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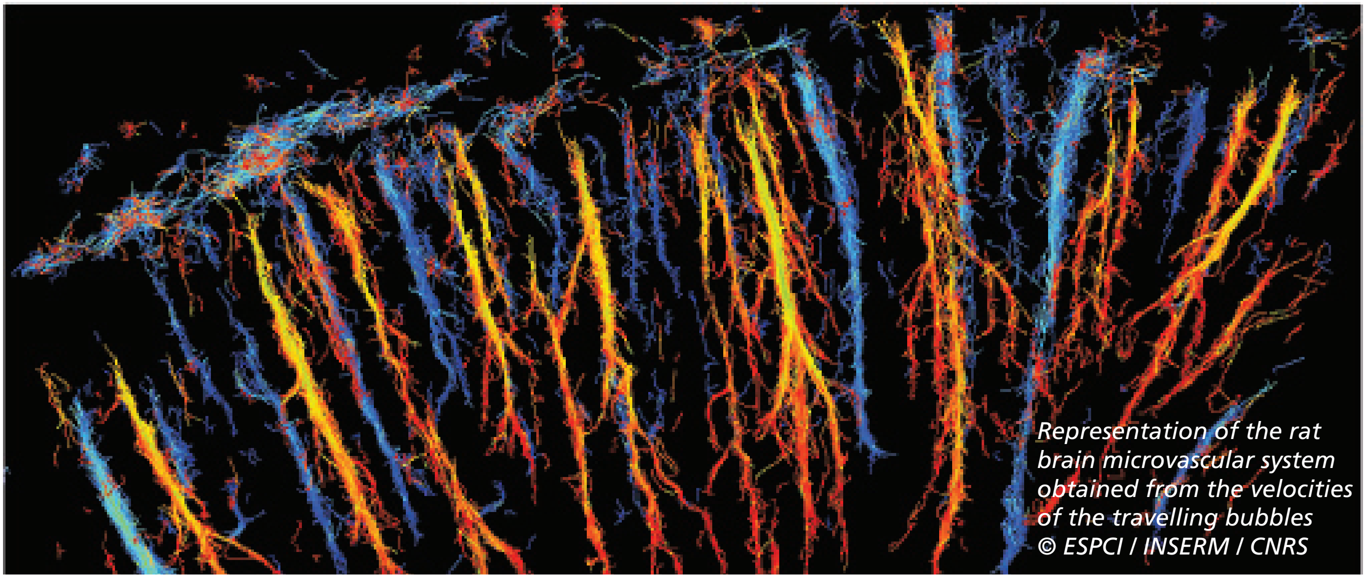
Biomedical imaging with microscopic resolution: the breakthrough of ultrasound

A team of physicists and neurobiologists from the ESPCI ParisTech led by Mickaël Tanter, Inserm research director (Langevin Institute, CNRS, Inserm), has just passed a crucial step towards super-high resolution medical imaging. Scientists managed to non-invasively map the living rat brain vasculature by using ultrasound with far higher resolution than any other existing technique. Very different from common ultrasound imaging, the technique was rather inspired by ultra-high optical resolution techniques such as FPALM, awarded with the Nobel Prize for Chemistry in 2014. Their work was published in the prestigious Nature journal and constitutes an important breakthrough for biomedical imaging. It is the first microscopic imaging technique allowing observation deep into living tissues. Potential applications are numerous, from the early detection of tumors to cardiovascular and neurologic pathologies.



Representation of the rat brain microvascular system obtained from the velocities of the travelling bubbles
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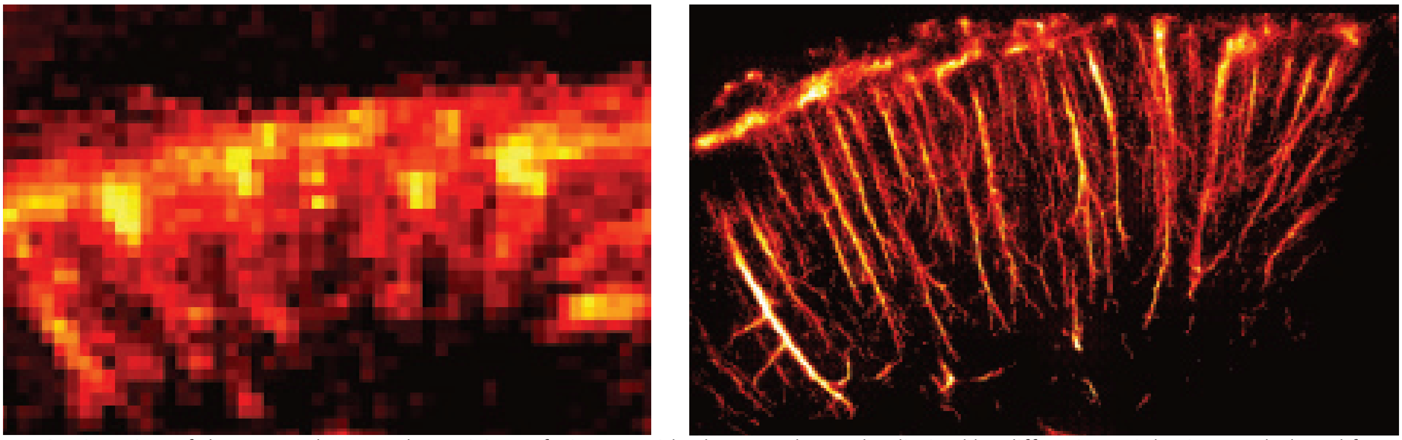
Observing microscopic details of living matter still represents a hard challenge to meet. No matter what technique used, scientists face the same obstacle: smaller wavelengths, optimal for high-resolution imaging, lead to higher absorption and scattering in tissues, lowering the depth of penetration of the signal. Scientists thus have to choose between depth penetration and image resolution. Yet, in the last twenty years considerable progress have been made in the ultrasound field particularly suitable for clinical or pre-clinical imaging, where Mickaël Tanter and his team are pioneers. These researchers have developed an ultrafast ultrasound imaging device, already available in many hospitals throughout the world. But this time, they made another important technical step forward, reaching an unprecedented spatial resolution in medical imaging: the micrometer scale (a thousandth of a millimeter).

All began in 2009, when Mickaël Tanter gave a lecture on ultrasound imaging in the United States, and attended a presentation of a new optical fluorescence microscopy technique with a resolution smashing the limit imposed by light diffraction for centuries, a step supposed to be impossible. The inventors of the technique were awarded with the Nobel Prize of Chemistry in 2014. The French scientist understood that the method of these American chemists and optics physicists, still restrained to surface imaging, could be transposed to the world of highly penetrating ultrasound imaging by using the ultrafast ultrasound technique of his laboratory. Once back in France, he and Olivier Couture, CNRS researcher in his team started to develop their own method based on ultrasound.

The scientists decided to use a contrast agent, microbubbles with a diameter of 3 µm, already used in medical diagnostics. As a part of several years of fruitful research collaboration with a team of neurobiologist led by Zsolt Lenkei, Inserm research director (ESPCI/CNRS), they injected the microbubbles in a rat vein and observed the living brain with their ultrasound device. The ultrafast acquisition rate of 5000 pictures per second allowed the very precise extraction of the individual signal emitted from each microbubble, an information usually drown into the noise of all the backscattered signals. Thus, their unique location can be well defined individually with micrometer precision during their travel in the brain vessels.

By tracing the exact location of several millions of bubbles at each imaging plane, researchers managed to rebuild a complete functional map of the cerebrovascular system in the living rat, in a few dozens of seconds. Details even permit to distinguish blood vessels separated by only few micrometers, although the diffraction-limited resolution limit was about a millimeter until now. Moreover, velocity of the blood flow was also measured with a large dynamic range, from several dozens of centimeters per second in the large vessels up to less than a millimeter per second in the smallest vascular systems.



In-vivo imaging of the rat cerebrovascular activity. Left: image with ultrasound Doppler, limited by diffraction. Right: image deduced from microbubbles localization. The gain in resolution is higher than 20. *© ESPCI / INSERM / CNRS*

Many direct applications

The excellent gain in resolution - about 20 times as compared to «standard» ultrafast ultrasound -, coupled with the non-invasive and fast properties of the technique may be really valuable for patients. *«We think we are entering a new paradigm in medical imaging,* says M. Tanter. *In a few dozens of seconds, we are already able to collect millions of signatures of our microbubbles and reach microscopic details even at several centimeters depth. We believe that we can still reduce the acquisition time to obtain images in a couple of seconds, paving the way for ultra high resolution functional imaging.*»

The technique will soon be used on humans, in particular to visualize the hepatic micro-vascularization of patients suffering from liver tumors or for high-resolution transcranial imaging of the cerebrovascular network in adults. There are many other potential applications, including the early detection of cancers, whose micro-vascularization is impossible to detect right now. In fact it will be possible to obtain a 3D vascular image of any organ, with microscopic resolution, by using a very compact device.

Although most of the current microscopic techniques rely on optical approaches limited to surface imaging, ultrasound came and solve the quest of imaging deep into organs at microscopic scales.

C.Errico, J. Pierre, S. Pezet, Y. Desailly, Z. Lenkei, O. Couture & Mickael Tanter, Ultrafast ultrasound localization microscopy for deep in vivo super-resolution vascular imaging, **Nature**, 2015
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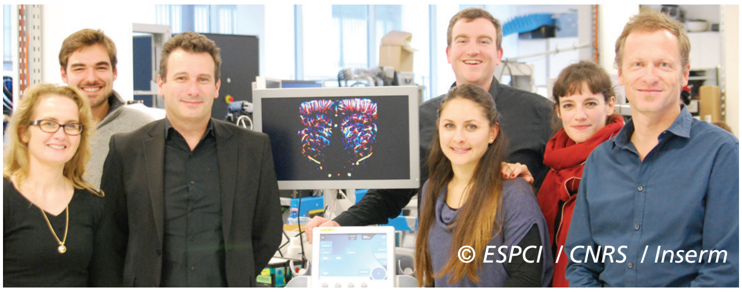
Research teams



«Wave Physics for Medicine and Biology» team

The team «Wave Physics for Medicine and Biology» (Inserm U979/CNRS UMR 7587/ESPCI) brings together physicists with a strong expertise in the field of wave physics dedicated to biomedical imaging and therapy. Scientists are working on new innovative techniques and devices for medical imaging and extracorporeal therapy based on the use of ultrasonic waves. They have indeed developed several unique in the world, allowing them to confirm the approaches from fundamental experiment to the clinical trial at patient's bed. It one of the world leading team working at the Physics/Medicine interface, with several major achievements in ultrasound imaging and therapy (ultrafast 2D and 3D ultrasound imaging, elastography, and functional ultrasound brain imaging...).

«Neuronal Structure and Dynamics» team

The team of Zsolt Lenkei, Inserm research director at the ESPCI-ParisTech (ESPCI-CNRS UMR8249), aims to better understand the effects of cannabinoids on neuronal structure and connectivity their potential implication in neuropsychiatric pathogenesis.
In order to enhance the experimental resolution in the study of neuronal dynamics at multiple spatiotemporal scales, the team develops strong interdisciplinary collaborations with physicists to build powerful novel imaging tools: use of advanced quantum dots, superresolution microscopy and functional whole-brain imaging with ultrafast ultrasound microscopy.

Institutions

ESPCI

L'ESPCI est un endroit unique, au cœur de Paris, où se conjuguent enseignement, recherche et innovation.
L'école, se démarque par sa formation scientifique de haut niveau, pluridisciplinaire, fortement adossée à une Recherche d'excellence et de renommée internationale, alliant science fondamentale et ouverture vers les applications et l'innovation. Elle forme chaque année 90 élèves-ingénieurs, recrutés parmi les meilleurs. Elle dispense une formation originale en physique, chimie et biologie, basée sur la recherche et les travaux pratiques.
Elle est reconnue dans le monde entier pour l'excellence de sa Recherche fondamentale et appliquée, génératrice d'innovations pour l'industrie.
C'est une école d'ingénieurs de la Ville de Paris fondée en 1882. Pépite de l'enseignement français, elle compte 6 Prix Nobel depuis sa création et est l'une des 2 meilleures écoles d'ingénieurs françaises au classement de Shanghai. Elle attire de plus en plus de candidats, et ses ingénieurs et ingénieurs-docteurs constituent un excellent vivier pour dynamiser les départements R&D des grands groupes industriels, ou alimenter la recherche fondamentale académique.

Inserm

Créé en 1964, l'Institut national de la santé et de la recherche médicale (Inserm) est un établissement public à caractère scientifique et technologique, placé sous la double tutelle du Ministère de l'Éducation nationale, de l'Enseignement supérieur et de la Recherche et du ministère des Affaires sociales, de la Santé et des Droits des femmes. L'Inserm est le seul organisme public français dédié à la recherche biologique, médicale et à la santé humaine et se positionne sur l'ensemble du parcours allant du laboratoire de recherche au lit du patient. Ses chercheurs ont pour vocation l'étude de toutes les maladies, des plus fréquentes aux plus rares. Avec un budget 2014 de 989 M€, l'Inserm soutient près de 300 laboratoires répartis sur le territoire français. L'ensemble des équipes regroupe près de 15 000 chercheurs, ingénieurs, techniciens, gestionnaires, hospitalo-universitaires, post-doctorants…