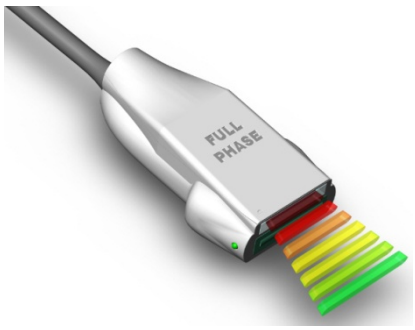
FULLPHASE

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



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FP7 Collaborative Project no. 318067

Publishable summary period 2

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Publishable summary

Project context and objectives

Due to the ageing population the demand for a change in healthcare delivery becomes inevitable. As people live longer the number of hospitalizations and clinical interventions rises. This upcoming increasing necessity for medical care is underlining the need for a cost effective change in healthcare delivery. Key items in this process of change are disease detection, improved diagnostics and therapy monitoring by means of point-of-care 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 FULLPHASE 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. 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 three disease domains: 1) Inflammation, 2) Skin and 3) Vascular.

PAI offers far greater specificity than conventional ultrasound imaging (USI) with the ability to detect haemoglobin, lipids, water and other light-absorbing chromophores at a depth out of range for pure optical imaging of comparable resolution. Besides visualizing anatomical structures such as the microvasculature with high resolution, PAI provides functional information such as blood oxygenation, blood flow and temperature. The technology is seen to be positioned in primary health care to prevent unnecessary hospital based and costly conventional scanning methods such as MRI and CT. The most important advantages of PAI are that it is non-ionizing, does not require contrast agents, and can deliver real-time images with high resolution, showing small structures that conventional acoustic or optical scanners would miss. A key aspect of PAI is the inherent ability to provide functional information regarding physical or chemical processes in tissue and their alteration through disease. This aspect makes PAI very suitable for a wide variety of applications in clinical medicine, preclinical research and basic biology.

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 merits 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 multimodality multi-wavelength portable, functional PA/US imaging system 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 laser diode technology instead of external fibre lasers. A drastic miniaturization of the laser diode 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 laser diode 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 cardio-vascular diseases (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 signal-to-noise ratio (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 PA systems will be the portability and the low cost by employing beyond state-of-the-art laser diode technology. This development together with the improvements in PAI depth will obtain the main emphasis in this project.

Work performed and the main results

The objective of FULLPHASE is the transition of PAI from a lab-based technique to a low-cost portable multi modality multi-wavelength combined PA/US imaging system. In the FULLPHASE consortium the partners are working on different scientific and technological challenges by means of specific knowledge, which is directed towards:

- Multi-wavelength laser diode beam sources with very high pulse powers (QUANTEL, OSRAM).
- Highly efficient laser diode driver (BrightLoop).
- Multi-wavelength diffractive optical beam shaping system (SILIOS).
- Optimal light delivery (QUANTEL, SILIOS, RUB, UNIBE, UTWENTE).
- PAI depth of a few centimetres (RUB, UNIBE).
- Advanced beam forming and research systems for evaluation (ESAOTE).
- Quantitative functional and structural imaging (UTWENTE).
- In vitro and ex vivo verification (UTWENTE, UNIBE, RUB, BMT, TU/e).
- Preclinical validation. (UTWENTE, UNIBE, RUB, ZGT)

Now after month 36 in the FULLPHASE project a great part of the items above, as described in this deliverable, are implemented, tested and validated. The preclinical validation started (M30) with a small clinical study on rheumatology, in vitro examination of CVD plaques and skin perfusion measurements. The start of the small clinical studies targeted at dermatology, burn wounds, skin cancer and neonatology are waiting for the medical ethical approval process. In conclusion we can say that now in month 36 of the FULLPHASE project:

- R&D is on track on all levels.
- The second prototype of PA/US probe, PAI system and high performance computing (HPC) framework are in use to perform 1) system tests, 2) in vitro testing and 3) perform small preclinical validations.
- A full test in relation to performance of the PAI system and PA probes has been carried out.
- The first preclinical studies to provide feedback for improvements have been started.
- There is an excellent **cooperation** and **interaction** in the FULLPHASE team.
- FULLPHASE results have been presented towards the public and the scientific/industrial community at numerous occasions.

Cooperation is one of the success factors for the project realization. Therefore, in FULLPHASE great attention is given to: a) direct communication, b) open discussions 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**) different phantoms were made for specific investigations and were successfully used to evaluate the performance of the FULLPHASE PA/US research system and probe for Doppler measurements and the development of a new method for the reduction of clutter and reflection artefacts. This new patented method is called PAFUSion which stands for (Photoacoustic-guided focused Ultrasound). Any dual mode PA/US system can incorporate the PAFUSion technique without any special changes to the system.

In period 2, **WP3** delivered ten 1-mJ prototypes at one wavelength (D3.3) for evaluation and feedback for the multi-wavelength PA/US probe. The testing and evaluation experiments led by RUB, UTWENTE, and UBERN of these PA/US provided the following feedback:

- Shortening the pulse width (optimum around 80-90 ns),
- Increasing the output peak power,
- Enlarging the beam on the skin,
- Improving the beam homogeneity.

This feedback was integrated in the final FULLPHASE PA/US probe (D3.4) in which:

- Pulse width has been decreased. It is now lower than the initial expected value. As a consequence performance of final FULLPHASE probes should greatly benefit from that reduction.
- Output energy is still at 1 mJ; but peak power was increased.
- Beam size on the skin was enlarged.

Moreover, homogeneity has been greatly improved by a modified optical system, and by enlargement of the output beam in the fast axis.

Discussions between all partners allowed identification of an attractive approach of using a new type of bars, which allows for decreasing the operating current at constant power which then facilitates the laser driver to support shorter laser pulse lengths. It was shown that this leads to a significantly improved energy yield for the system's signal generation and detection.

In **WP4** different experiments were done to provide feedback for the development of the multi-wavelength PA/US probe. The illumination simulations led to a change in the design of the multi-wavelength PA/US probe, which should lead to a more homogeneous illumination profile and thus better images as well. Experiments by RUB on the effect of changing the light pulse duration allowed maximizing the SNR of the signal received by the transducer. Additionally, a general form for the pulse coding techniques was found by RUB that allows optimization of arbitrary applications. The technique can be applied in any situation as long as multiple wavelengths are involved. The work on penetration depth showed that large improvements have been made on the second prototype leading to a visible image of the graphite rod down to a depth of about 18 mm. The contrast in those images was also greatly improved due to the noise reduction efforts taken.

The work in **WP5** was targeted at improvements of imaging depth by means of several new methods: a) displacement compensated averaging (DCA), b) frequency back-propagation approach, c) speed of sound imaging and d) aberration correction of B-mode ultrasound and PA images for an inhomogeneous distribution of speed of sound. PA imaging of the carotid artery is possible when implementing DCA. To achieve robust displacement tracking over several heart cycles, a tracking rate of 200 fps is required to cope with the fast motion of the artery. Imaging the speed of sound is possible based on pulse-echo signals, and a contrast resolution of around 1 m/s is achieved in phantom experiments. The contrast resolution in real tissue is much lower, limited by artefacts. These artefacts could be partially reduced, so that the different speeds of sound of the different tissue layers in the abdominal cavity and the neck became well distinguishable.

The complete process of implementation, testing, validation and small clinical studies is accumulated in the FULLPHASE PA/US research platform (**WP6**). The research platform makes all these developments possible. The platform was available already in an early phase of the project (M12) and has been modified during the project based on feedback from the different groups acting in the different WPs. The significant results in period II where:

1) Modifications to the PAI research system to connect the different PA/US probe prototypes.
2) Solving the common mode noise problem by connecting the ground plane of the US probe to the ground plane of the PA driver.
3) Safety measure implementation, verification and validation of an PA/US probe orientation detection mechanism for controlling the integrated laser source.

Moreover, there was a successful demonstration of the FULLPHASE prototype system at the QUANTEL booth on the Photonics West conference held on February 2015, in San Francisco, California, United States. There was a great amount of attention for the system and the PA/US probe.

The clinical validation **(WP7**) related to inflammation, oncology, perfusion and vascular diseases reached the following results: a) design and construction of a working experimental set-up for testing of (human) arterial tissue samples using ultrasound and photoacoustics, b) succesfull imaging of intra-plaque hemorrhage using the imaging set-up and the 2nd prototype FULLPHASE probe, c) perfusion validation in phantoms, using the 2nd prototype FULLPHASE probe, and power-Doppler validation, d) perfusion measurements in reactive hyperaemia in healthy volunteers e) perfusion changes in rheumatoid arthritis: visualization of increased perfusion using PA, validated with power-Doppler and f) initial measurements on tumor imaging using PA, validation with high-frequency ultrasound.

In **WP8,** focused on dissemination, commercial take-up preparation and training the following significant results where reached: a) extension of the Medical Resonance Board, from the disciplines of paediatric dermatology (Van Brussel, Van Royen-Kerkhof), Neonatology (Nelle) and Burns (Behr), b) the dissemination and exploitation plan has been updated, providing a detailed survey on the markets, the possibilities and risks of commercialisation of FULLPHASE technology, c) update of the IPR survey and d) online training courses available via the public FULLPHASE website www.fullphase-fp7.eu. Moreover, there was a remarkable number of publications, conference contributions and PR activities.

A smooth project management (**WP1**) ensured timely fulfilment of the research and development tasks, stimulated active collaboration within the consortium and finally supported a close communication for knowledge exchange. The management structure, i.e. administrative (tp21), overall technical (ESAOTE) and WP (WP-leaders) management enabled an efficient progress monitoring and document elaboration and storage.

In conclusion the progress in month 36 of the FULLPHASE project is achieved on all levels from basic research via engineering towards in vitro studies in phantoms and the start of the preclinical validation, with a small clinical study on rheumatology, in-vitro examination of CVD plaques and skin perfusion measurements.

Expected final results and their potential impact

Translation of PAI into clinical practice

Although PAI has proven its applicability, it still mainly resides in the academia and (pre)clinical research, and is not yet used in daily clinical practice. Therefore, here is the focus in the FULLPHASE project on the development of a multi modality multi-wavelength PAI system with beyond state of the art properties: a) portability, b) beyond state-of-the-art laser diode technology, and c) a hand-held PA probe. The FULLPHASE PAI system will bring cost-effective new avenues in health care delivery that

cannot be obtained with any other imaging modality. The system is targeted at three different disease domains: 1) Inflammatory disease, 2) Skin disease and 3) Vascular disease to bring functional imaging methods, under development in the research labs, to the patient's bedside.

1) Inflammatory disease

Rheumatoid arthritis (RA) is a painful inflammatory disease, which causes joint damage and affects quality of life. The shift toward early structure-modifying treatments prompts the call for imaging modalities that are sensitive to the initial pathological changes. PAI provides both the structural and functional information of intra-articular tissues and appears more promising in detecting and quantifying synovial inflammatory neovascularization. The University of Twente and the ZGT hospital are working together on a pilot study on RA. They investigate to what extent blood vessels in photoacoustic images correspond to existing modalities, and whether we see more vasculature with PAI. In the future, they aim to prove photoacoustic imaging of outwardly quiet RA can predict disease flares.

2) Skin disease

Currently, skin cancer is being diagnosed with a combination of visual inspection of colour and structure, and histological analysis of biopsied tissue. In particular melanoma is often difficult to diagnose due to its similarity to benign moles in particular dysplastic nevi. Normal ultrasound imaging will only have a limited added value for skin cancer diagnosis, multi-wavelength PAI, by its combination of structural and functional imaging, will aid in skin cancer diagnoses since it helps to identify various aspects, such as the spatial distribution of melanin, newly grown blood vessels and blood hypoxia, as signs of enhanced metabolism. Another aspect will be the identification of sentinel lymph nodes and the presence of melanotic metastases. FULLPHASE is targeted to identify skin cancer with higher sensitivity and specificity leading to a decrease in false positives, while reducing biopsies.

In burn wounds, it is often unclear whether the tissue is vital or necrotic and therefore needs surgical debridement. In general, the aim is to resect as little tissue as possible, since the scar quality and quality of life tends to be significantly better with parts of the dermis of the patient intact. Conversely, leaving necrotic tissue endangers the patient for infections including sepsis, which is a life-threatening complication of burn wounds. However, current imaging techniques lack resolution and contrast. The FULLPHASE PAI technology has the potential to support the determination of the optimal amount of tissue required for resection by assessing tissue perfusion, oxygenation and the position and status of major feeding vessels (perforators).

3) VASCULAR related diseases

The brain is the most vulnerable organ in preterm infants. It is most at danger shortly after birth when the circulatory state is instable. During the critical first days on intensive care unit it is most risky to transport the preterm infants, so only bedside imaging methods can be applied. Currently, routine diagnostics is based on standard cerebral US scans, which provide anatomical images and detect haemorrhage and chronic already irreversible stage of white matter injury (WMI), but not acute ischemia and hypoperfusion, i.e. cerebral circulation. With its spectral sensitivity of blood oxygenation the FULLPHASE PAI will provide a unique and safe bedside imaging method that can detect acute ischemia.

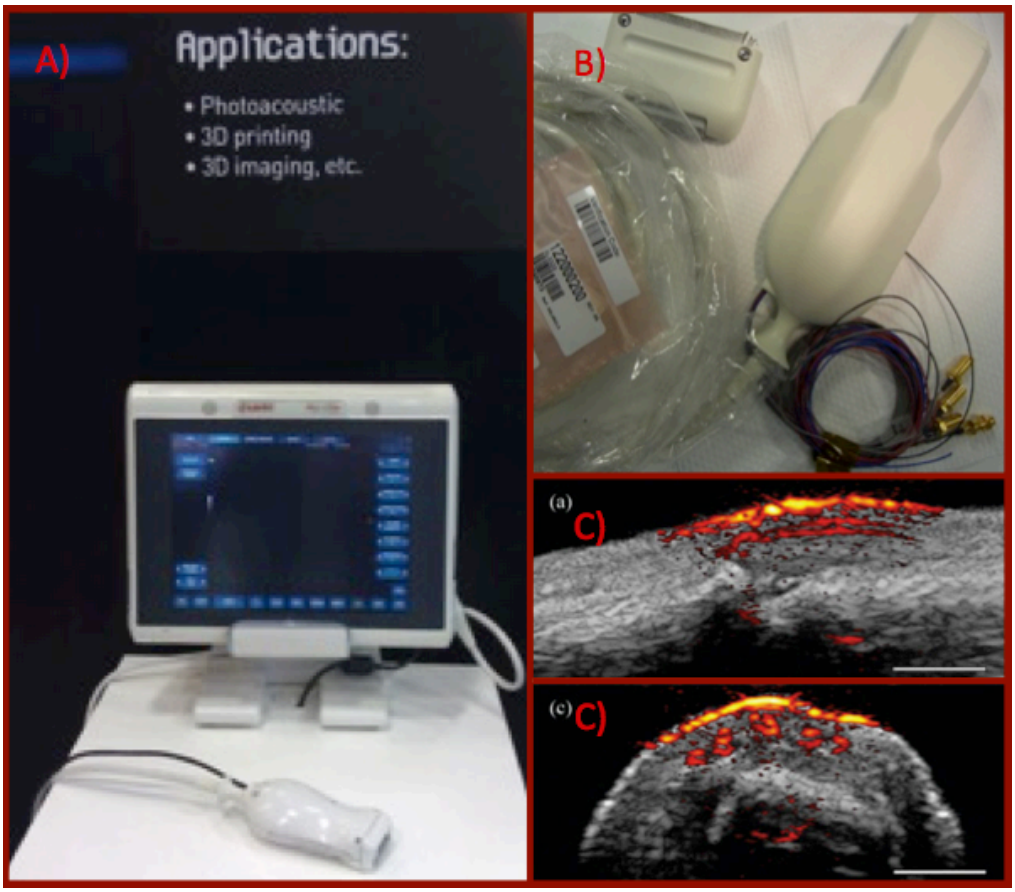
Stroke is a major cause of disability and death in Western society and is caused, in 20-25% of all cases, by an embolus that is the result of rupture of an atherosclerotic plaque. Retrospective studies revealed that in five out of six cases, the invasive procedure of choice (endarterectomy) was unnecessary, as well as the risks imposed to the patient. Improved detection and diagnosis of vulnerable carotid plaques will enable timely treatment to reduce severe overtreatment in vascular surgery, which is only feasible with costly MRI. For that purpose, PAI will be introduced. Carotid plaques of a small number of patients (30-50) scheduled for surgery will be studied preoperatively (in

situ/in-vivo). Thus, PAI can be compared with more invasive experimental methods. Additionally, pilot studies on other superficial arteries (brachial arteries, iliac, etc.) will be performed. A PAI based functional imaging method will be devised to assess plaque morphology and rupture risk.

As for burn wounds the characterization of ischemic tissue and the monitoring of vascular remodelling during treatment is the main objective of PAI in diabetic peripheral arterial disease (PAD). Besides wound healing and development as well as progression of necrosis, tissue vascularisation and oxygenation are significant parameters for decision-making about conservative or surgical treatment in the lower leg and feet of diabetes patients suffering from PAD. Thus, the aim is to investigate the suitability and quantitativeness of PAI to characterize ischemic tissue at the extremities in small animals and patients.

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 change in healthcare delivery.

Photographs illustrating and promoting the work of the project



Figures: A) The ergonomic housing of the FULLPHASE PA/US probe version 2 B) The compact portable FULLPHASE system with PA/US probe demonstrated at the the Photonics West conference in February 2015 C) Two ultrasound images of the finger of an healthy volunteer with colour coded photoacoustic data overlay as made with the FULLPHASE PA/US imaging system.

FULLPHASE public website: www.FULLPHASE-FP7.eu