoparticle and reproducible gold nanoparticle arrays, have been presented. An approach towards chip-based DNA

detection is currently under development. Obviously the SERS technique fulfils two important requirements for powerful analytics, which are high specificity combined with high sensitivity, due to the combination of the highly specific Raman spectroscopy with the highly sensitive plasmonic approach. Therefore the SERS technique is a powerful technique to solve a wide range of analytical tasks within the field of Biophotonics.

Acknowledgement

The research project "Jenaer Biochip Initiative (JBCI)" within the framework "InnoProfile – Unternehmen Region" is financially supported by the Federal Ministry of Education and Research (BMBF) Germany.

References

1. Petry, R.; Schmitt, M.; Popp, J. *Chem-PhysChem* 2003, 4, (1), 14–30.
2. Hering, K.; Cialla, D.; Ackermann, K.; Doerfer, T.; Moeller, R.; Schneidewind, H.; Mattheis, R.; Fritzsche, W.; Roesch, P.; Popp, J. *Analytical and Bioanalytical Chemistry* 2008, 390, (1), 113–124.
3. Kneipp, K.; Kneipp, H.; Itzkan, I.; Dasari, R. R.; Feld, M. S. *Journal of Physics: Condensed Matter* 2002, 14, (18), R597–R624.

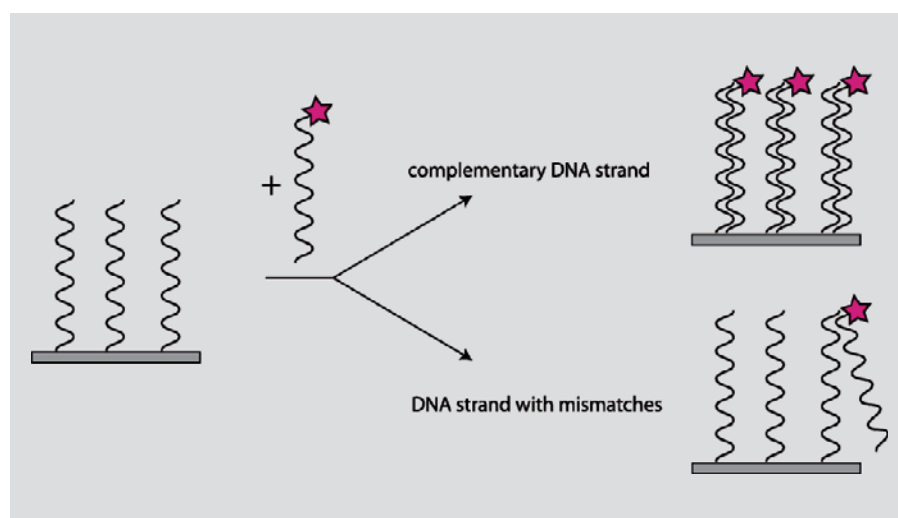


Fig. 4. Schematic identification of organism by means the detection of their DNA. Capture DNA is immobilized on a micro-chip. If the target DNA is complementary to the capture DNA the formation of a DNA double strand takes place. However, if the target DNA strand is not complementary, than the DNA is not or is only weakly bound. The linking between the target DNA and the capture DNA can be detected e. g. by the use of fluorescence labels or by label-free techniques like Raman spectroscopy.

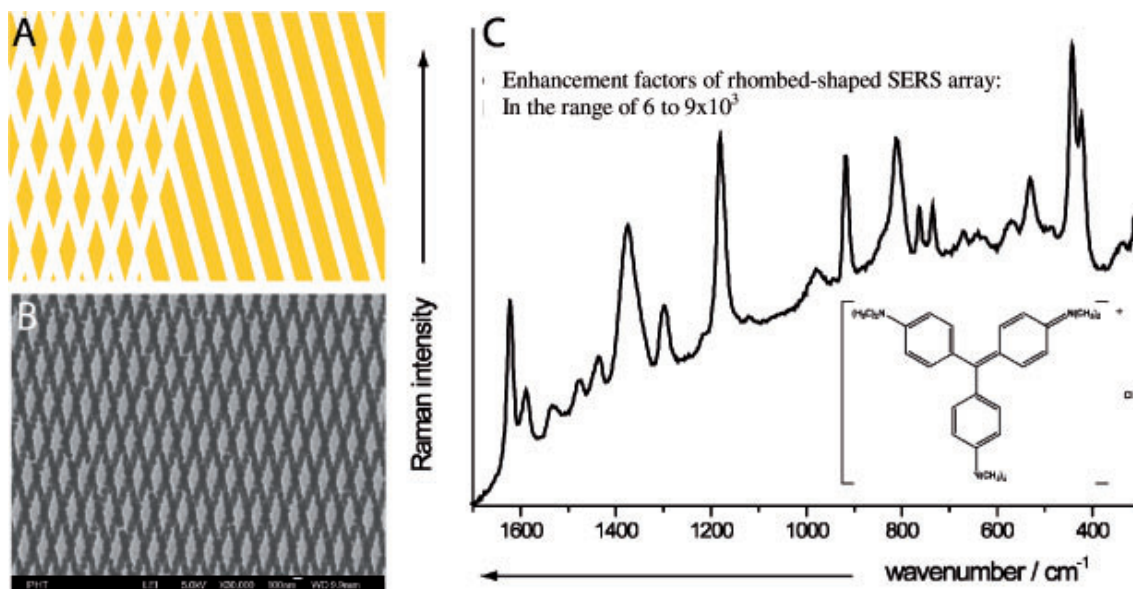


Fig. 6. Regular patterned SERS arrays for chip-based analytics. (A) The preparation of a regular patterned SERS array is performed by a two stage electron beam lithographic process. (B) Resulting SEM image shows the reproducibility of this approach. (C) Mean value SERS spectrum of approximately 100 single SERS spectra of nearly monolayered crystal violet. The enhancement factor is in the range of 6 to 9×10^3 .

- Anker, J. N.; Hall, W. P.; Lyandres, O.; Shah, N. C.; Zhao, J.; Van Duyne, R. P. *Nature Materials* 2008, 7, (6), 442–453.
- Graham, D.; Faulds, K. *Chemical Society Reviews* 2008, 37, (5), 1042–1051.
- Schatz, G. C.; Van Duyne, R. P. *Handbook of Vibrational Spectroscopy* (Wiley & Sons, Chichester) 2002, 1, (eds. Chalmers, Griffiths), 759–774.
- Arenas, J. F.; Lopez-Tocon, I.; Castro, J. L.; Centeno, S. P.; Lopez-Ramirez, M. R.; Otero, J. C. *Journal of Raman Spectroscopy* 2005, 36, (6/7), 515–521.
- Willets, K. A.; Van Duyne, R. P. *Annual Review of Physical Chemistry* 2007, 58, 267–297.
- Doerfer, T.; Schmitt, M.; Popp, J. *Journal of Raman Spectroscopy* 2007, 38, 1379–1382.
- Kottmann, J. P.; Martin, O. J. F. *Optics Express* 2001, 8, (12), 655–663.
- Xu, H.; Aizpurua, J.; Kaell, M.; Apell, P. *Physical Review E: Statistical, Nonlinear, and Soft Matter Physics* 2000, 62, (3), 4318–4324.
- Strehle, K. R.; Cialla, D.; Roesch, P.; Henkel, T.; Koehler, M.; Popp, J. *Analytical Chemistry* 2007, 79, (4), 1542–1547.
- Ackermann, K. R.; Henkel, T.; Popp, J. *ChemPhysChem* 2007, 8, (18), 2665–2670.
- Hering, K. K.; Moller, R.; Fritzsche, W.; Popp, J. *ChemPhysChem* 2008, 9, (6), 867–72.
- Jin, R.; Cao, Y. C.; Thaxton, C. S.; Mirkin, C. A. *Small* 2006, 2, (3), 375–380.
- Cialla, D.; Huebner, U.; Schneidewind, H.; Moeller, R.; Popp, J. *ChemPhysChem* 2008, 9, (5), 758–762.
- Huebner, U.; Boucher, R.; Schneidewind, H.; Cialla, D.; Popp, J. *Microelectronic Engineering* 2008, 85, 1792–1794.

Contact

Dana Cialla, Anne März, Katharina Strelau, Robert Möller,
Thomas Mayerhöfer and Jürgen Popp
dana.cialla@ipht-jena.de

Announcement: Training on Entrepreneurship in Biophotonics

Brussels, Belgium, September 7 – 18, 2009

The European Network of Excellence "Photonics 4 Life" and the Vrije Universiteit Brussel (VUB) organise the first intensive training on Entrepreneurship in Biophotonics. This training will take place from 7 to 18 September 2009 in Brussels, Belgium. The programme will consist of 3 modules. The first module lasts 3 days and covers an introduction to business economics and high tech entrepreneurship (understanding industry dynamics, business project assessment tools, venture capital, finance, IPR, personality & team aspects, marketing). The second module lasts 2 days and covers business economic aspects of biophotonics, focused on medical imaging and lab analysis equipment (overview of industry, existing & competing technologies, key players, business models, sales & marketing, clinical trials, case studies). The third module lasts 5 days and consists of guided work on

your biophotonics business project. Courses will be lectured by professors of the Solvay Business School, and keynote addresses will be given by experts in the field of biophotonics research, industry and sales. The target group consists of researchers of P4L members, researchers of universities or research institutes, employees of biophotonics related companies, lawyers, business angels, consultants,... In short: the training is open to everybody who is interested in entrepreneurship in biophotonics. Important notice: please keep in mind that the number of places will be limited. If you are interested, please send an email to tguldemo@vub.ac.be, and we will keep you up-to-date about the latest developments. For more information, you can consult the website of Photonics4Life, <http://www.photonics4life.eu/>.

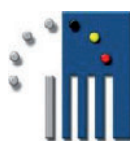
IEEE/LEOS Summer Topical Meeting

Acapulco, Mexico, July 21 – 23, 2008

In July 2008 the IEEE/LEOS Summer Topical Meetings (<http://www.ieee.org/organizations/society/leos/LEOSCONF/SUM2008/index.html>) with the session on Optofluidics took place in Acapulco, Mexico. The presentations gave a good overview on the current activities in optofluidics. Special interest was on optical particle guiding. Plasmonic tweezers using focussed polarized light on an Au-surface were shown as well as integrated optofluidic traps. Image based technologies were also demonstrated for particle sorting. For in vivo detection and tracking of non-fluorescent nano objects (membrane proteins) in live cells photothermal effects were used. Several approaches for single virus detection were discussed, using optofluidic chips out of SiN, SiO₂ and Si while the sensing was based on liquid core wave guiding or micro optical cavities. In the diagnostics session approaches for microscopy of Au-nanoshells in tumors using two-photon photoluminescence were presented. Results on sub-diffraction imaging by nano light emitting probe tips are encouraging.

Photonics@be

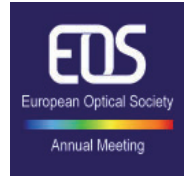
Oostduinkerke, Belgium – March 2008



The annual doctoral school of the Belgian Photonics@be network (IAP) was organized by VUB-TONA near the Belgian seacoast at Domein Westhoek, Oostduinkerke in March 2008 and focused on Biophotonics. During two consecutive days of intensive lectures more than 30 young researchers got crash courses in biosensors, light scattering, optical micromanipulation, holographic interferometric optical metrology for life science, and photonic technologies in clinical diagnostics. Several of these high quality tutorials were given by keynote speakers from Photonics4Life.

EOS Annual Meeting and EPIC Industrial workshop

Paris, France, September 29 – October 02, 2008



The 2008 annual meeting of the European Optical Society was held recently at the beginning of October in Paris and featured a topical meeting on Biophotonics, chaired by Photonics4Life consortium members Prof Gert Von Bally and Dr Mark Neil with Prof Ivo Rendina from the Institute for Microelectronics and Microsystems in Napoli. Concentrating on Nano-biophotonics and Biosensors the meeting attracted over 40 oral presentations.

Alongside the topical meeting ran an industrial workshop organised in conjunction with the European Photonics Industry Consortium (EPIC) and focusing on transforming innovative ideas from the laboratory to commercially successful products. Prompted by four presentations from both small and large

industrialists working in the field, the 35 participants broke up into working parties to discuss key issues. A full report of the proceedings is available free of charge on

CD-ROM from EPIC (www.epic-assoc.org) and the results are feeding into the considerations of the Photonics4Life industrial workpackage.



Industrial Workshop organising committee and presenters, Left to Right, Ivo Rendina (IMM Napoli), Gert von Bally (University of Munster), Jürgen Fleischer (Leica), Géraldine Andrieux (Yole Finance), Peter Höjerback (Serstech AB), Tom Pearsall (EPIC), Jean-Luc Ayrat (Force-A) and Mark Neil (Imperial College).

Biophotonik Symposium

Jena, Germany – September 23 – 25, 2008

About 200 representatives from German industry and science were informed by Prof. h.c. Gert von Bally about the aims of the Network of Excellence Photonics4Life in the framework of the congress "Photonics meets Life Sciences". The congress took place from the 23rd – 25th of September 2008 in Jena under the patronage of federal secretary of research Dr. Annette Schavan. Among the audience of the lecture "Photonics4Life: Die Europäische Biophotonik-Forschung bündelt ihre Kräfte (The European biophotonic research concentrates its forces)" were beside scientists also many doctors and engineers. To enforce the interdisciplinary dialogue was one of the most important aims of the event, which

was organized by the Institute of Photonic Technology in cooperation with the BMBF-"Forschungsschwerpunkt Biophotonik".

Within the frame of this event, the meeting of the Working Group on Biophotonics of the German Society for Applied Optics (DGaO) took place. This series of meetings is especially interesting for industry, since traditionally there are given information on future funding of joint industrial-academic projects on biophotonics by the German Ministry of Education and Research (BMBF).

Event Calender

■ (co-)organized by photonics4life ■ contribution from photonics4life partners

Date	Event	Location	Link
February			
2 – 13 February	ICTP Winter College on Optics in Environmental Science	Trieste, Italy	http://cdsagenda5.ictp.trieste.it/full_display.php?smr=0&ida=a08142
March			
8 – 13 March	PittCon 2009 – Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy	Chicago, USA	http://www.pittcon.org/
April			
5 – 8 April	FOM 2009 - Focus on Microscopy	Krakow, Poland	http://www.focusonmicroscopy.org/
13 – 16 April	VI. International Workshop TecnoLaser 2009 and II. Meeting Optics, Life & Heritage	Havanna, Cuba	http://www.ceaden.cu/tecnolaser/index_ing.asp
May			
27 – 29 May	4th Asian and Pacific Rim Symposium of Biophotonics (APBP 2009)	Jeju Island, Korea	http://www.apbp2009.org/home/main/main.asp
June			
2 – 5 June	DGaO Annual Meeting 2009	Brescia, Italy	http://www.dgao.de/info/tagung09_d.php
6 – 13 June	4th International Graduate summer school – Biophotonics ,09	Ven, Sweden	http://www.biop.dk/biophotonics09/School/School.asp
8 – 11 June	Scandinavian Symposium on Chemometrics	Loen/Stryn, Norway	http://www.kj.uib.no/ssc11/index.htm
10 – 12 June	4th EOS Topical Meeting on Advanced Imaging Techniques	Jena, Germany	http://www.myeos.org/jena
11 – 14 June	12th International Conference on Photorefractive Materials, Effects and Devices – Control of Light and Matter	Bad Honnef, Germany	http://www.uni-muenster.de/Physik.PR09/
14 – 18 June	ECBO – European Conference on Biomedical Optics	Munich, Germany	http://www.osa.org/meetings/topicalmeetings/ecbo/
July			
13 – 17 July	ICAVS-5: 5th International Conference on Advanced Vibrational Spectroscopy	Melbourne, Australia	http://www.chem.monash.edu.au/biospec/icavs/committee.html
August			
26 Aug – 3 Sep	ASCOS 2009 – Optical Chemical Sensors for Environmental and Food Safety	Madrid, Spain	http://www.ascos.org/
28 Aug – 02 Sep	ECSBM2009 – XIII European Conference on the Spectroscopy of Biological Molecules	Palermo, Italy	http://www.ecsbm.eu/
September			
7 – 18 Sep	Training on Entrepreneurship in Biophotonics	Brussels, Belgium	http://www.photonics4life.eu/
22 – 25 Sep	Saratov Fall Meeting 2009 -XIII International School for Junior Scientists and Students on Optics, Laser Physics & Biophotonics	Saratov Russia	http://optics.sgu.ru/SFM/
October			
7 – 9 October	ICO Topical Meeting on „Emerging Trends & Novel Materials in Photonics“	Delphi, Greece	http://www.ico-photonics-delphi2009.org/
18 – 22 October	FACSS, the Federation of Analytical Chemistry and Spectroscopy Societies, conference	Louisville, USA	http://facss.org/facss/index.php

Editor

European Network of Excellence for Biophotonics – P4L

Coordinator

Prof. Dr. Jürgen Popp
Institute of Photonic Technology
Albert-Einstein-Straße 9
07745 Jena, Germany
juergen.popp@ipht-jena.de

Network support officer

Dr. Thomas Mayerhöfer
Institute of Photonic Technology
Albert-Einstein-Straße 9
07745 Jena, Germany
thomas.mayerhoefer@ipht-jena.de
Phone: +49 (0) 3641 206-040
Fax: +49 (0) 3641 206-399

Editorial staff

Dr. Jürgen Mohr, Forschungszentrum Karlsruhe, Germany
Georg Obermaier, Forschungszentrum Karlsruhe, Germany

Arrangement

Forschungszentrum Karlsruhe, Typography

Print

Elser Druck, Mühlacker, Germany

Next issue

July 2009

Editorial deadline

15th May 2009

For additional information please visit

<http://www.photonics4life.eu>