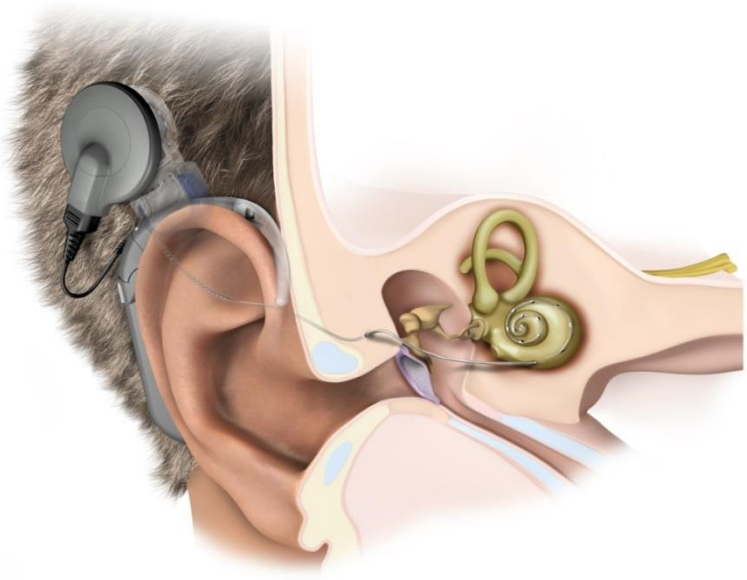
ACTION

ACTive Implant for Optoacoustic Natural sound enhancement

Publishable Summary

1 October 2013 – 31 December 2016



EU project ID 611230

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Contents

1 Executive Summary

The aim of the project is to develop a novel type of cochlear implant; a medical device used to restore auditory sensations for hearing-impaired listeners. An important part of the implant is the electrode, which is placed into the inner ear, also known as the cochlear. Currently available solutions use electric stimulation to generate a signal in the spiral ganglion neurons. ACTION will instead use optoacoustic stimulation to trigger the available residual hair cells. To this end, very small lasers - so called VCSELs - will be placed in the cochlear to stimulate the hair cells using the optoacoustic effect (see 2.1 for a description).

The device developed in the framework of ACTION comprises several components:

- Miniature laser source (i.e. VCSEL)
- Collimating optics (i.e. lens)
- Hermetic and biocompatible micro-package to accommodate VCSEL and microlens
- Biocompatible lead (i.e. flex substrate) to connect the VCSELs with the power supply circuitry
- Anti-fouling protection layer to prevent growth of a (light absorbing) biofilm on the package
- Signal generation electronics, firmware and software to run the device in a lab environment

The integration of above components into a device usable in a laboratory environment was a major achievement of the project and allowed MHH to do cutting edge research in the optoacoustic stimulation in the cochlea.
The main results were achieved with a custom designed system (referred to as System B in this report), which allows the researcher to define stimulation pulses via a GUI and drive up to three VCSELs (or other diode based light sources).
We are convinced the research shows that the optoacoustic effect is indeed responsible for measured compound action potentials (CAP). The amplitude of the response is linearly proportional to the electric current flowing through the VCSEL (a direct measure of the optical output) and has a peak for pulse lengths of around 50 µs. System B was also capable of providing bursts of nanosecond pulses to simulate a single longer pulse. This is a successful approach to protect the VCSEL from overheating while achieving similar levels of CAP amplitudes.
A further miniaturisation and upgrade of System B let to System C (see section 3.4.1). This device incorporates CAP measurement capabilities and laser driving circuitry into a single small device. It is available to the consortium members and the industry and has the potential to be used in all fields of optical stimulation research. It also includes a battery and may run autonomously for up to 24 hours. Acquired data is sent wirelessly to a nearby computer.

ACTION is a collaborative research project of seven partners. The project is funded by the Seventh Framework Programme (FP7) of the European Union and it runs under the Project **ID 611230** within the funding scheme "Small or medium-scale focused research project (STREP)". It is part of the work programme topic: Objective ICT-2013.3.3 3.3 Heterogeneous Integration and take-up of Key Enabling Technologies for Components and Systems.

The project started on 1 October 2013 and ran for a period of 39 months until December 2016.

2 Project Context and Objectives

2.1 Introduction

Traditional cochlear implants are based on the concept of electrically stimulating nerve fibres. Put simply, an electric field is generated inside the cochlea, which causes the nerve fibres to send a signal to the brain. Our brains interpret this signal as sound.
The geometric conditions inside the cochlea limit the options to focus the electric field. Since the cochlea has a tonotopic structure, targeting one specific tone usually triggers others as well. This may lead to a reduction of the quality of hearing. Some CI users retain hearing in the low frequency region and can use a special speech processor including a hearing aid. However this requires an earmould to be used, which is not always acceptable to the recipient. Use of the implantable laser developed in this project will allow sound transmission without an earmould.
Essentially, the so-called opto-acoustic stimulation can be explained as follows: The laser, which is placed inside the cochlea, generates a very short pulse of infrared light. The pulse is absorbed by the liquid inside the cochlea. This causes the absorbing local portion of the liquid to heat up and, consequently, expand rapidly. This expansion creates a sound wave, which travels through the cochlea. The opto-acoustic stimulation is similar to natural hearing, which relies on a sound wave being generated by the stapes pushing against the oval window at the base of the cochlea.

2.2 Project Context

Many cochlear implant recipients have residual inner hair cells in the apex of the cochlea. Over the last decade there has been an increasing demand in preserving the low frequency hearing after electrode insertion (using short, more flexible electrode arrays) so that the patient's residual natural low frequency hearing can be used (through amplification of natural sound using a hearing aid located in the speech processor) together with electrical stimulation in the high frequency region. Today there are many cochlear implant users enjoying the combination of natural low frequency sound and electrical stimulation in the high frequencies. In most cases this leads to better sound quality and speech understanding. More recently, surgeons have developed techniques to allow preservation of hearing even after deep electrode insertion. The combined stimulation approach has been named 'electro-acoustic stimulation' or 'EAS'.
EAS is well established in clinics, however there are remaining challenges to be solved:

1) Hearing can be lost during the electrode insertion and during the weeks and months after implantation. The encapsulated light source developed in ACTION will be initially targeted for use as a simple single channel, (click and click train) sound stimulator for assessment of changes in hearing status within the implanted cochlea (Figure 1). A neural response feedback system may be developed which will allow automated sound threshold assessment.
2) A number of subjects prefer not to use hearing aids located in the ear canal, due to the feeling of occlusion due to medical problems. This can result in reduced sound quality through the use of the electrical stimulus alone. Trains of clicks from the optoacoustic effects can be used to elicit pitch perception in a patient with residual hearing. Thus, harmonics and other features of a sound can be applied to the cochlea directly using the VCSEL light source in patients with significant residual hearing after implantation. Certain impulsive features of the sound will also be transferred by the temporally precise stimulus. There is therefore the potential to create an acoustic stimulator without any components located in the ear canal, offering the patient a greater degree of freedom.

Furthermore, in cases of mixed loss (including a conductive component) the middle ear function can be bypassed altogether.

3) The quality of sound achievable from the residual hearing is limited by the paucity of the remaining outer hair cells, which reduces the frequency resolution of the system and 'blurs' the perceived sound. A multi-channel system may provide region specific optoacoustic stimulation to the cochlea. This will require beam shaping through micro-optics included in the packaging.
4) There is a large population of partially hearing subjects made up from sufferers of progressive and age-related hearing loss, or 'presbycusis'. There is therefore a market for a low cost, smart, implantable combined device (electric plus optical) that can adjust its output according to the time varying needs of the patient. All of the features described for the previous aims can be combined in such a device.

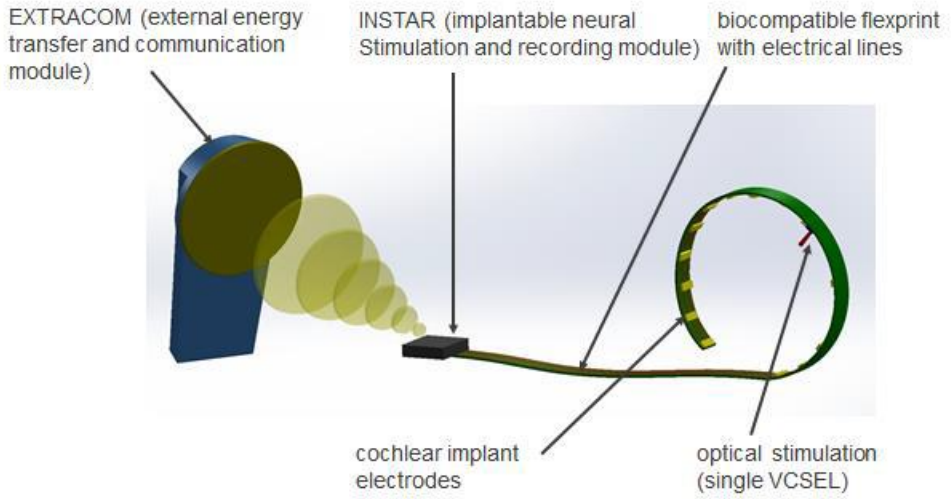

Figure 1: Single optical channel (i.e. VCSEL) integrated in a cochlear implant with stimulation electrodes.

2.3 Clinical Needs

Without doubt cochlear implantation is the treatment of choice in case of severe to profound bilateral deafness. Advances in speech coding strategies have contributed to a significant increase in performance of cochlear implant users. Especially the increased temporal and spectral information may improve the ability to hear speech in noise and enjoy music. However, even with enhanced speech processing strategies, the ability to hear in adverse real-world listening situations remains a challenge for cochlear implant recipients. For patients with residual hearing, hearing preservation surgery can be attempted and if successful, a combined electric acoustic stimulus approach (EAS) can be employed. As previously mentioned, hearing can be lost during the electrode insertion and during the weeks and months after implantation. Detection of this loss during surgery would allow adoption of a different device or strategy, and detection of the loss at any stage after the procedure would allow remediation therapy using drugs or alteration of the sound coding approach. However such detection currently requires external equipment and trained audiologist involvement. The encapsulated light source developed in this project will be initially targeted for use as a simple single channel, click and click train sound stimulator for assessment of changes in hearing status within the implanted cochlea. This ability has been demonstrated in a number of animal studies.

For clinical use, an automated system is very desirable due to the complex equipment and clinical skill required to assess hearing intra-operatively, and to allow the patient to be alerted immediately to changes

in status during the weeks and months after implant activation. Early detection of hearing loss leads to improved chances of success of remediation therapy. The active system needs to select the appropriate stimulus parameters for threshold assessment, apply a series of stimuli according to a pre-determined algorithm, record the optoacoustically evoked compound action potential, and assess the threshold level of the optoacoustic stimulus. The implant user (and/or clinician) then needs to be alerted to any change in hearing threshold.

2.4 System Overview

Laser-based stimulation requires research in and development of various components which need to be combined to a device. These components are (see also Figure 2):

- Miniature laser source (i.e. VCSEL)
- Collimating optics (i.e. lens)
- Hermetic and biocompatible micro-package
- Biocompatible lead (i.e. flex substrate)
- Anti-fouling protection layer
- Signal generation electronics, firmware and software, and more.

The VCSEL and the light source are assembled inside the package. The package is then hermetically sealed to protect the VCSEL and the microlens from the body fluids and vice versa.
Furthermore, research into the actual optoacoustic effect, development of stimulation patterns and investigation of efficacy and safety are needed. The project relies on the expertise of its members in the fields of medicine, biology, chemistry, implant technology, laser technology, electronics, optics and packaging. The following sections describe the progress in the respective fields in the period from 1 October 2013 to 31 December 2016.

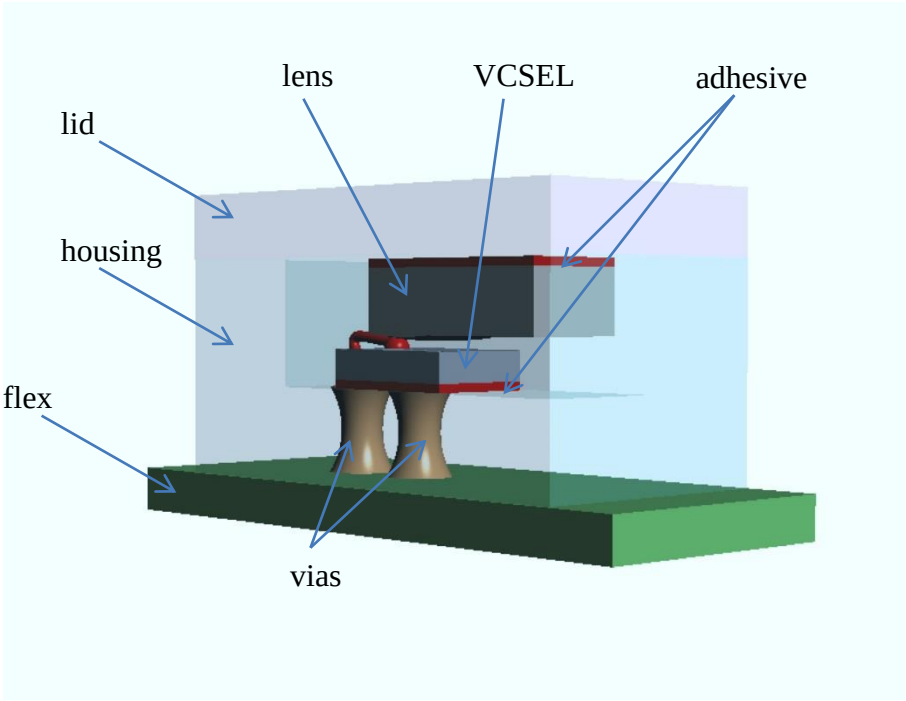

Figure 2: Major components of the implantable laser source. The vias are electrical feedthroughs, which provide electric current to the VCSEL inside the hermetic package (i.e. housing and lid).

3 Results and Foreground

3.1 Optical System Development

3.1.1 Long-Wavelength VCSEL arrays

With the first demonstration of long-wavelength VCSEL arrays around 1.55 µm emission wavelength some years ago, the InP-based buried tunnel junction (BTJ) technology as shown in Figure 3 (left) has been successfully demonstrated by Vertilas to serve as an ideal platform also for high power near infrared laser sources up to the watt regime. The BTJ-technology allows for an easy scaling of relevant device parameters such as array dimensions for customer specific output powers, chip footprints and wavelengths. By tailoring the VCSEL layer compositions and thicknesses, wavelengths between 1.3 µm and 2.3 µm can be achieved. The substantial high efficiencies at human body temperature are realized by optimized laser designs, with regard to improved thermal, optical and electrical device characteristics. Specifically an optimized wall plug efficiency close to 20 % is achieved for the 10 µm wide BTJ used here (Figure 3 right), not yielding a pure single mode spectrum. However, single mode operation is not required, as the whole emitter device is an array.

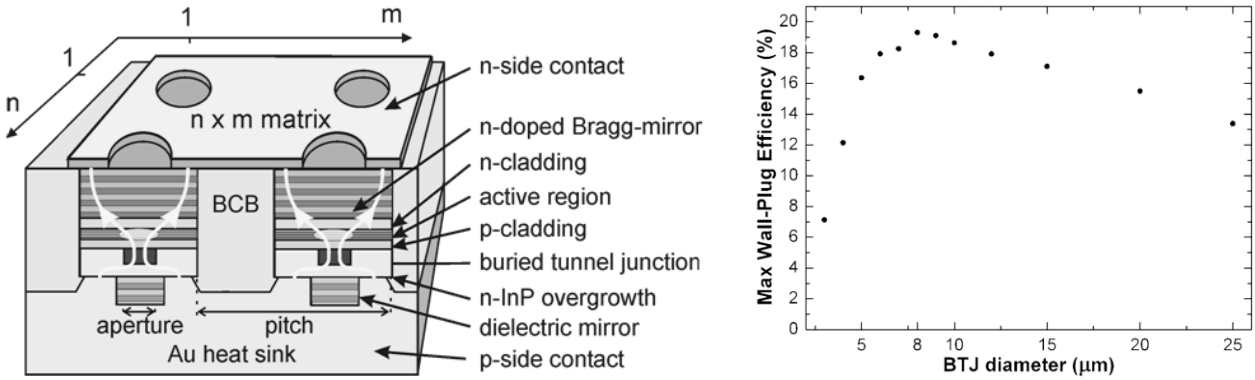

Figure 3: Left: Cross section of 2D BTJ-VCSEL array Right: Wall plug efficiency as function of BTJ diameter

A number of 7, 14 and 19 individual emitters, i.e. apertures in the specific array configurations shown in Figure 4 (left) are fabricated and investigated to enable power scaling. A hexagonal geometry with a 50 µm pitch between apertures is chosen.

Figure 4 (right) depicts the optical power versus current characteristics of the three aperture configurations, when operated with a constant bias. It can be seen that the maximum power per aperture increases as expected. The threshold current increases with the number of apertures and generally a rollover can be seen at high currents. These two features are attributed to the heating of the device, which is much less pronounced when operated in pulsed mode, as foreseen in the application here. Finally the 19 aperture device was selected due to its highest power output.

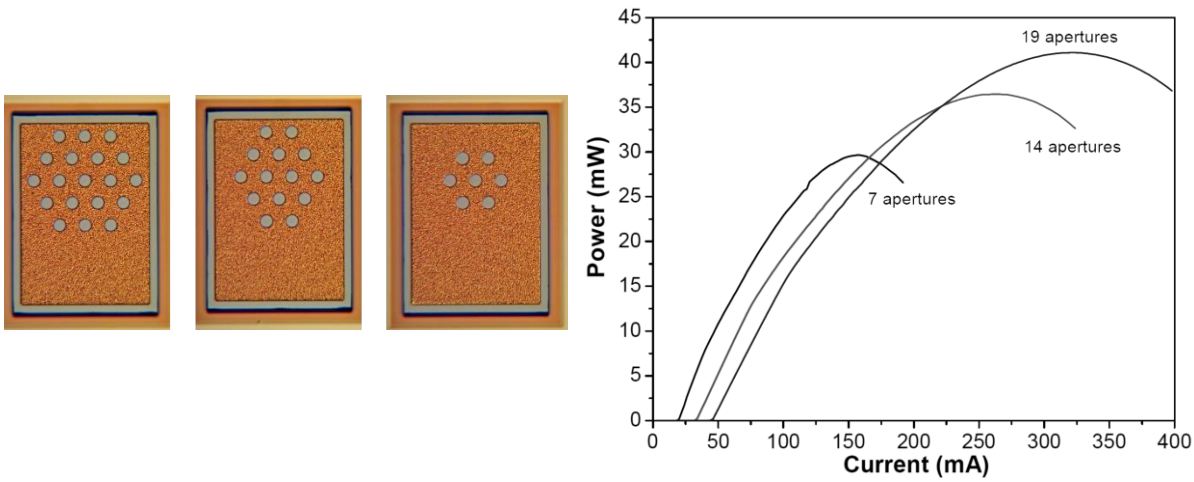

Figure 4: Left: Top view of laser diced arrays with 19, 14 and 7 apertures Right: Power vs. current characteristics

3.1.2 Collimation Optics

A wafer level process is used by SUSS MicroOptics to fabricate Si-lens arrays to collimate the VCSEL light. There is indication that higher intensity light is more likely to generate an audible sound wave in the cochlea fluid. Figure 5 shows a section of the wafer with microlenses and alignment features (left) and the designed lens profile (right). The lens is 15 µm high and the underlying slab of silicon is polished down to 150 µm to comply with the space constraints for the implant. A unique feature is the development of a single-mask & single-etch process that allowed the simultaneous fabrication of the alignment marks and the micro-lenses. VCSEL and lens are made of non-biocompatible materials. In order to protect the devices from the harsh environment of the body and to protect the body from potentially toxic materials, VCSEL and lens have to be hermetically sealed. The packaging approach is described in the next subsection.

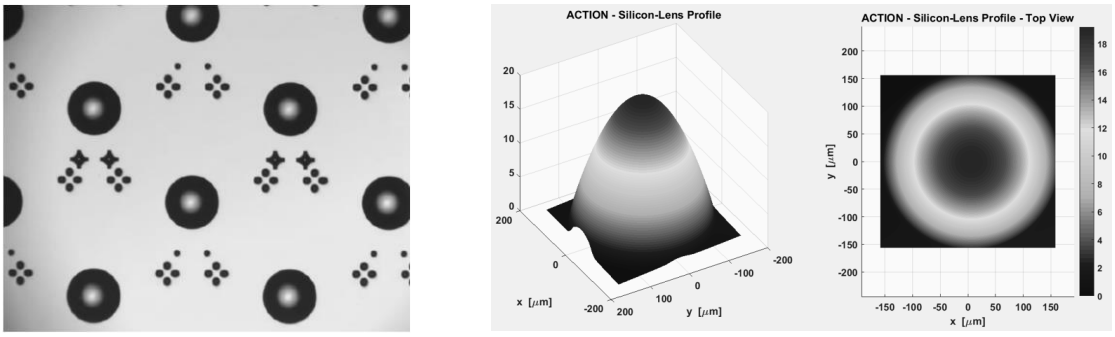

Figure 5: Left: Single micro-lens before dicing including alignment marks Right: Lens profile

3.2 Packaging and Fabrication Process

3.2.1 Hermetic Package

Packaging of Active Implantable Medical Devices (AIMD) involves the hermetic sealing of active circuitry inside a package and feed-through to transfer input/output (I/O) signals to the outside of the package. For long-term implantable medical devices, all the materials that come in contact with the human body must be biocompatible and provide long-term biostability. The materials that can be used protecting AIMD's are limited. Most materials fall short of the requirements for one of the following reasons:

- Toxic to the body
- Not long term hermetic
- Not biostable

To give the reader a few examples:

1. Certain metals are toxic to the body: Lead, copper, silver etc.
2. Some glasses are biostable and even biocompatible. Yet they do not provide an adequate hermetic sealing level for long-term implants of miniscule size. This is also true for many polymers such as silicone, PU, PTFE, PC, PE, HDPE, UHMWPE, LCP, polyimide.
3. Although gold is an inert material, it seems to dissolve rather quickly in biological fluids, particularly if an electric voltage is applied. This is a reason why gold is only used as temporary electrodes in neural stimulation applications.

The materials which do not fall short and have a proven track record in the medical device industry is relatively short. The list includes metals such as platinum and some platinum alloys, titanium and some titanium alloys, certain steels, tantalum and tungsten. Furthermore, ceramics such as alumina (Al_2O_3) and zirconia (ZrO_2), aluminium nitride (AlN) and silicon carbide (SiC). Particularly alumina has a strong record in the medical implant industries.

A further class of materials, which are less studied in the medical industries, are crystals made of biocompatible constituents. This includes our choice for the package: Sapphire is aluminium oxide in a single crystal form.

Of specific need for this application is an optically transparent package to hermetically encapsulate the non-biocompatible devices (VCSEL, lenses). Further, the maximum size available for any part to be implanted in the cochlea (at the widest part of the scala tympani) is about 1 mm in diameter. Depending on how deep into the cochlea it needs to be implanted, the available area would be as small as 0.3 mm diameter.

Beside the reasons mentioned above, sapphire has been chosen as the material for the package housing because of its good transmission characteristics over the visible and near IR spectrum, high mechanical strength, chemical resistance, thermal conductivity and thermal stability. In alignment with the wafer level availability of lens and VCSEL, sapphire wafers in 2'' to 6'' are commercially available. The most important material property of sapphire within this project is the high biocompatibility, which makes it the first choice for implants to remain in the body for the patient's entire lifetime. As sapphire is a single crystalline material with high purity, it has very low permeability to gases including helium and water vapour. This is very important as the package wall thickness becomes very small with miniaturization.

A proprietary technology to CSEM has been applied to fabricate the feedthroughs and for sealing the sapphire housing. Vias are machined into the sapphire substrate and then filled with a conductive material. Platinum/PtIr wires are used to hermetically seal the feedthrough vias at the bottom of the package. The feedthroughs are manufactured in such a way that the package can be attached to a platinum wire or a

substrate using laser welding or resistance welding techniques. Then the active device (i.e. VCSEL) is die and wire bonded inside the package for electrical connection to the feedthroughs.
The maximum temperature the active devices are specified for is 250°C for 5 seconds, which is the standard reflow process temperature. The applied laser-assisted bonding process used to bond the lid to the housing generates very little heat and does not damage any electronic components inside the package. The components inside the package stay well below 200 °C. The lens is attached to the inside of the lid. A micrograph of package with VCSEL & feedthroughs at the backside can be seen in Figure 6.
The developed miniaturized package has dimensions down to 0.6 x 1 x 2 mm^3 with a smaller cavity of 0.6x0.7x1.5 mm3. A shear strength of higher than 100 MPa has been measured for both the seal and feedthroughs. Hermeticity was confirmed using destructive helium spraying leak testing. The test showed that the packages were leak tight below the noise floor of the measurement equipment, $1x10^{-10}$ atm cm^3 s^{-1}.

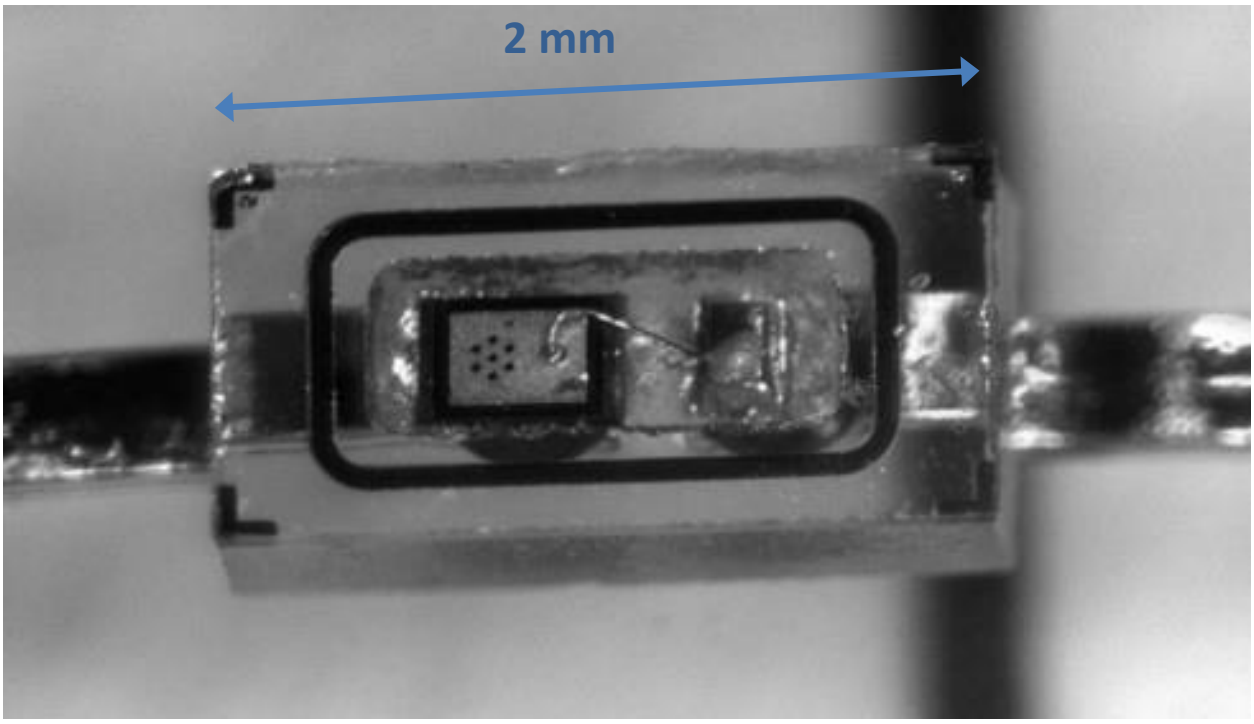

Figure 6: Micrograph of a hermetic micro-package made of sapphire, including a 7 aperture VCSEL. No lens is attached. The feedthroughs connect to the two platinum ribbons at the bottom of the package, which extend to the sides beyond the picture.

3.2.2 Flexible Substrate

The hermetically packaged VCSELs, as described in above section 3.2.1, require electrical connection the circuitry providing the electric current. These connections are provided by platinum ribbons cut from a larger platinum foil. For reasons of electric insulation and handling robustness, these ribbons need to be insulated and protected. We chose a silicone rubber to encapsulate the ribbons along with the sapphire packages. Figure 7 shows a fully assembled device (hermetic packages with platinum ribbons encapsulated in silicone rubber). Its size is compared to the tip of a match. It contains two packaged VCSELs at the distal end. Three platinum ribbons provide anodic and cathodic connections to the circuitry.
Figure 8 shows an array of packaged VCSELS on platinum ribbons. The devices are overmoulded with silicone rubber. All Previous processing steps have designed to be compatible with an array of devices in order to reduce fabrication complexity and costs. The process flow is shown in Figure 9. These are the process steps:

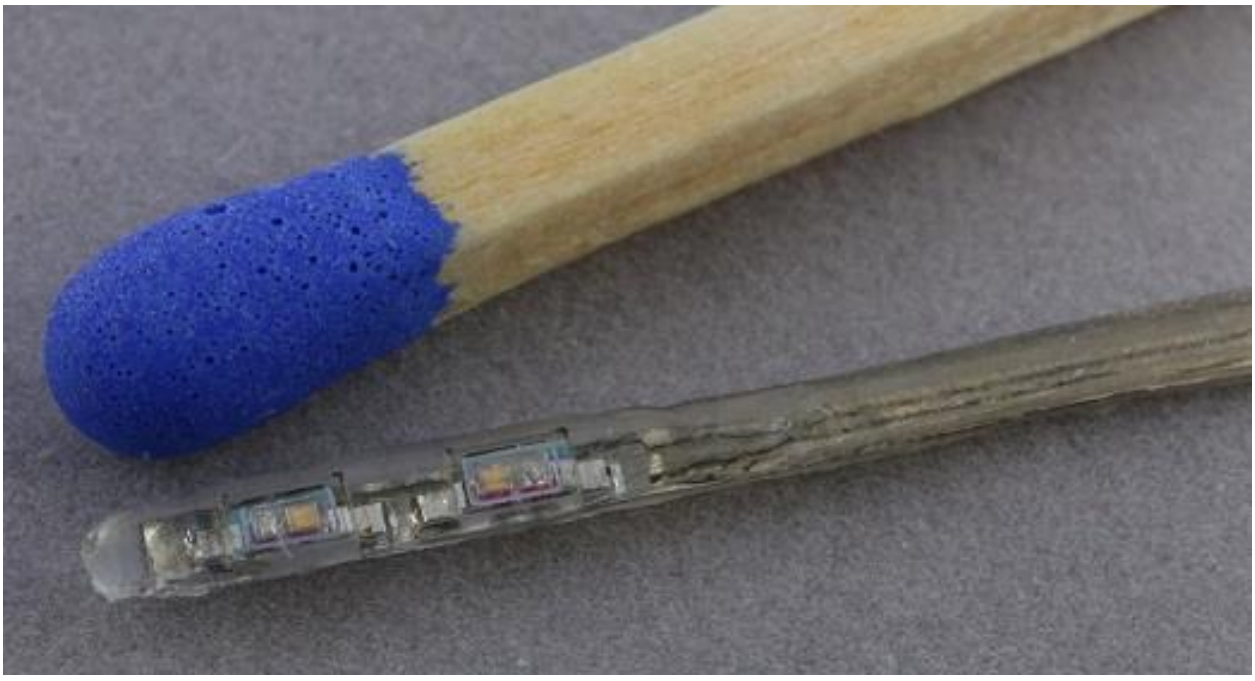

Figure 7: Long term implantable optical electrode for optoacoustic sound enhancement. The implant contains two hermetically packaged VCSELs (see Figure 6 Error! Reference source not found.**), which are oulded in silicone. The device is 10 cm long. Only the distal end is shown. The match is for size comparison.**

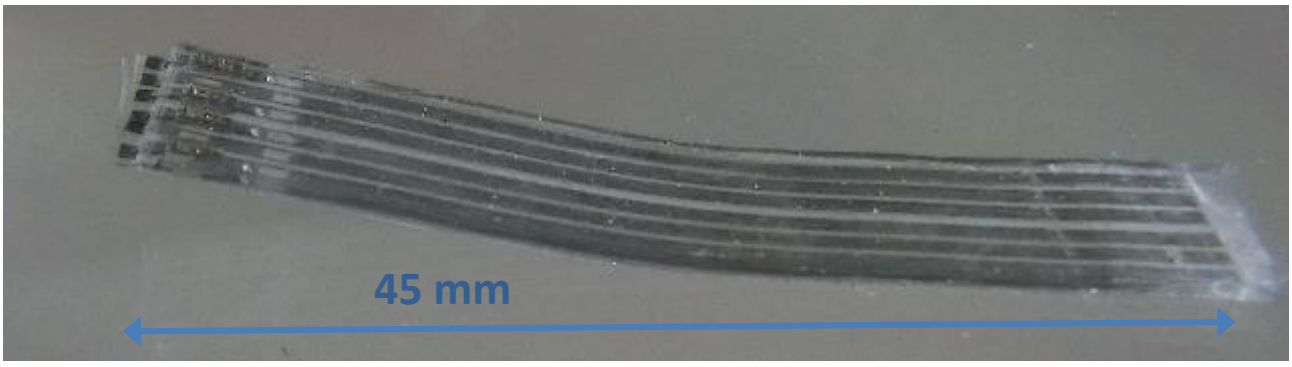

Figure 8: Array of moulded devices (as shown in Figure 7) before singulation.

1. A platinum foil is bonded to a support carrier (e.g. POM) with a temporary adhesive. The platinum foil is then structured with a UV picosecond laser and cleaned to remove the debris.
2. A non-stretch fabric is saturated in liquid silicone rubber and placed on the platinum foil. The liquid silicone rubber is allowed to cure. Bond strength to the platinum foil is limited.
3. The structured platinum foil and the impregnated fabric are removed from the temporary carrier.
4. The sapphire packages are welded to the platinum foil bond sites.
5. The array of devices is placed in a cavity milled in a low surface energy polymer and coated with the liquid silicone rubber used in 2.
6. The finished array is removed from the cavity and singulated, i.e. cut into single devices.

The designed process is a potential improvement over current manufacturing methods of implantable electrodes, as it uses manufacturing techniques which can be automated (i.e. laser machining) or which allow the user to handle a large number of devices arranged in an array.
The flexible substrate is currently capable of accommodating three metal lines (in the shape of ribbons). This limits the number of VCSELs to two. Increasing the number of VCSELs requires both reduction of metal line thickness and pitch between two metal lines as well as adding a second layer or several layers of platinum ribbons. Adding more layers would significantly increase the process flow complexity. Limiting the flex substrate to a single layer and assuming a metal line width of 25 µm and a line to line pitch of 50 µm, further assuming a total substrate of 600 µm, the flex substrate could accommodate twelve metal lines. Current cochlear implants feature up to 22 metal lines and electrodes.

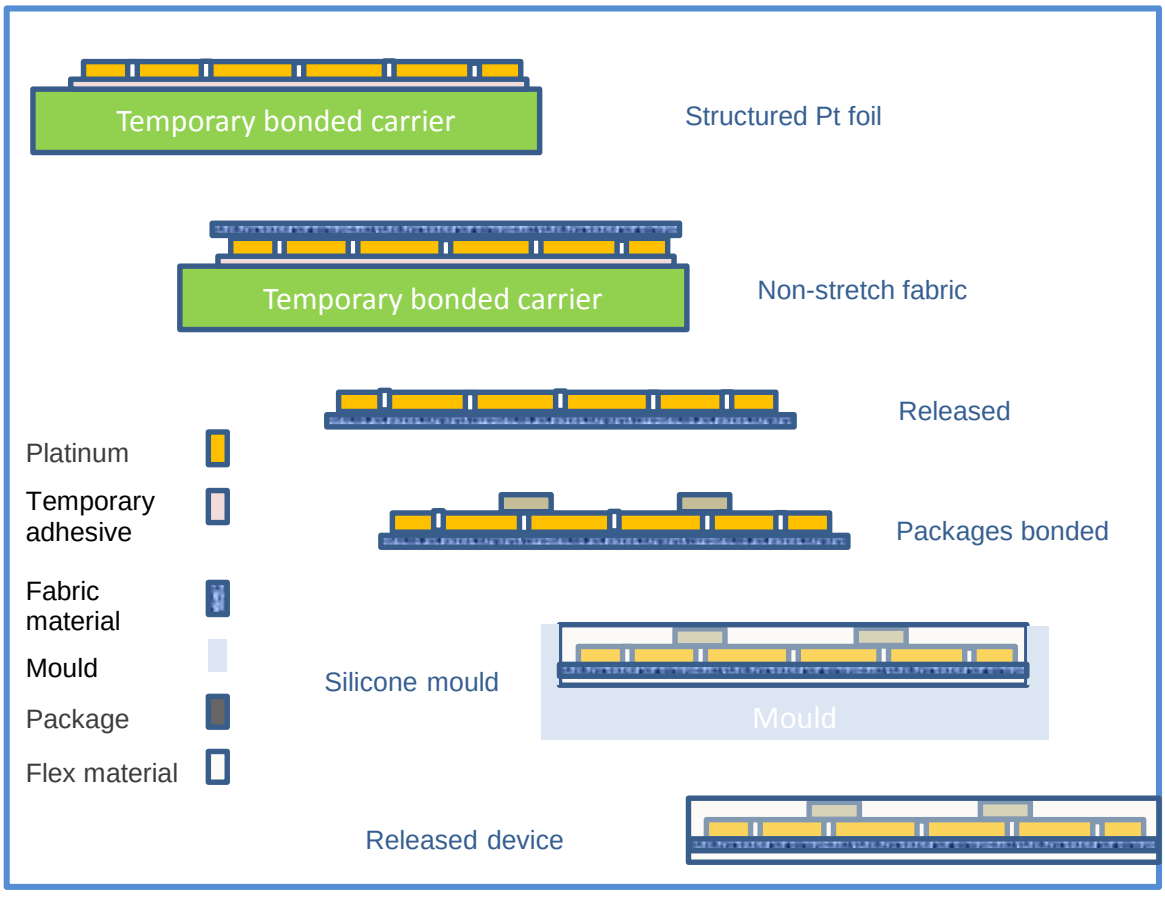

Figure 9: Process flow for the flexible substrate. See main text for detailed description.

3.3 Antifouling Coatings

In order to face the issue of protein adhesion, which is not only directly connected to bacterial growth but which may also result in reduced transparency of the windows of the device, three new types of coatings were introduced. All coatings are based on polyethylene glycol (PEG)-type polymers, prepared by either direct surface modification (PEG-silane), in-situ polymerization (SET-LRP) or post-functionalization of mixed titanium dioxide/silver layers prepared by atomic layer deposition (ALD-PEG).
The coatings, which were deposited on top of silicone (PDMS) substrates, have a thickness ranging from a few units up to a few tens of nanometres, and are essentially transparent at the working wavelength of the optoacoustic device (1550 nm).

The adsorption of bovine serum albumin (BSA) and Fibrinogen (Fg) on the coated surfaces was studied by Quartz Crystal Microbalance (QCM-D). **All coatings were found to possess excellent antifouling properties, with a reduction of protein adsorption exceeding 90% and in some cases close to 100%** (Figure 10, left). **Furthermore, the performance was essentially maintained after storage for up to two months in physiological saline solution.** A slight deterioration was found only for ALD-PEG coatings.

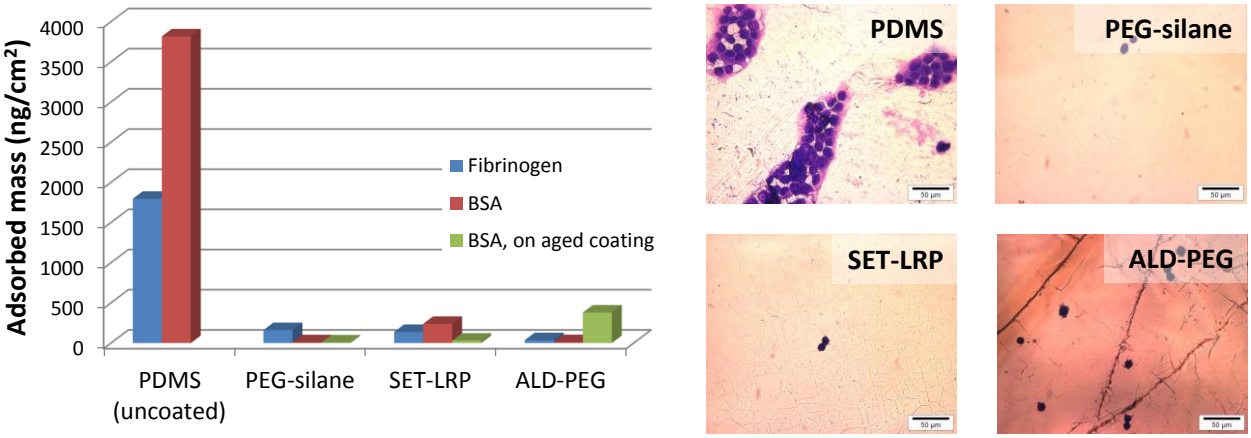

Figure 10: *Left*: Protein adsorption as determined by QCM-D. BSA adsorption tests were performed also on aged coatings, after two months (PEG-silane, SET-LRP) or one month (ALD-PEG) of incubation in physiological saline solution. *Right*: Optical microscope images of surfaces incubated with fibroblasts.

The adhesion of fibroblast cells on the coatings was also studied, albeit at a more qualitative level. As it can be seen from the right side of Figure 10, the presence of fibroblasts was clearly reduced on the coatings. Antimicrobial activity was evaluated for PEG-silane coatings, indicating a reduction of cell adhesion, which was however not particularly high already on uncoated PDMS surfaces.
The implant is expected to experience significant bending upon insertion into the cochlea, possibly affecting coating integrity. In order to simulate these conditions, bending tests were performed on coated silicone sheets. A higher number of cracks was observed in the samples after bending, however this appears to be due to amplification of cracks which are already present in the starting silicone material. In order to verify whether this effect has an impact on the antifouling performance, the samples were incubated with a solution of fluorescein-labelled bovine serum albumin (BSA-FITC) and imaged by epifluorescence microscopy (Figure 11). The adhesion of the protein on uncoated PDMS was revealed by a diffuse green fluorescence, which was instead absent in coated samples (Figure 11a-b) before bending. After bending, some degree of fluorescence appeared along the cracks, however protein adsorption remained confined and vastly reduced in comparison to uncoated surfaces (Figure 11c-d). Extended duration experiments may indicate whether this could eventually lead to non-negligible adverse effects in a longer term.

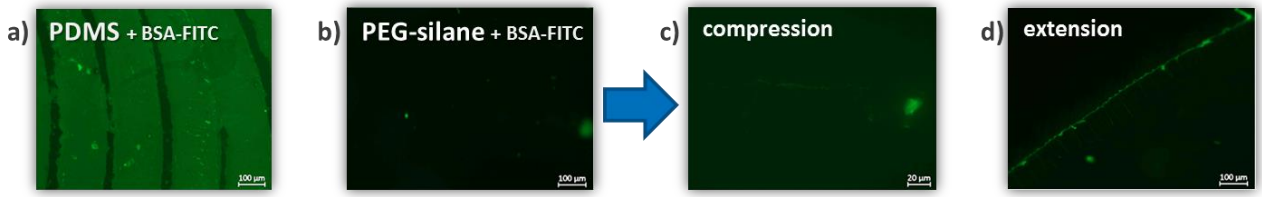

Figure 11: Epifluorescence microscopy images of (a) uncoated and (b) coated PDMS incubated with the fluorescently labelled protein BSA-FITC; (c) and (d) images of coated samples incubated with BSA-FITC after bending, on the compression and extension sides. Brightness was increased by 50% for all images.

Part of the activities involved also a qualitative level evaluation of the overall sustainability of the production process of the cochlear implant. Information relative to the processes and materials used in the preparation of the optoacoustic implant was collected by means of a two-round survey in which all project partners were involved. All materials used in production were listed, and their individual toxicity and potential for recovery were evaluated; particular attention was devoted to the availability and price level of the metals used in the production process. The type and amount of waste generated in each production step was also assessed whenever possible.

In spite of certain limitations on available data (e.g. confidential processes, components produced by external suppliers, etc.), a qualitative analysis was carried out which allowed to look for possible improvement areas in the production process.

Based on the information received, the manufacturing process of the cochlear implant was not found to cause significant environmental concerns. No highly toxic chemicals are used, with very few exceptions where waste generation is very small. The generation of electronic waste is also very low, and this waste is reported to be recycled. Process steps involving organic solvents may be improved by reducing solvent volumes and/or by their reuse and on-site recovery.

Finally, the high worldwide consumption rate of certain metals used in the production may eventually lead to increasing material prices and thus to a reduction of their future economic sustainability. In principle, finding low-price and more abundant alternatives for the precious metals and the materials used in the permanent magnet could prove beneficial, even though this is clearly not a straightforward task.

In conclusion, based on the assessment of the material characteristics and waste, the manufacturing process of the cochlear implant does not cause significant risks for the environment, although some possible areas for further improvement were identified.

3.4 Stimulation Platform Integration

It was a main task of the project to combine the expertise and technologies of all consortium partners to develop prototype optoacoustic cochlear implants. Section Packaging and Fabrication Process3.2 describes the activities to develop an implantable package that contains the VCSEL. It is necessary to protect the VCSEL from aggressive body fluids and the body from toxic or potentially carcinogenic materials. We further had to develop the electronics to drive the VCSELs and accommodate the firmware to run the stimulation programmes. Originally, it was foreseen to run in-vivo experiments with the fully long-term implantable packages. It became clear early in the project that this is a major development occupying the engineers for the most part of the project duration. It was, hence, decided to develop a short-term implantable version of the VCSEL (Figure 12) and connect it to the custom developed electronics, as depicted in Figure 13. This system, as referred to as System B, requires external power to drive three VCSELs in parallel. The custom developed graphical user interface and firmware allow the user to programme and run the devices from a computer. The connection is made by a USB cable. Both power supply and USB have to be connected at all times during the experiment, as data logging is done by the computer.

System B provides the experimenters with the new capability of generating light pulses as short as 50 nm. Previously, pulses in the microsecond range were possible. This new feature allowed us to generate bursts of lights with an envelope in the range of e.g. 50 µs, each burst made up of short pulses in the range of 50 ns

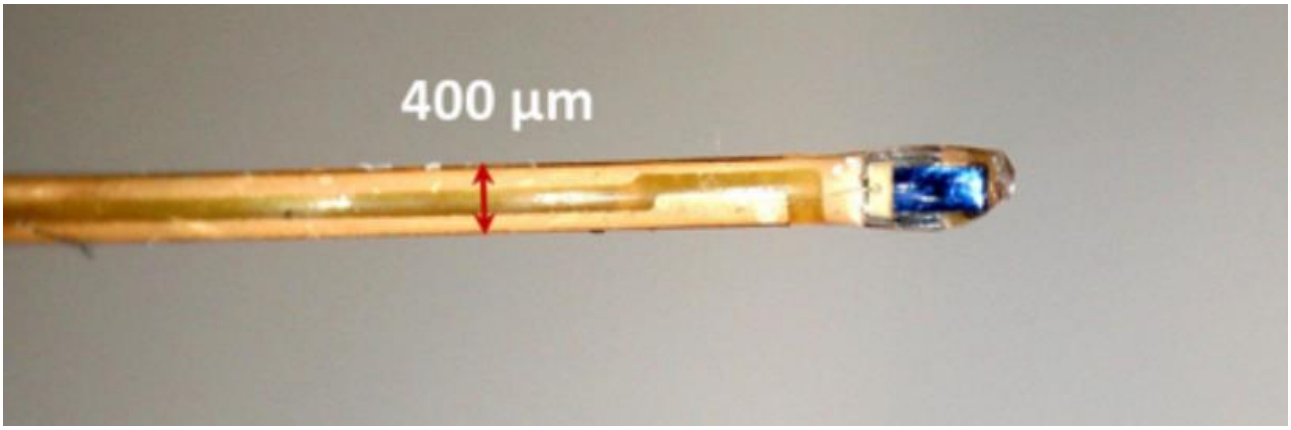

Figure 12: Kapton substrate with VCSEL and silicon lens at the distal end (right), referred to as A++ electrode.

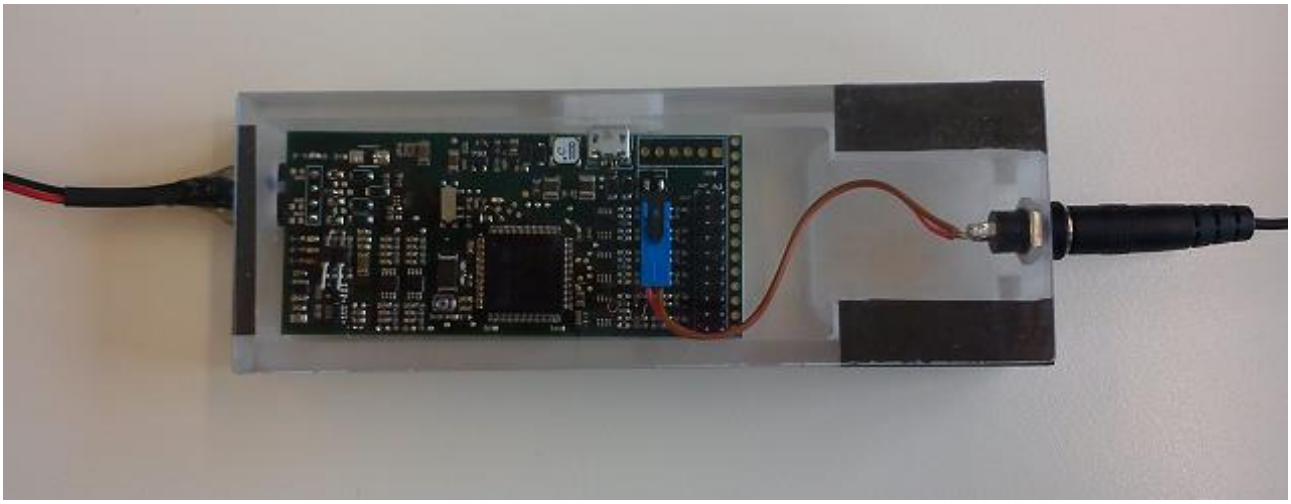

Figure 13: Custom developed electronics board to drive up to three stimulation VCSELs simultaneously.

and a duty cycle as low as 10 %. Such a burst may potentially generate the same oaCAP response as a long continuous pulse while preventing VCSEL overheating and reducing power consumption considerably. First tests were positive, oaCAPs were indeed generated with such bursts of lights. Although the amplitude of the oaCAPs is reduced compared to a single long pulse with identical electrical current, the reduction in power consumption is significant and more than compensates for the signal attenuation.

3.4.1 System Evolution

First, MHH used a standard off-the-shelf laser driver unit to run the trials with an A++ electrode. The commercial equipment was limited in terms of pulse length (i.e. shortness) and operator flexibility. As a first step towards the development of an implantable device, we developed a VCSEL driver unit to be operated from a computer. System B (as referred to, see Figure 13) consist of an electronics board with lateral dimensions of 36 mm x 80 mm. It is protected by a basic machined polymer case, which is about twice the size of the PCB. It connects to a 9 V power supply and the computer via USB cable. A GUI on the computer allows the operator to define custom pulses and even bursts of pulses. The pulse length may be as short as 50 ns. System B connects to A++ electrodes and has been used to replace the commercial driver unit.
Finally, System B was further miniaturised down to a size of 90 mm x 40 mm x 15 mm and renamed System C, indicating the evolution towards an implantable device (Figure 14 and Figure 15). System C comprises a miniaturised System B circuit board and has following additional features:

- Recording of oaCAP electrodes
- Wireless transfer of measured oaCAPs to computer for data storage
- Wireless transfer of stimulation parameters from compute to system C
- Battery for autonomous operation up to 24 hours.
- Housing with features for strapping during tests running several hours or days.
- Plug for battery recharging

System C has not been used yet but is available to the project partners for future trials. It is compatible with A++ electrodes but can drive any type of diode (laser diode, LED or VCSEL). New potential research fields include optogenetics, as the device is wavelength specific.

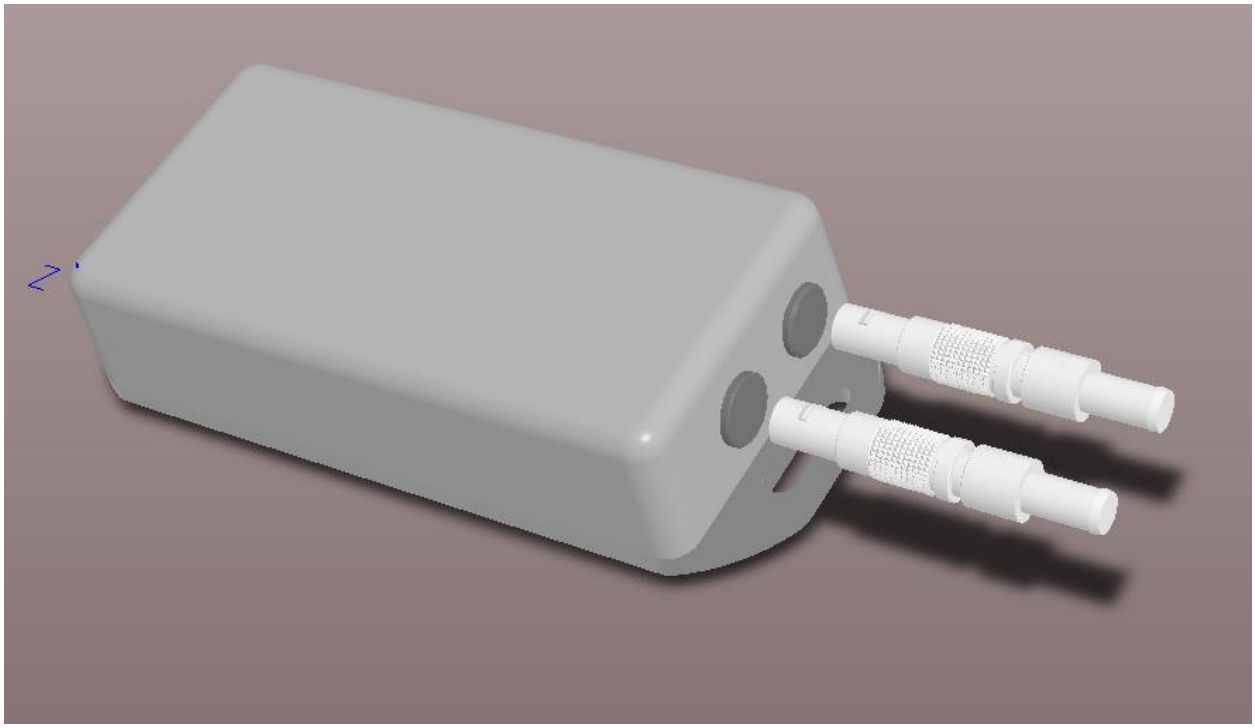

Figure 14: System C housing with connections for VCSELs (one connection) and oaCAP electrode.

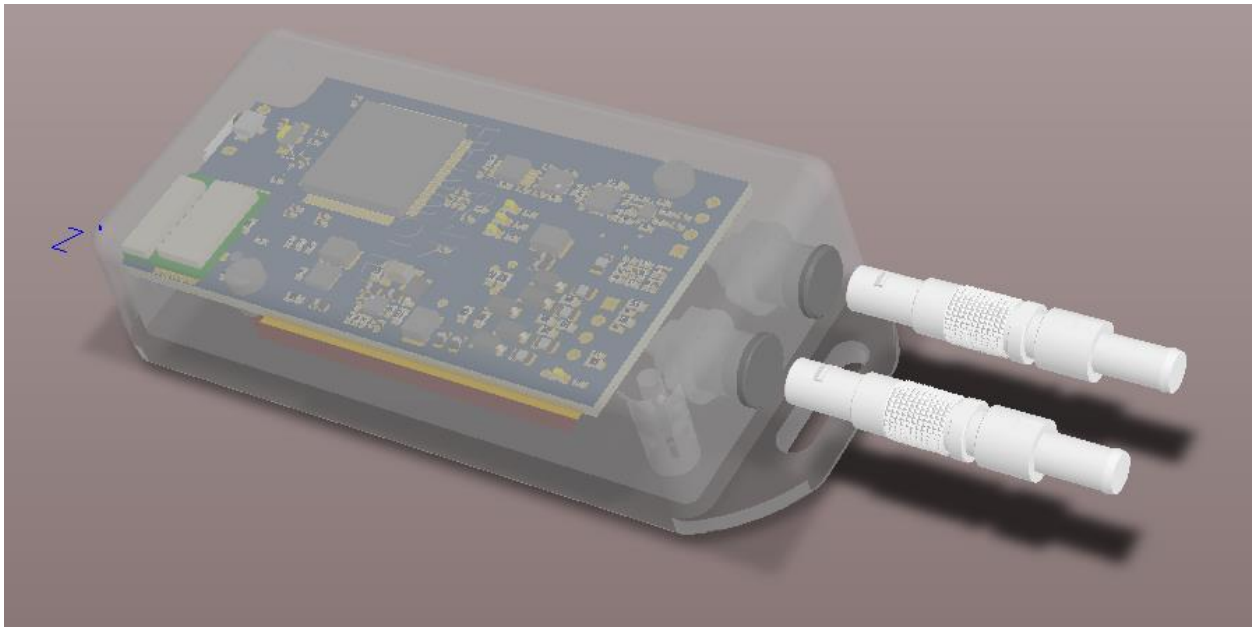

Figure 15: System C (as in Figure 14) with translucent housing to reveal internal components. It contains the circuit board (miniaturised version of System B), a battery below the board and additional circuitry to record the oaCAP signals.

3.5 Implant Studies

Several in-vivo experiments were performed in Dunkin Hartley guinea pigs of either sex. All experiments were performed in accordance with European guidelines for animal welfare and were approved by German state authorities. The VCSELs were either placed on the round window for stimulation through the round window membrane or inserted through a cochleostomy into the first half of the basal turn of the guinea pig cochlea. Under general anaesthesia, a cochleostomy was drilled into the wall of the Scala tympani, approximately 1 mm below the round window opening. The coated flexprint with the VCSEL at the tip was carefully inserted through the cochleostomy to avoid damage to the basilar membrane.

The VCSEL with the collimating microlens was oriented towards the basilar membrane. Compound action potentials (CAPs) were recorded from a silver ball-electrode placed in contact with either the outer cochlear wall (round window stimulation) or placed on the round window membrane. The recording reference electrode was fixed in the retro-auricular skin. CAPs in response to acoustical and optical stimuli were subsequently recorded.

The example in Figure 8 shows a comparison of a CAP signal generated by laser stimulation and a “control” signal generated by an acoustic click. The laser pulse with 50 µs duration, 250 mA current and 40 mW pulse peak power has been applied at t = 0 ms. For comparison at t = 20 ms an acoustic click is released with 32 dB SPL (sound pressure level). Both stimuli generate CAPs which match in form and amplitude.

Figure 9 in the following shows the linear dependence of the generated CAP amplitude (first negative to second positive peak) of the applied current strength for this experiment with 50 µs laser pulse duration. It is reasonable to assume that we have not reached a maximum and that the curve would continue to rise for increased electric current.

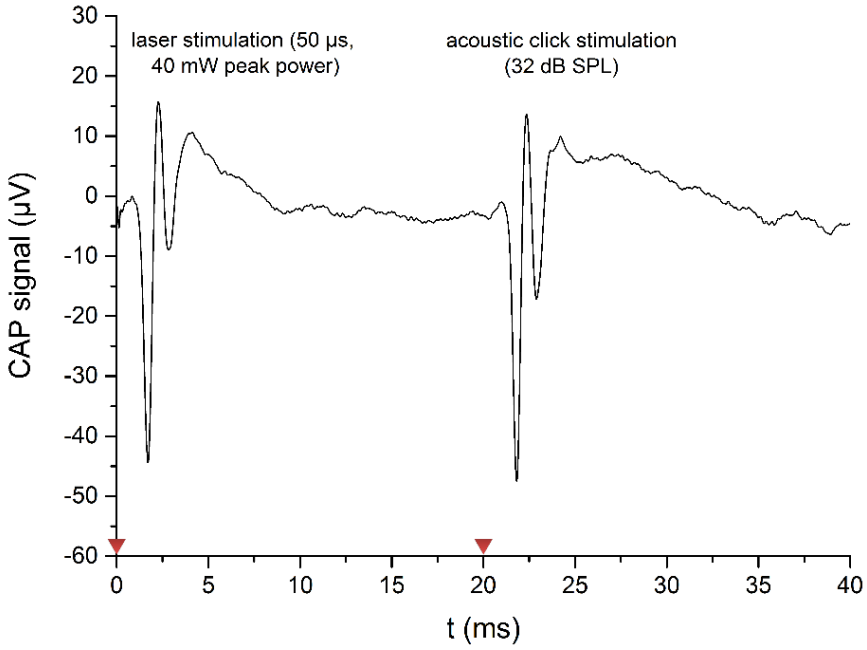

Figure 8: Comparison between CAP induced by intracochlear laser stimulation (50 µs pulse, 250 mA current) and a CAP generated with an acoustic click stimulation of 32 dB SPL. Triangles mark the time points of stimulation.

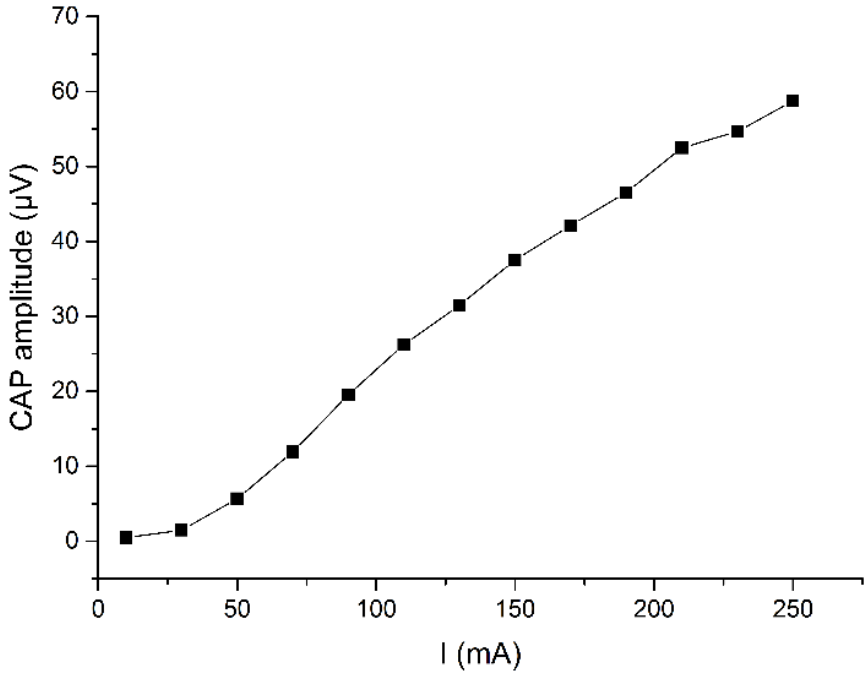

Figure 9 Dependence of the CAP amplitude on the applied electrical current to the VCSEL with a pulse duration of 50 µs.

4 Potential Impact

As ACTION is a research project, direct impact on the European economy and society will be minimal. Assuming a best cast scenario, based on this research, optoacoustic cochlear implants could complement standard cochlear implants. The purpose of this add-on feature is potentially twofold:

1. It could increase hearing quality in the low-frequency range near the apex of the cochlea. Many patients have residual hair cells in this domain.
2. As a sound stimulator for assessment of changes in hearing status within the implanted cochlea. A neural response feedback system may be integrated in the standard cochlear implant.

The outcome of this project might have an impact on the development of implants for the vestibular system to restoring balancing. A device with as few as three channels (i.e. light sources) could restore balancing in patients with issues in the vestibular system.

4.1 Dissemination Activities

The ACTION consortium published all relevant public information on its website (www.action-project.eu). The main channel of dissemination is through presentations at conferences in Europe and also the USA. Furthermore, several articles have been published in peer-review journals and some journals addressing the wider public.
The entire list of our publications, as found on our website (under dissemination), is reprinted below:

- **SPIE Photonics West - BiOS Symposium 2017**
  San Francisco (USA) 28.01.- 02.02.2017
  S. Mohrdiek et al. (CSEM) Active implant for optoacoustic natural sound enhancement

- **innoLAE 2017**
  Genome Campus Conference Centre Cambridge 31.01.17- 01.02.17
  M. Fretz (CSEM) ACTION - ACTive Implant for Optoacoustic Natural sound enhancement

- **Scientific Reports (a natureresearch Journal)**
  Scientific Reports 6, Article number: 28141
  N. Kallweit et al. (MHH) Optoacoustic Effect Is Responsible for Laser-induced Cochlear Responses

- **ARO 39th Midwinter Meeting 2016**
  San Diego (USA) 20-24.02.2016
  P. Baumhoff et al. (MHH) Optoacoustic Effects Explain Cochlear Laser Responses

- **19. Jahrestagung Deutsche Gesellschaft für Audiologie**
  Hannover (DE) 09-12.03.2016
  A. Rettenmaier et al. (MHH) In-situ-Untersuchungen laser-induzierter Basilarmembranschwingungen auf Grundlage des optoakustischen Effekt

- **14th International Conference on Cochlear Implants and Other Implantable Technologies**
  Toronto (CA) 11-14.05.2016
  A. Kral (MHH) Optoacoustic Effects Cause Cochlear Laser Responses

- **87. Jahresversammlung Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde**
  Düsseldorf (DE) 04-07.05.2016
  A. Rettenmaier et al. (MHH) Nutzung des optoakustischen Effekts in einem neuartigen Cochlea-Implantat: In-situ-Untersuchungen laser-induzierter Basilarmembranschwingungen

- **53rd Workshop Inner Ear Biology 2016**
  Montpellier (FR) 17-21.09.2016
  A. Rettenmaier et al. (MHH) Optical Stimulation of Spiral Ganglion Neurons and Laser-induced Cochlear Responses Depend on Different Mechanisms

- **The 3rd International Conference on Bioinspired and Biobased Chemistry & Materials**
  Nice (France), 16–19.10.2016
  R. Milani et al. (VTT) Antifouling Coatings for Optoacoustical Cochlear Implants

- **Nordic Polymer Days 2016**
  Helsinki (Finland), 30.5–1.6.2016
  Y.Y. Liu et al. (VTT) In-situ Polymerized Antifouling Coatings for Cochlear Implants

- **Nordic Polymer Days 2016**
  Helsinki (Finland), 30.5–1.6.2016
  A. Griffo et al.(VTT) A New Flexible Antifouling Coating for Biomedical Devices

- **CMM international**
  17 October 2016
  R. Jose James (CSEM): The Tiny Active Implants That Could Make the Difference

- **microNews November 2015**
  M. Fretz (CSEM): Hören mit Licht

- **CSEM Scientific Report 2015**
  M. Fretz, R. Jose James, G. Spinola Durante, T. Burch, S. Bitterli (CSEM) Active Implants for Optoacoustic Natural Sound Enhancement - ACTION

- **MNBS 2015**
  A. Steinecker (CSEM): ACTION - ACTive Implant for Optoacoustic Natural sound enhancement

- **13th International Baltic Conference on Atomic Layer Deposition**
  September 28-29, 2015, Tartu, Estonia
  M. Putkonen et al. (VTT): Antimicrobial properties of ALD films

- **FLAIR 2014 - Field Laser Applications in Industry and Research**
  Pratolino (FI), Italy, May 5-9, 2014
  M. Ortsiefer (VERTILAS): Achievements and prospects for long-wavelength VCSELs in optical sensing applications

- **European VCSEL Day 2014**
  Rennes, France, 22nd and 23rd May 2014
  M. Ortsiefer (VERTILAS): Recent Progress of InP-based Long-Wavelength VCSELs for Communications Applications

- **CSEM Scientific Report 2014**
  R. Jose James, M. Wannemacher, G. Spinola Durante, M. Fretz, D. Fengels, S. Mohrdiek (CSEM): Optical Cochlear Implant

- **IMAPS Advanced Technology Workshop on Microelectronics, Systems and Packaging for Medical Applications**
  December 10th - 11th, 2014. Lyon, France
  Guido Spinola Durante, Rony Jose James, Ch. Bosshard, Stefan Mohrdiek (CSEM): Micropackaging of long-term implantable Active Medical Devices

- **COMPAMED HIGH-TECH FORUM by IVAM**
  COMPAMED 2014, 12.-14. Nov. 2014, Düsseldorf, Germany
  Alexander Steinecker (CSEM): Bio-Compatible Microsystem Packaging of VCSEL Laser for Implantable Devices

- **Workshop on Micro-Nano-Bio Convergence Systems, MNBS 2014**
  21-22 October 2014, LAAS-CNRS, Toulouse, France
  Stefan Mohrdiek (CSEM): ACTION - Optical cchlear Implant Project

- **EPoSS Annual Forum**
  Torino, Italy, 25th Sept. 2014
  "Best Practices in the European Smart Systems Integration Ecosystem: From Education to Markets"
  Alexander Steinecker (CSEM) Bio-Compatible Microsystem Packaging of VCSEL Laser for Implantable Devices

- **Forum Program SMT Hybrid Packaging 2013**
  Matthias Krieger (CSEM) Advanced optoelectronic packaging for demanding high power laser applications, including small series production

- **microNews November 2013, News, page 8**
  Erfolg für das CSEM in Europa

4.2 Exploitation

MHH as a user of the developed devices furthered the research into optoacoustic stimulation. Their cutting edge research improved the understanding of the scientific community of the acoustic and optoacoustic stimulation. Beyond these obvious benefits, several consortium partners advanced their technologies and commercialised new products:

- Commercialisation of the microlens by SUSS MicroOptics
- Commercialisation of the custom developed VCSEL by VERTILAS

- Application of a patent on micro-packages by CSEM.
- VTT developed novel antifouling coatings for silicone surfaces

Several consortium partners are in bilateral talks on how to further exploit the results. These talks are confidential and cannot be disclosed at this stage. For more details, please refer to section 4.2, Use and dissemination of foreground, in the Project Final Report for ACTION:

5 Contact Details

5.1 Website

The ACTION website address is: https://www.action-project.eu/

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6 Project Logo

7 Project Team

The ACTION team, the PO and the reviewers at the year three review meeting in Hannover, December 2016