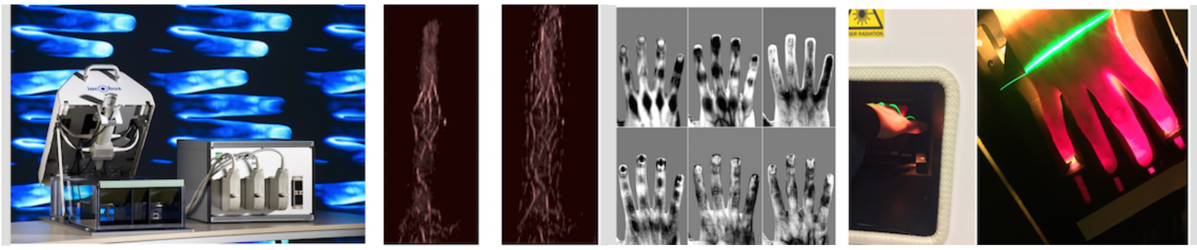

Publishable summary
of the 2nd period activities and results

Grant Agreement Number: **305760**

Project acronym: **IACOBUS**

Project title: Diagnosis and Monitoring of Inflammatory and Arthritic diseases using a COmbined approach Based on Ultrasound, optoacoustic and hyperSpectral imaging

Period covered: from **01.07.2014** to **30.06.2016**

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Publishable summary – period 2

Project context and objectives

Rheumatoid arthritis (RA) is a destructive inflammatory polyarthritis with a prevalence of 1-2%. The prevalence for rheumatoid arthritis increases with age and approaches 5% in women older than 55. Both incidence and prevalence of rheumatoid arthritis are two to three times greater in women than in men. Psoriatic arthritis (PSA) is another destructive arthritis which is associated with the chronic immune-mediated skin condition psoriasis vulgaris. PSA typically appears about 10 years after the onset of psoriasis, but can develop spontaneously without earlier skin symptoms in up to 30% of the cases. It has a prevalence of 0.25 – 0.75% equally distributed between women and men. Both types of arthritis lead to joint destruction and deformation which result in loss of joint function. Since hand and finger joints are commonly affected, the progress of the disease severely affects the patient's quality of life. Untreated or insufficiently treated arthritis often leads to disabilities including an inability to work.

Since the detection of early pathophysiological changes such as inflammation-mediated hyperperfusion of finger joints is critical to match the therapeutic window of opportunity, the objective of the IACOBUS project was to make available a novel image based diagnostic and monitoring approach for arthritic inflammation of finger joints which significantly exceeds the existing standards in terms of image resolution and sensitivity and thereby allows an earlier and more reliable diagnosis. In order to be widely usable as a screening tool, the technology has to be based on a non-invasive and cost-efficient imaging approach.

To achieve early diagnosis and treatment of arthritis within the window of opportunity, a combined multimodal imaging approach was chosen. The hybrid approach integrating different imaging modalities combines high resolution with high sensitivity while being affordable to healthcare systems. This allows the potential use as a screening tool in non-specialized medical settings. Furthermore, the developed platform represents a new imaging tool potentially being usable by the preclinical research community working with small animal models.

In order to achieve the described goals and to overcome the limitations of available techniques, the IACOBUS technology is based on a hybrid imaging system with iterative use of hyperspectral imaging for overview screening and close-look high resolution optoacoustic/ultrasound imaging for detailed investigation of small finger joints. While ultrasound is well established in clinical routine, optoacoustic imaging is an emerging technique combining the benefits of optics and ultrasound. When irradiated with short laser pulses, biological tissue generates broadband ultrasound waves with amplitudes proportional to the local optical absorption coefficient. Optoacoustic imaging therefore allows non-invasive in-vivo imaging with acoustical resolution and the high contrast of optical modalities. In the overview screening mode, hyperspectral imaging provides a wide-field scan of the affected hand and allows the identification of potential sites of inflammation based on the detection of local hyperperfusion. In this mode, broadband white light is shone through or onto the hand (in transmission or reflection mode, respectively) and the acquired data is spectrally analyzed for identifying signatures resulting from absorption by hemoglobin.

In the optoacoustic mode, the strong absorption of laserlight by hemoglobin leads to the generation of high-amplitude optoacoustic signals.

Optoacoustic imaging benefits from proven sonographic image formation procedures but permits overcoming the low acoustic contrast of soft tissue by using the target structures (e.g. microvasculature) as a sound source themselves.

The objective of the project was to make use of this effect for detection of hypervascularisation, which is a characteristic pathophysiological feature of arthritis.

Work performed and the main results

During the IACOBUS project, significant innovative technology was developed in different disciplines such as capacitive micromachined ultrasound transducer (cMUT) probes, diode-pumped lasers, combined multichannel ultrasound and optoacoustic electronics, hyperspectral imaging devices and algorithms.

At the beginning of the project, specifications for the imaging platform consisting of the hyperspectral imaging (HSI) and the acoustic/optoacoustic imaging (US/OAI) subsystems were elaborated jointly by the consortium partners. In order to facilitate full-view tomographic imaging of the smaller finger joints, the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints, as well as a top and bottom view of the metacarpophalangeal (MCP) joints, a special probe geometry and scanning concept were developed. The probe developed by VERMON consists of 4 sub-probes with a total of 768 elements. The sub-probes are curved with curvature radii of 15 or 30 mm depending on the placement in the final setup and cover an angle of 90°. They consist of a set of 32-element cMUT apertures arranged on a polygonal shape. The cMUTs were designed for a frequency maximum at 10 MHz according to the resolution needs of the application. Furthermore, their design consisted of a compromise between the requirements of maximum sensitivity in optoacoustic and ultrasound mode. The mechanical scan concept induces a motion along the longitudinal axis of the fingers, so that a multitude of cross-sectional images can be acquired for the purpose of generating a combined US/OAI 3D dataset of a finger. The uniqueness consists in the ability of the device to image all finger joints (DIP, PIP and MCP). After having acquired 360° tomographic images of the DIP and PIP joints, the mechanics decouple two of the sub-probes such that a scan can proceed over the MCP joint and acquire data in a top/bottom view. The multitude of cMUT elements has strongly affected the design of the multichannel electronics system. A 6-to-1 multiplexer board allowing for a distribution of the 768 elements onto the available 128 channels of the electronics was developed accordingly. In order to achieve fast imaging, the focus of the system development was set on a high repetition rate. Currently, the system allows acquiring datasets at a rate of several kHz. Timing issues between the laser and the digitizing electronics presented a further challenge. The multichannel electronics and the mechanical concept were developed by FRAUNHOFER.

The laser itself consists of a diode-pumped Nd:YAG whose fundamental wavelength is converted into a tunable radiation between 690 and 900 nm by means of an optical parametric oscillator (OPO) crystal (developed by EKSPLA). A special feature of the device is the high pulse repetition rate (PRF), which could be augmented to 100 Hz for enabling a higher image acquisition rate.

Delivery of light was a further challenge in IACOBUS, given that the laser light needs to be brought precisely to the region of interest corresponding to the focus of the probe in order to ensure high-sensitivity imaging capabilities.

With respect to hyperspectral imaging, a first-of-its-kind hand scanner was developed by the project partners NEO and NTNU. The device allows both transmission and reflection mode imaging of human hands. Advanced data processing algorithms have furthermore been developed for analysis of the spectral signature of the light for identification of inflamed joints.

With respect to the combined ultrasound/optoacoustic system, evaluation has been performed both on finger mimicking phantoms and on probands. In a first approach, the reproducibility of the measurements (low intra- and inter-user variability) have been demonstrated. Furthermore, the performance of the device has been characterized and a resolution in the range of 150 µm could be achieved. First measurements on probands have shown the ability of the technology to detect and visualize vasculature in fingers. The sensitivity and specificity of the technology for detection of joint inflammation in comparison to existing standard diagnostic techniques are still under evaluation.

Expected final results and their potential impacts and use

At the end of the project, two fully integrated systems for hyperspectral imaging and combined ultrasound/optoacoustic tomography have been developed. The systems have been fully tested with respect to all relevant standards according to the MDD 93/42/EEC for being usable in a clinical environment.

Furthermore, first tests on probands have been conducted showing the systems' usability in an in vivo setting. Images of the hands/fingers and the subcutaneous vasculature could be obtained with both of the developed technologies. Although the actual performance and sensitivity of the systems for detection of early signs of arthritis, especially when compared with currently existing gold standard methods, is still under final evaluation, a first assessment of the capabilities of the systems has highlighted their diagnostic potential. In addition to the scientific impact, the project has led to significant exploitation options for the involved partners. The expertise generated with respect to cMUT technology and especially regarding integrated electronics for impedance matching and pre-amplification developed by VERMON will allow improving the performance of future cMUT-based products. The laser developed by EKSPLA within IACOBUS has already been released as a new product. This diode-pumped OPO represents a new benchmark in terms of high PRF performance. In addition, IACOBUS has allowed NEO to expand their expertise from defense, underwater and NDT (non-destructive testing) applications to the biomedical field and to develop a hyperspectral imaging system being close to market maturity. FRAUNHOFER could strengthen its expertise in acoustic imaging by developing a first-of-its-kind tomography system combining optoacoustics and ultrasound. The technology developed, especially with respect to dual-imaging mode multichannel electronics, is of highest relevance for future applications involving multimodal imaging. Finally, NTNU has developed algorithms for automated analysis of hyperspectral data of biological tissue. This could not only be published in renowned scientific journals, but will also serve as a basis for future developments with respect to automated disease-recognition in optical (hyperspectral) data. Through the tests conducted with both the hyperspectral and the combined US/OAI technology, the partners JLU and NTNU (through the collaboration with St. Olav's Hospital Trondheim), have contributed to making new sensitive, non-ionizing and non-invasive diagnostic imaging modalities available to patients. The performed tests have demonstrated the usability of the technologies in a realistic clinical environment and have underlined the potential of the IACOBUS approach for an improved diagnosis of arthritis. The IACOBUS consortium will jointly seek for opportunities to pursue this research further with the ultimate goal to transfer the developed technologies from a research environment to clinical routine.