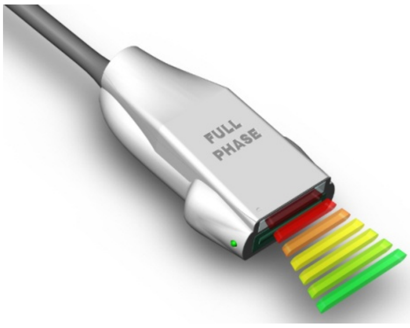
FULLPHASE
Fully integrated real time multi-wavelength photoacoustics
for early disease detection



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FP7 Collaborative Project no. 318067

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Project context and objectives

With the aging population, healthcare delivery at affordable cost will become a major challenge, supporting the need for early disease detection and improved diagnostics by functional imaging. Within this context, the objective of FULLPHASE is the transition of photoacoustic imaging (PAI) from a lab-based technique to a low-cost portable multi wavelength combined PA and US system.

A number of partners already successfully collaborated within other EU projects. For FULLPHASE, other complementary partners have been added, aiming at a swift translation of research into practice. Throughout the project, existing collaborations are fostered and new collaborations are created. The combination of engineering, basic research, clinical practice and cutting-edge PAI in the FULLPHASE project makes that the partners are able to bring about a change in healthcare delivery. The impact of the FULLPHASE system will be shown in rheumatology, oncology, and cardio vascular disease (CVD).

In the last three decades, light has been recognized to offer promises for medical diagnosis. Living tissue has a strong interaction with light via scattering and absorption. Optical scattering is caused by refractive index variations while, optical absorption is associated with physiological properties, such as hemoglobin concentration and oxygen saturation. Pure optical imaging techniques using wavelengths in the range of the diagnostic window are however burdened by strong tissue scattering. This either limits the imaging depth to less than a millimeter or restricts the spatial resolution to several millimeters. PAI overcomes both the imaging depth limitation and the low resolution by using the fact that local absorption of pulsed light creates sources of ultrasound (US) inside tissue via a thermoelastic effect.

Therefore, by the combined use of light and US in PAI, the contrast is provided by light, image resolution is governed by the US propagation and imaging depth by a combination of both. Thus, PAI enables tissue imaging that exploits the advantages of both modalities.

In awareness of the situation portrayed, the **main objective** of FULLPHASE is the transition of PAI from a lab-based application to a portable, functional PAI system combined with US for early disease detection, improved diagnostics by functional imaging and point-of-care treatment monitoring. The integrated set of research and development activities, related to the **main** FULLPHASE objective, will focus on:

- **Portability:** Combined PA/US imaging with the laser source directly integrated in a hand held probe using diode laser technology instead of external fibre lasers. A drastic miniaturization of the diode laser driver will be realized by using an innovative resonant topology that recycles the energy stored in parasitic elements.
- **Multi-wavelength functional PAI:** A multi wavelength diode laser will be developed for tissue irradiation using 4 different wavelengths, and a multi-wavelength Diffractive Optical Element for optical beam shaping will be integrated together with the laser source in the hand held PA/US probe for illumination of the tissue.
- **A clinically suitable PA imaging depth:** In order to achieve the required imaging depth for CVD, dedicated data processing for improved image contrast and clutter will be implemented. In addition to that, fast laser pulse sequences for coded excitation will be applied to increase SNR.
- **High temporal resolution and sensitivity:** One-shot multi-channel parallel detection and reconstruction instead of traditional US line-by-line scanning will bring a revolutionary increase in frame rate and thus temporal resolution and sensitivity of US imaging.

The breakthrough compared to existing clinical PA systems will be the portability and the low cost by employing beyond state-of-the-art diode laser technology. This development together with the improvements in PAI depth will obtain the main emphasis in this project.

Work performed and the main results

In the first 18 months of the FULLPHASE project five prototypes of the portable FULLPHASE PAI system based on a handheld PA probe with integrated diode lasers are realised, optimised, and tested in in-vitro setups and the first in-vivo measurements are obtained. These five prototypes give feedback for R&D of the 10 prototypes of the multi wavelength handheld PA probe. In the first 18 months of the FULLPHASE project:

- R&D is on track on all levels.
- The first Prototype of PA/US probe, PAI system and high performance computing (HPC) frame work are in use.
- A full test in relation to performance of the PAI system and PA probe has been carried out.
- The first in-vivo measurements have been carried out.
- There is an excellent **cooperation** and **interaction** in the FULLPHASE team.

Cooperation is one of the success factors for the project realization. Therefore, in the FULLPHASE project there is full attention for: a) direct communication, b) open discussion between all levels and all disciplines, c) problem isolation, understanding and solving, d) exchange of PhD students and project members and e) regular meetings between the different partners to increase common knowledge and common understanding.

In WP2 with research targeted on functional imaging progress is made in: (1) real-time visualization of small pulsating blood vessels in the finger by means of the prototype of the FULLPHASE PA Probe, (2) the feasibility of using PA multi wavelength imaging for reducing reflection artefacts.

In WP3 where engineering takes place on the development of the PA probe progress is made in: (1) using a new generation of multiple Quantum-Wells laser diodes, (2) high efficiency ultra-short laser pulse driver, (3) multi-wavelength optical diffractive homogenizer and (4) highly integrated multiple laser diode packaging.

In WP4 with research targeted on irradiation geometry and imaging depth progress is made in: (1) information about irradiation geometry by means of simulations and in-vitro experiments showing that an given irradiation angle is optimal, (2) a photoacoustic sensitivity map of the PA probe, (3) knowledge about resolution with simulations and experiments about light pulse duration and (4) influence of irradiation geometry on contrast.

In WP5 with research targeted on image reconstruction and rendering progress is made on: (1) sound speed imaging showing already the first volunteer results, (2) successful phantom results of aberration correction of US and PA, (3) successful volunteer results of clutter reduction and (4) nonlinear image reconstruction using the Kaczmarz method. In addition, we showed that the unwanted noise caused by recharging the laser driver capacitors after a laser pulse can be reduced by ferrite cores in the power lines of the PA probe.

In WP6 where engineering takes place on system integration progress is made on: (1) the realization of five prototype PA/US system to be used for feedback on: a) system performance, b) PA probe sensitivity, c) PA probe temperature and d) US system distortion caused by laser pulsing, (2) the realization of a high performance computing (HPC) framework and (3) the design and integration of the PA probe prototype.

In WP7 where clinical validation of the PA/US system takes place progress is made on: (1) the realization of an in-vitro setup for PAI, (2) PAI of a plaque and (3) tissue perfusion measurements.

In WP8 on dissemination, commercial take-up and training progress is made on: (1) the development of course material explaining PAI to the public, (2) internal training activities by means of workshops on: a) laser diode technology, b) laser diode beam shaping, c) ultrasound technology, d) PA imaging principles and e) PAI clinical applications.

A smooth project management ensured timely fulfilment of the research and development tasks, stimulated active collaboration within the consortium and finally supported a close communication for knowledge exchange.

In conclusion the progress in the first 18 months of the FULLPHASE project is achieved on all levels from basic research via engineering towards in vitro studies in phantoms and the first in vivo studies in healthy volunteers.

Expected final results and their potential impact

Since many tissue pathologies come with an enhanced vascularisation and deviating blood oxygenation, spectroscopic photoacoustic imaging (PAI) is generally recognized as a potential diagnostic tool. However, the existing PAI systems on the market are hampered by large and expensive Nd:YAG lasers, and the bulkiness of the PA/US probes due to the external light delivery. Therefore, the focus for the development of the FULLPHASE multi wavelength PAI system is on: (a) portability, (b) beyond state-of-the-art laser diode technology, and (c) a hand-held PA probe. The FULLPHASE multi wavelength PAI system will bring cost-effective new avenues in health care delivery that cannot be obtained with any other imaging modality. The system will make new ways of treatment possible in: rheumatology, oncology, burn wound healing, neonatology, cardiovascular disease (CVD) and diabetic care.

Rheumatology: High frequency US measurements of joint space are robust and allow reproducible delineation of synovial thickening in the small joints of the hands in patients with active inflammatory chronic arthritis. However, analysis of such images does not demonstrate clear relationships with clinical assessments of disease activity. Therefore, there is a need for the assessment of vascularisation of the joint. Multi wavelength PAI will show the vascularisation of the joint, in a very early stage.

Oncology: An important aspect for tumor staging and its metastasis through the lymphatic channel is the identification and status of the neighboring lymph nodes that drain the tumor. At present the standard technique is using a blue dye and a radioactive tracer. Multi wavelength PAI will be able to determine blood oxygenation and tissue composition.

Burn wounds: In order to reduce scarring and improve quality of life in burn care patients, it is paramount to distinguish between superficial and deep burns. While existing optical imaging methods mainly utilize optical scattering, multi wavelength PAI will make discrimination between vital and necrotic tissue possible.

Neonatology: The combination of PAI and US in one fully integrated multimodal portable imaging system will enable to map both, tissue structures and oxygen saturation of the brain of newborn infants, in order to early detect ischemia and thus prevent brain lesions. The resulting real-time high resolution images of the brain will allow to detect cerebrovascular dysfunctions and to monitor pathogenic processes directly at the bedside.

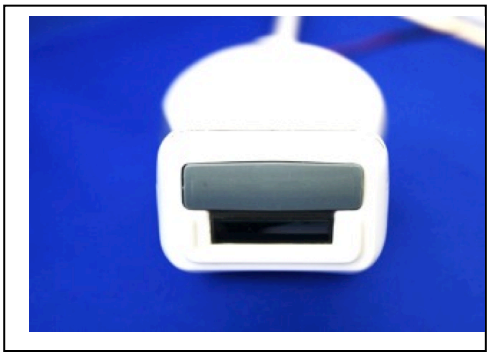
Cardiovascular disease: The assessment of rupture risk of plaques is one of the holy grails of vascular disease assessment. To date, none of the existing imaging modalities are capable of detecting and combining geometry, deformation, and perfusion of a vulnerable plaque. However, multi wavelength PAI enables the differentiation between different types of tissues and thus provides detailed information on plaque composition. Together with strain imaging methods and accurate flow rate assessment, this provides a complete view on the mechanical environment of a plaque.

Diabetic care: As for burn wounds the characterization of ischemic tissue and the monitoring of vascular remodelling during therapy is the main objective of PAI in diabetic care. While the structure of the computer aided diagnosis system developed for burn wounds and this application will be similar, the disease states and their photoacoustic spectral characteristics are different and have to be trained on different data sets. In addition, characterization of ischemic tissues by the endogenous contrast will be possible.

With an emphasis on a portable, low cost, multi wavelength PAI system using innovative and ground breaking technology, the FULLPHASE research and development project is fully dedicated on creating a beyond state-of-the-art change in healthcare delivery.

Photographs illustrating and promoting the work of the project

Figure 1: Prototype of the handheld FULLPHASE PA probe.



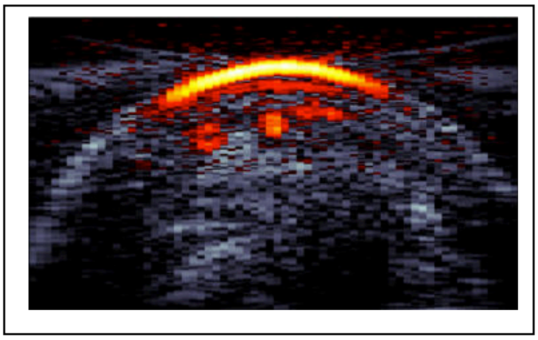


Figure 2: In vivo measurement on the finger of a healthy volunteer with a prototype of the FULLPHASE PAI system