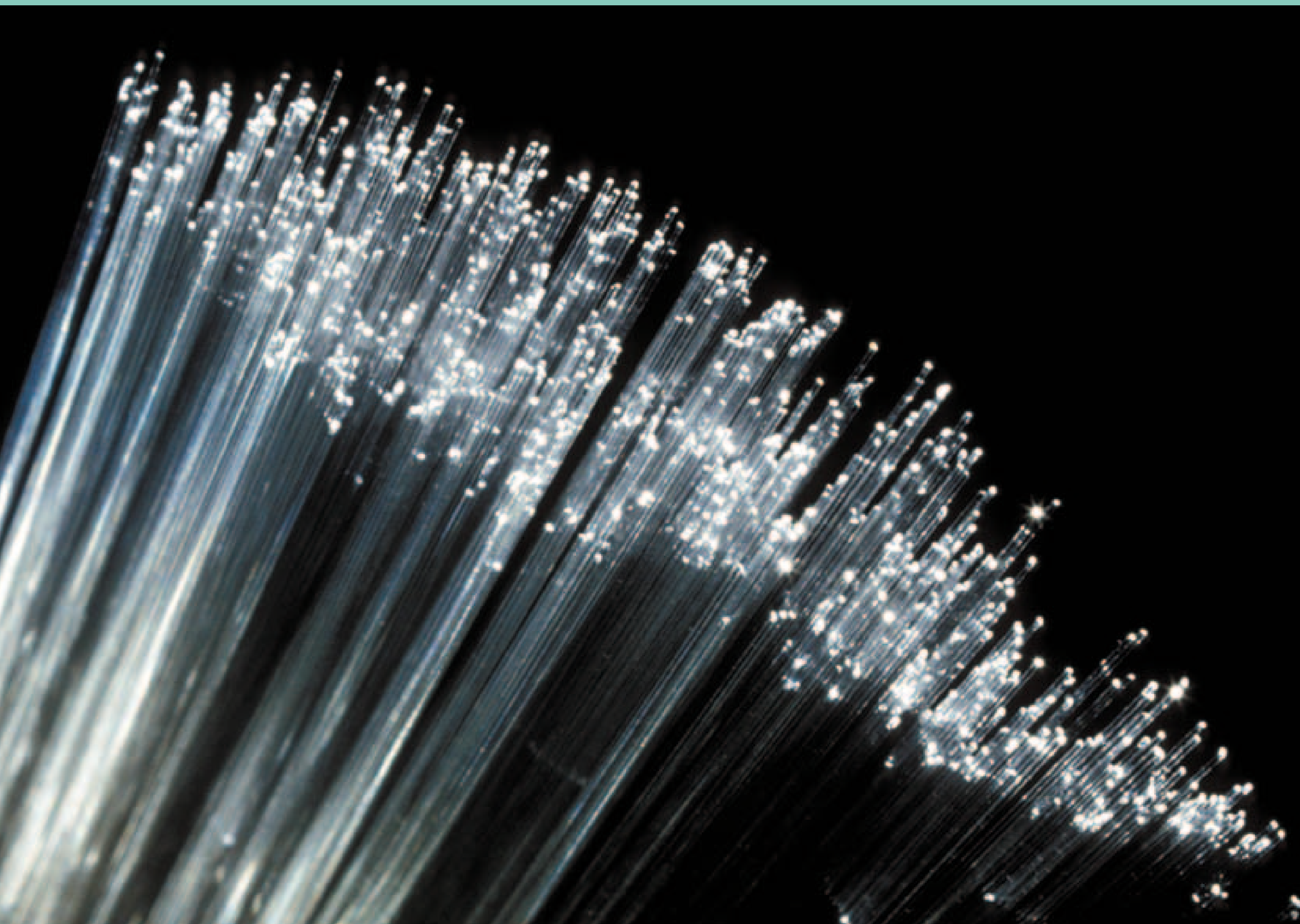
NL Agency
Ministry of Economic Affairs

IOP Photonic Devices
Focusing on photons

The IOP Photonic Devices aims to strengthen both existing networks and the ongoing collaboration between research institutions and companies, and in doing so, to turn new possibilities for photonic devices into socially relevant and sustainable business applications.

>> Focus on Innovation



Contents

Photonics

In the world of photonics, everything revolves around light. Photonic components can generate, detect and manipulate light. The discovery of the laser in 1960 and the rise of optical fibres as a means of transmitting information formed the basis for this discipline. The subsequent linkage with semiconductors and far-reaching miniaturisation led to a boom in applications for telecom and consumer products, with the Internet and the CD being the best-known examples. But the developments are still going on: just think of the recent development that LEDs have undergone in lighting and displays, for example. In the meantime, photonic components have become indispensable in the medical world, both for diagnostics and for therapeutic purposes. They are also being applied on a large scale for chemical and biological detection, manufacturing processes and security surveillance. The annual European turnover of products with photonic components is estimated to be EUR 250 billion.

Two themes

Photonics is an incredibly wide-ranging discipline with innumerable possibilities for applications. In its second phase (2010–2014), the IOP Photonic Devices is concentrating on two themes within that discipline: new photonic devices based on generic technology and new applications for photonic devices in health and medicine.
The Netherlands has a substantial pool of sophisticated expertise with regard to these themes, in addition to a relatively large number of companies that are capable of converting both existing and yet-to-be-developed knowledge into innovative products. As a result, considerable new economic activity is taking place in the Netherlands within the framework of these two themes. The first theme focuses on the development of technologies that can help accelerate the introduction of new photonic devices on the market. Indeed, users are already being encouraged to use a limited number of generic technologies as much as possible in the design chain, in the processing stages at foundries and in industrial assembly and packaging. As for the second theme, the possibilities for using photonic technologies for diagnostics and therapy seem endless. That holds both for invasive use – involving the insertion of probes into the body – and non-invasive use – including optical mammography or white-light reflection microscopy for examing tissue, both of which dramatically reduce the number of sections required for research. Other examples include using light to analyse breath or measuring blood-sugar levels through the skin. All these applications could have a huge impact on society.

“The Netherlands has numerous excellent research groups in the field of photonics, both at research institutions and at a number of large companies. There are also many companies that are interested in the applications of photonics and prepared to invest in those,” says Dr Bart Verbeek, chairman of the IOP Photonic Devices advisory committee. “While the efforts are still rather fragmented, the possibilities for applications in the medical sector, for example, seem endless. By strengthening collaboration and the formation of clusters, we can take better advantage of the new possibilities for photonic devices to develop socially relevant and sustainable applications.”

The role of companies

In the framework of the Dutch innovation-oriented research programmes (IOPs), grants are awarded for the implementation of innovation-oriented technological research projects in specific thematic areas that are consonant with the strategic research needs of the business community in the Netherlands. An IOP aims not only to develop knowledge, but also to encourage interaction between companies and research institutes, since the synergy between them will both lead to new networks and reinforce existing ones. An IOP gives the innovation process an open character. The partners within any IOP project include at least one Dutch research institution and two Dutch companies. Over the course of a number of years (usually four), the partners work closely together in carrying out a research project.

An IOP project offers companies the opportunity to be in direct contact with scientists from research institutions as well as researchers from other companies. Those who take part in an IOP build new personal networks and gain insight into the existing research capacities in the Netherlands. Besides being able to contribute intensively to the implementation, companies can be part of an industrial user group consisting of representatives from companies and research institutions. Each project has such a group that meets twice a year to monitor the quality and progress of the project concerned, to advise on any adjustments in terms of the direction the research is heading, and to draw attention to potential applications. In this way, the participating companies can strengthen their contacts with research institutions and other companies and remain up-to-date on the latest developments in the discipline concerned. Moreover, companies can also take part in the other activities of the IOP and, in doing so, gain insight into the developments.

"Companies can also take part in the other activities of the IOP and, in doing so, gain insight into the developments"

Tenders and projects

Following the initial project tender in the first phase of the IOP (2006–2009), four projects were awarded grants with a joint budget of EUR 5.2 million. On the basis of the second tender, an additional five projects were awarded grants with a joint budget of EUR 4.85 million. Finally, following the first tender of the second phase (2010–2014), five new projects were awarded grants with a joint budget of EUR 5.3 million. Detailed information (in Dutch) about forthcoming IOP tenders can be found on the webpage of the IOP Photonic Devices: www.agentschapnl.nl/IOPPhotonicdevices.

The following pages contain descriptions of the various projects, based on interviews held with the project leaders of the four projects from 2006, the five projects from 2008 and the five projects from 2010. Please note that in each case the interviews were held at the start of the project.

Chairman Verbeek:

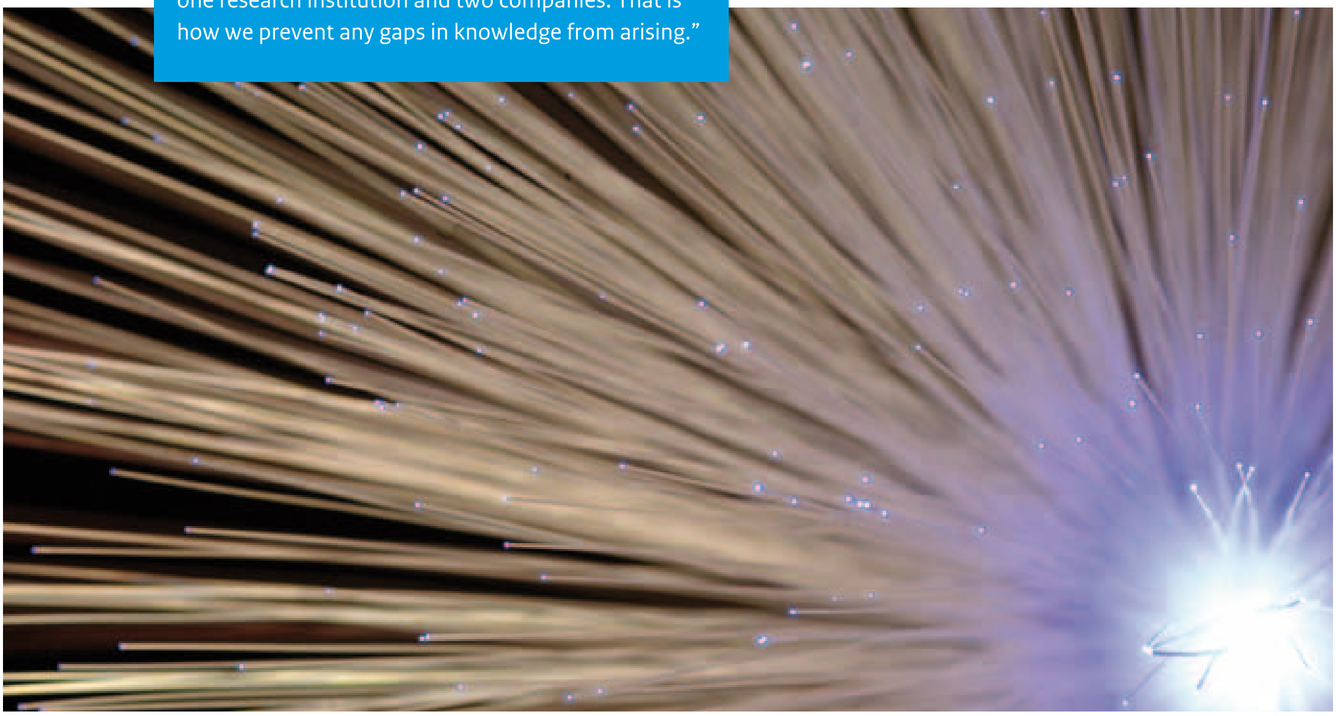
"An IOP isn't just about developing knowledge. After all, it is precisely by applying that knowledge that we can help strengthen the economy. That is why, in this IOP, companies are involved in the projects already at an early stage and each consortium comprises at least one research institution and two companies. That is how we prevent any gaps in knowledge from arising."

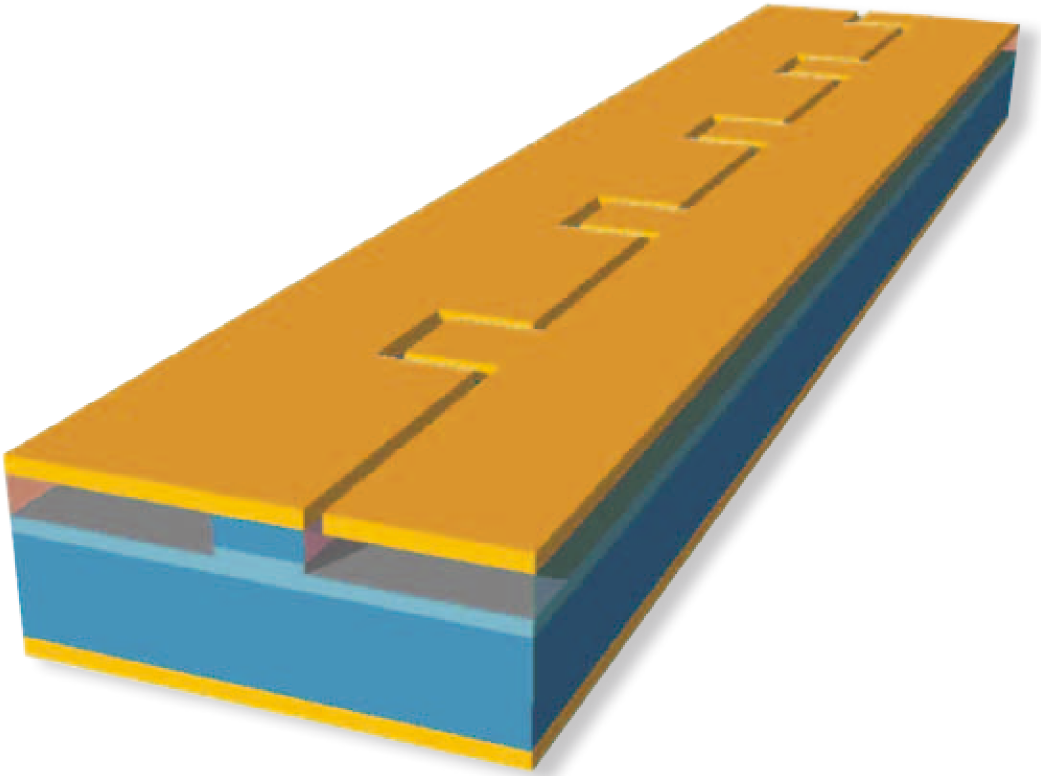
Opportunities for valorisation

The IOP attaches great importance to valorisation: the translation of research results into products, processes and services that add economic value to the results. Besides the close collaboration between companies and research institutions, numerous other activities aimed at stimulating valorisation are organised on a regular basis over the course of the IOP, ranging from valorisation workshops to an annual photonics event.

Networking

Within the IOP, considerable attention is also given to cluster support: transferring knowledge, forming networks, determining focal points and embedding expertise. The idea is that the photonic devices cluster will develop into a platform in which researchers, suppliers and manufacturers can find each other and jointly develop activities that will strengthen the expertise and market position of all parties in the chain. One example of this is the large-scale photonics event (www.fotonica-evenement.nl) that the IOP Photonic Devices organises each year, together with Mikrocentrum and Photonics Cluster Netherlands. Platform meetings, regional network sessions and Holland Pavilions (at trade fairs) are organised as well, and the IOP Photonic Devices works expressly together with other programmes such as the Technology Foundation STW's Smart Optics Systems and Generic Technology of Integrated Photonics Programmes.





Project number: IPD067774
Project name: IR Swept source for high resolution functional imaging in medicine
Goal: to develop a broadband laser source for OCT

Schematic model of an optical semiconductor amplifier for short light pulses.

Going beyond the surface *with optical coherence tomography*

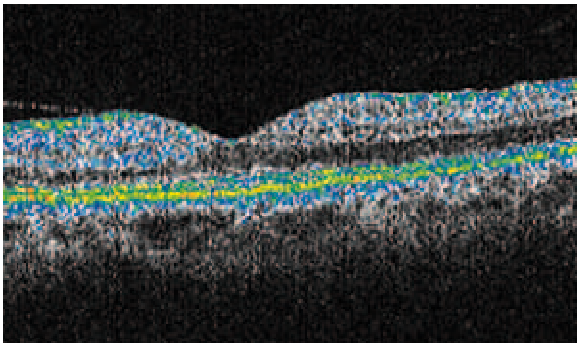
A consortium including the Eindhoven University of Technology is working on the application of a laser in optical coherence tomography. One of its focal points is the possibility of integrating the laser on a single chip together with the necessary integrated optical switches. The technology being developed will make it possible to speed up the imaging and look deeper inside the tissue, benefitting both the specialist and the patient.

Optical coherence tomography (OCT) is currently being applied primarily in the field of ophthalmology. This technology enables the imaging of a cross section of tissue in a resolution at the micrometre (μm) level. Depending on the type of tissue concerned, an eye specialist can 'look' to depths of between 1.5 and 2 millimetres (mm). OCT works as follows: A light source is linked to a beam splitter that divides the light bundle. Part of the beam of light is focused on a particular point in the research area, while the rest is diverted in a different direction. The imaging takes place on the basis of the reflection of the light emitted.
What is special in that regard is that, to form the image, the reflection of the focused light is blended with that of the diverted light, as those interfere with each other.
The strongest signal arises when the distance to the tissue and back is the same as the distance travelled by the diverted light.

Laser supersedes LED

"That fact is related to one of the problems with the current technology," says Dr Erwin Bente of the Opto-Electronic Devices group within the Electrical Engineering Department at the Eindhoven University of Technology. "To be able to create an in-depth image, the optical path of the diverted light needs to be adjusted point by point. That is done mechanically, with mirrors being moved point by point. But that takes a lot of time: not only does the patient need to lie still for a very long time, but also the specialist is occupied for quite some time before the final image has been constructed." There are already some leads as to how the technology can be improved. Bente: "Ideally you'd like to create a real-time video image. That could be done by applying a broadband laser light source with integrated optoelectronics, which would eliminate the need for the mechanical process with the mirrors."

Applying a broadband laser light source with integrated optoelectronics eliminates the need for a mechanical process with mirrors

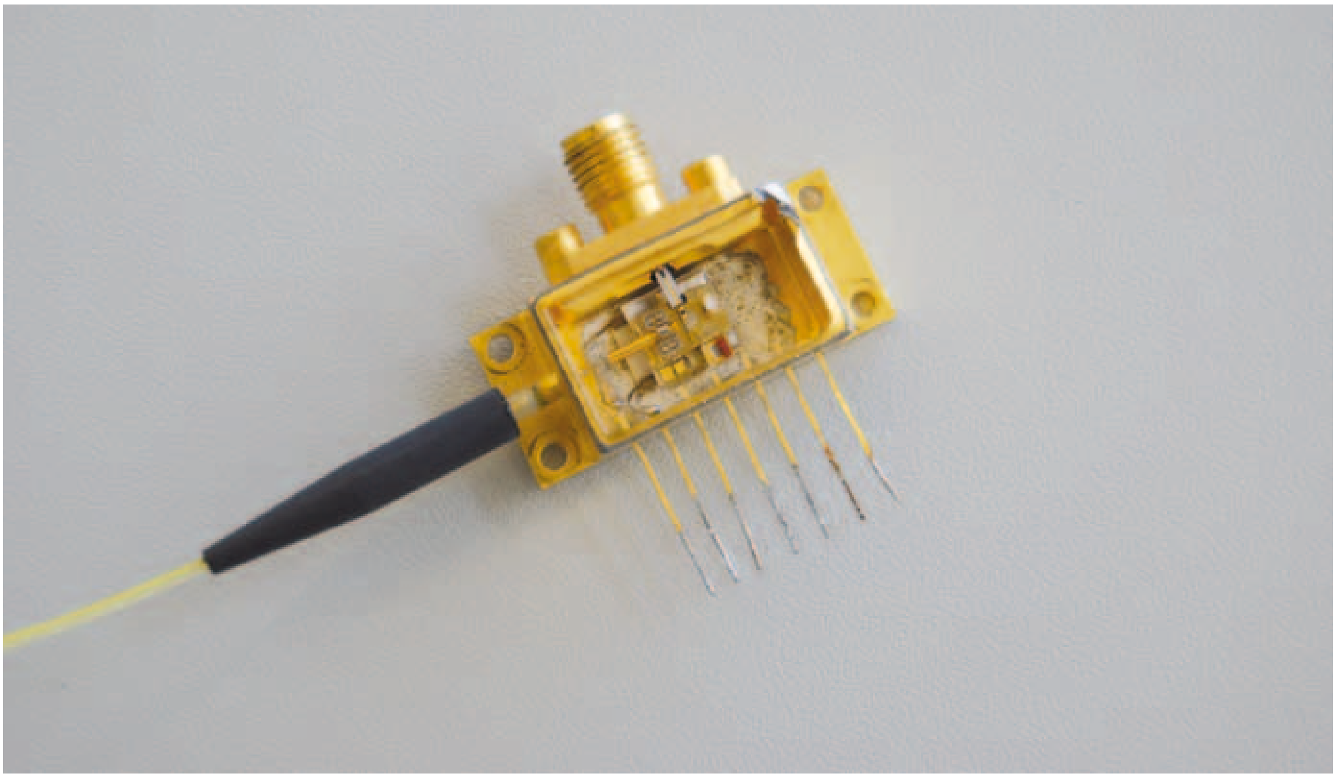


Cross section of the eye's retina recorded using OCT technology.

It is just like fog: the tissue's scattering of light determines how deep OCT can look. The less 'fog' (i.e. scattering) there is, the deeper OCT can penetrate into the tissue. And the longer the wavelength of the light, the less scattering there will be. That means that a longer wavelength of 1600 to 1800 nanometres (nm), reaching further into the infrared zone, appears to be best for peering deeper into the tissue.

Using quantum-dot materials

For that laser to work in the 1600nm to 1800nm range, two technologies need to be joined together. New semi-conductor materials bring that goal within reach by enabling the integration of both the laser and the necessary optical integrated circuits (ICs) in a single chip. In the existing technology, the optical amplifier for the laser is made of semiconductor material that is built up of thin layers. Bente: "That material is not suitable for obtaining the wavelength we are aiming for. But with new quantum-dot materials (material with tiny quantum wells based on indium phosphide), we will be able to build the laser amplifier we need. With that material, the necessary optical integrated circuits can be integrated into the chip. The ICs contain the components – some of which are transparent – that can determine and vary the wavelength of the laser light, among other things." Those are built up of tiny 'light channels' that guide the light. Using both laser technology and the ICs in one and the same chip of about 2mm by 10mm in size, it should in principle be possible to make chip wafers with large numbers of 'monolithic lasers' that would be relatively inexpensive per piece.



Example of a packaged integrated photonic circuit.

"A lot still has to happen before those chips are there, however. We know that it works at these wavelengths, but it has yet to be done in an adjustable laser system. Another thing we need to think about is how to control the size of the wells in the quantum material. In fact, that control would have a broader application than just medical technology; it would be important to laser technology and broadband optical amplification as a whole."

The new technology will increase the field of application of OCT

New research possibilities

But the advantages for the medical technological applications are already interesting enough; a more rapid imaging would benefit both the doctor and the patient. Bente: "In the field of ophthalmology, the possibility of penetrating deeper into the tissue would be a very concrete advantage. The current OCT technology only reaches 0.5 mm deep in the tissue surrounding the lens, which scatters light very strongly. Since that is not deep enough, the patient must undergo unpleasant ultrasound examinations with a contact fluid. With our OCT technology, however, the depth we can reach could actually be adequate." In addition, the new technology will increase the field of application of OCT. "Our research partners at the Laser Centre of the Academic Medical Center (AMC) in Amsterdam and at MicroVision Medical are very interested in the possibilities for research on skin and blood vessels. Skin contains extremely tiny veins, thinner even than the blood cells that need to 'wrestle' their way through those veins. The behaviour of those blood vessels provides a wealth of information about a patient's physiological condition, indicating for example whether he or she is in a state of shock. The potential for a new application in this area is another reason why the breakthrough we are working on is so desirable."

Participants:
- Eindhoven University of Technology
- AMC Laser centre
- TOPCON Europe Medical BV
- MicroVision Medical Holding BV

Contact:
Dr E.A.J.M. Bente
T: +31 (0)40 247 51 06
E: e.a.j.m.bente@tue.nl

Project number: IPD067767
Project name: Raman Pen
Goal: to develop a compact pen-size RAMAN spectrometer for tissue diagnostics

In-vivo skin analyser based on Raman spectroscopy.

Raman spectroscopy: *Characterising tissue with a pen*

"The project we are currently working on is a direct result of the first meeting of the IOP Photonic Devices", says Dr ir Gerwin Puppels, CEO of River Diagnostics BV in Rotterdam and a co-founder of the Center for Optical Diagnostics & Therapy at Erasmus Medisch Centrum in Rotterdam. "At the kick-off meeting, I mentioned that ours was the world's first Raman spectroscope. My question was: how can we accommodate that technology – which currently comes in a desk-top unit – at least a hundred times less expensively in a pen-sized device? The audience reacted enthusiastically."

Raman spectroscopy has interesting applications in medical research and diagnostics. A normal microscope sees no difference between plastic and cartilage, for example, whereas tissue engineering requires making such a distinction. There, cells are placed in a structure of biodegradable polymers, for example to repair a damaged ear. As the cartilage starts to grow, the polymers disintegrate. To be able to monitor the progress of that process directly in the patient, there needs to be a detection technology that can distinguish the cartilage molecules from the polymer molecules. Raman spectroscopy can do that.

This is a non-destructive optical technology, based on the scattering of monochromatic light by molecules ('Raman scattering'). The possibility of distinguishing between the two materials is based on differences in the energy levels that a (laser) light source can cause in terms of the vibrations and rotations of the atoms in a molecule. When interaction takes place between a photon and a molecule, part of the energy of the photon can transfer to the molecule. This has consequences for way in which the atoms move around in the molecules. When this phenomenon occurs, the energy of the photon decreases by the amount of energy that the molecule absorbs. How much energy is transferred depends on the atomic composition of the molecule. That means that Raman spectra are molecule-specific. By measuring the energy differential between the entering and exiting photons, it is possible to determine which molecules are concerned.

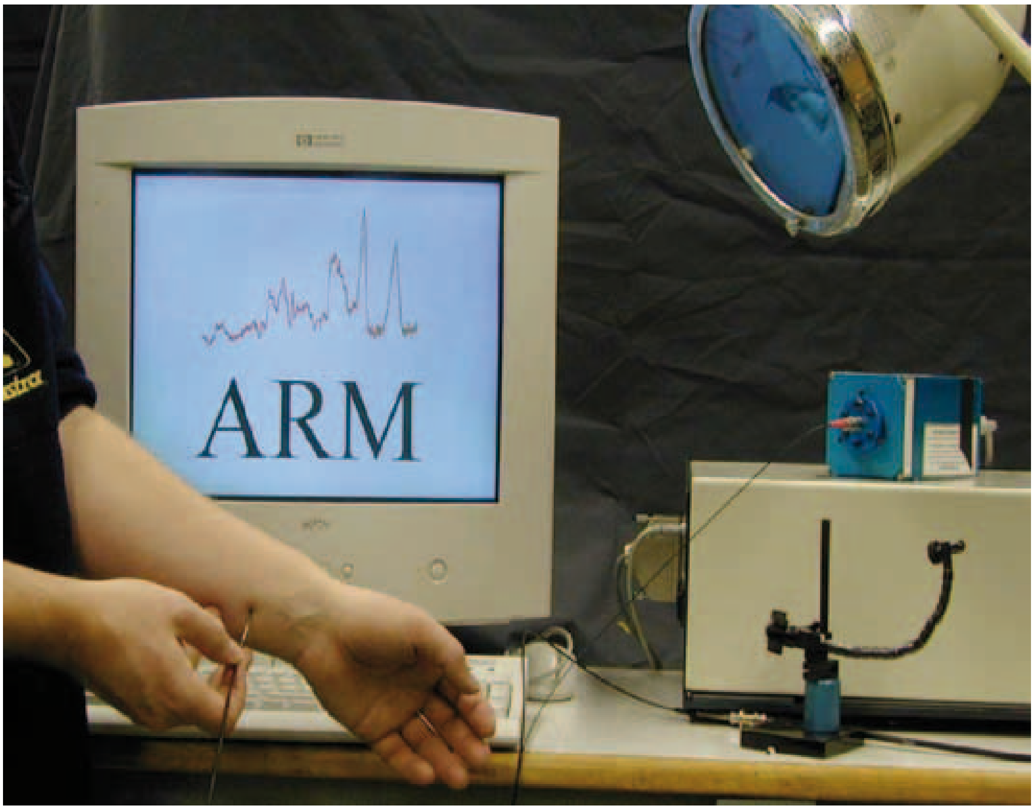
"We need to bring the technology from the high-end market down to the realm of daily life"

Detailed information

River Diagnostics has been able to characterise tissue and cells with a Raman spectroscope since 2004. The field it serves: *in-vivo* research applications and diagnostics. Puppels: "We provide a complete solution – the device, the specialised software, and the expertise for the clinical application – to enable the correct analysis of the data obtained. Our product provides detailed information about the composition of the skin, as well as about the agents that are applied to the skin. That in turn provides answers to questions such as: which component of the agent, and how much of it, actually penetrates the skin? How rapidly and how deeply does that penetration take place? Which metabolites are formed in the process?" The answers to those questions are of great importance for medical research, dermatological diagnostics and research in the personal-care industry. Aside from their importance for product development, they are especially vital for substantiating claims. "The fact that classical optics are among the components of a Raman spectroscope makes it an expensive instrument. Research environments are practically the only ones that can afford such an expense," says Puppels.

Rapid development

Puppels realized that the functionality of Raman spectroscopy could be much more widely applicable if both the price and the size of the device were reduced. "We need to bring the technology from the high-end market down to the realm of daily life. If the price were reasonable, all doctors could carry a few Raman pens in their breast pocket, enabling them to do specific *in-vivo* analyses. During operations, specialists would no longer need to rely on their *Fingerspitzengefühl* to determine whether or not certain tissue is part of a tumour and needs to be removed. Instead, they could do that objectively by means of the Raman pen. The quality of a donor organ would become clear at a glance. And pharmacists or chemists could recommend the right lotion or cream to their customers on the basis of skin analysis."



Optical fibre conducts laser light to the tissue.

"Something that would have been at least 1.5 metres ten years ago now fits on half a fingernail and costs a fraction of the price"

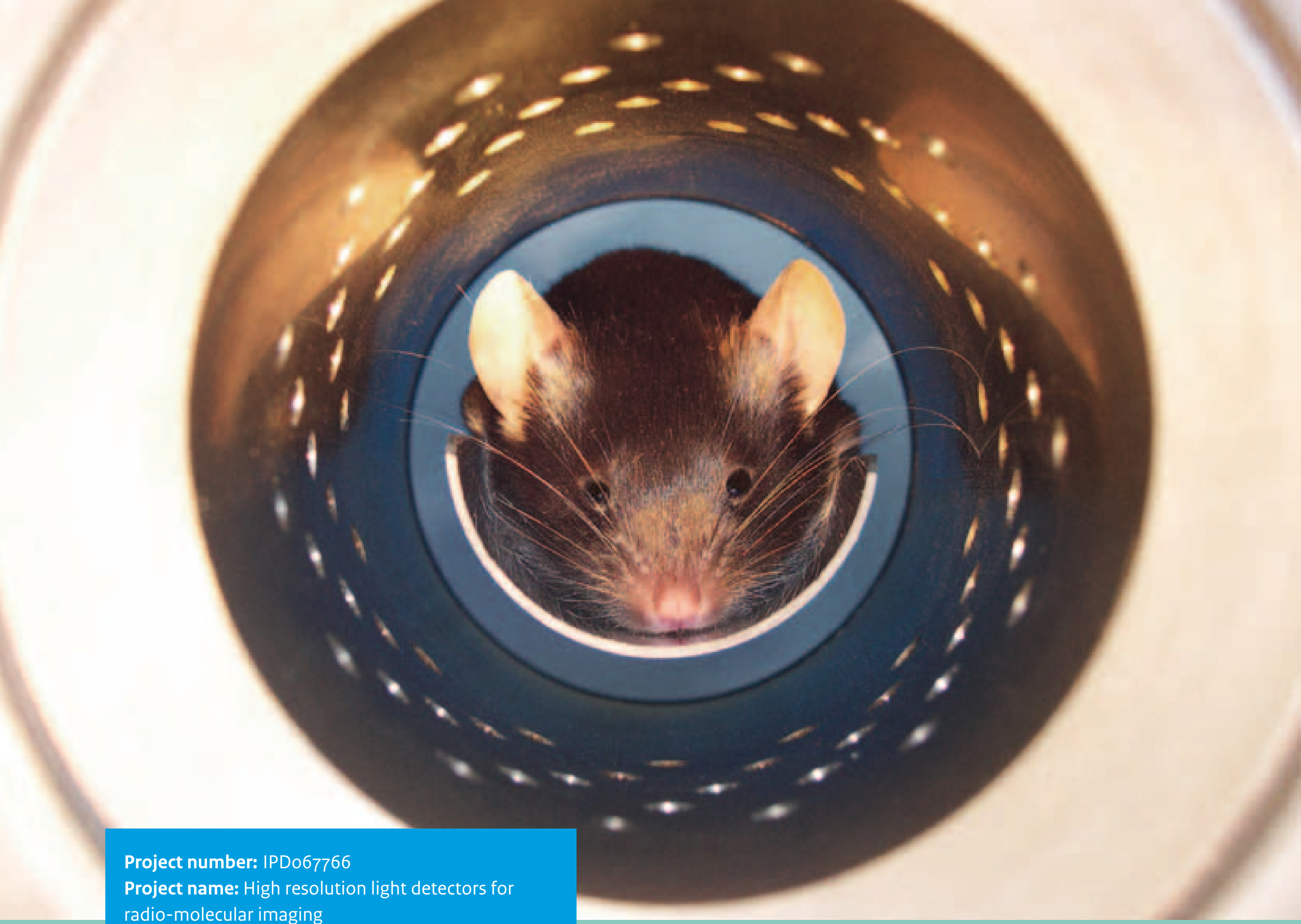
Developments in the field of integrated optics and lasers are taking place at a rapid pace. "Something that would have been at least 1.5 metres ten years ago now fits on half a fingernail and costs a fraction of the price," Puppels explains. "That needs to happen with Raman spectroscopy, too. That will require not only the development of completely new technology, but especially also the integration and adjustment of inexpensive existing components. And it will require a design that can be mass produced."

Worlds come together

That is why the 'Raman pen' project is bringing together two different worlds. The first of those worlds comprises the parties that have been working on Raman spectroscopy for years already. They know the technology and the possible applications, so they are able to formulate the required specifications for the second world, which comprises specialists in the fields of integrated optics, photonic crystals and lasers. With the input from the latter group, the Raman specialists can set to work testing and evaluating prototypes. Puppels: "In that respect, the IOP programme has been working fantastically ever since the kick-off. It has brought together parties that would not otherwise have been apt to find each other. And that always results in the most exciting and interesting projects."

Participants:
- Erasmus Medical Center
- River Diagnostics BV
- NRC Institute for Biodiagnostics (Canada)
- University of Twente
- Delft University of Technology
- Lionix BV
- 2M Engineering

Contact:
Dr ir G.J. Puppels
T: +31 (0)10 408 79 89
E: g.puppels@erasmusmc.nl



Project number: IPD067766
Project name: High resolution light detectors for radio-molecular imaging
Goal: to develop a new camera for single photon emission computed tomography

A mouse being scanned in the super high-resolution U-SPECT scanner at UMC Utrecht.

Better signal-to-noise ratio *for SPECT*

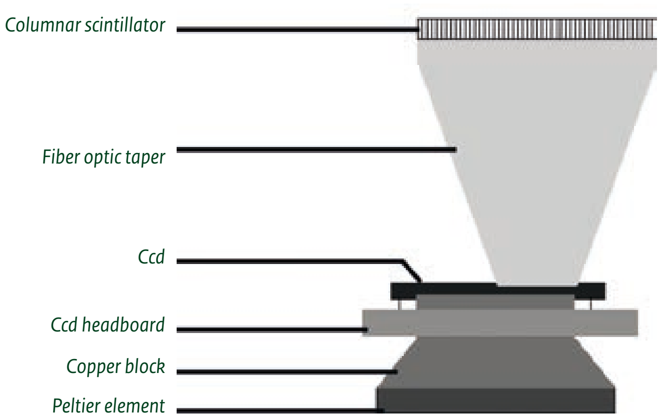
It has proved very difficult to develop effective therapies for diseases such as Alzheimer's and Parkinson's or for brain tumours. Nevertheless, there has been progress in that area, and new medicines are being made available. Medical researchers now want to know precisely where those medicines end up in the body. Do they go where they are supposed to go? And if they do reach their target, do they continue to work effectively? The ongoing development of single photon emission computed tomography (SPECT) technology should provide the answers in a practical way.

While it is currently already possible to determine the location of impact and the effectiveness of the medicines, doing so remains difficult. To find the answers in mice, the laboratory animals with cancer need to be killed. The researchers then need to freeze them and cut them in paper-thin slices to be able to examine the tissue under a microscope. "And even then, the result provides only a snapshot of the situation," says Prof. Dr ir Albert Theuwissen, who specialises in Solid State Image Sensors at the Delft University of Technology. "That is why we want to be able to visualise the effectiveness of medicines *in vivo* and to follow that over time. To begin with, we want to do that with living mice. That would ultimately enable us to follow the effect of medicines in people, too."

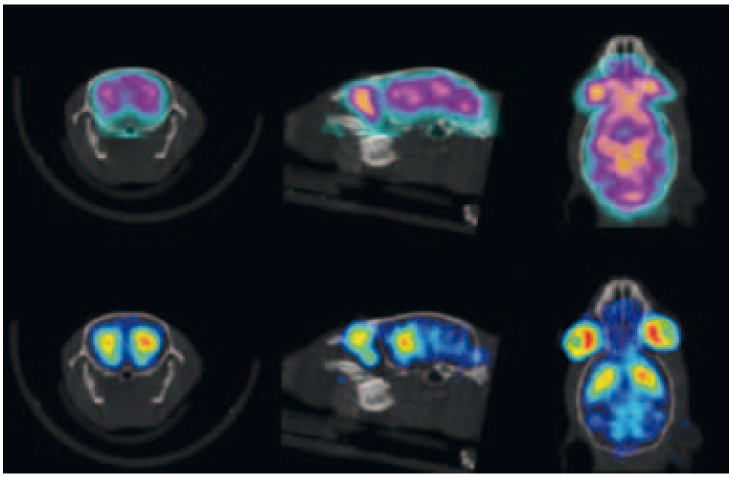
"It's a matter of fibre optics: an 'eye-of-the-needle' camera that can capture the light of a single gamma photon"

Oversized equipment

The technology that will be used makes use of labelling of the medicines. SPECT is used to make that labelling visible. Theuwissen: "The labelling of the medicines is done with radioactive gamma rays in extremely low doses. To be able to follow the medicines through the body, we need to convert the residual radiation in the body into visible light: 'green' photons. Detecting those requires extremely sensitive devices that also need to be very small. It's a matter of fibre optics: an 'eye-of-the-needle' camera that can capture the light of a single gamma photon." Such equipment does exist, but there are quite a number of disadvantages to the technology in its current state, emphasises Theuwissen. "While the actual camera may be small, the device as a whole, including the instrumentation surrounding it, is quite voluminous. That complicates matters. To be able to study a patient's head, for example, a researcher will want to set up a ring of cameras around the patient. That ring needs to be as small as possible for the right imaging. The size of the current device doesn't allow for such a ring. Moreover, researchers can only work with the camera if the temperature of the entire device has been brought to -60 °C. Not only does it take a while for the device to get that cold, but its effectiveness is also highly sensitive to fluctuations in temperature."



While the high resolution of the prototype CCD detector for SPECT (UMC Utrecht) is unprecedented, it still has low sensitivity and requires extreme cooling.



In vivo images of a mouse brain with MILabs' VECTor/CT scanner. Top: 3D map of glucose consumption in the brain. Bottom: 3D map of density of dopamine neurons. Both images are acquired simultaneous.

Optimal signal-to-noise ratio at -60˚C

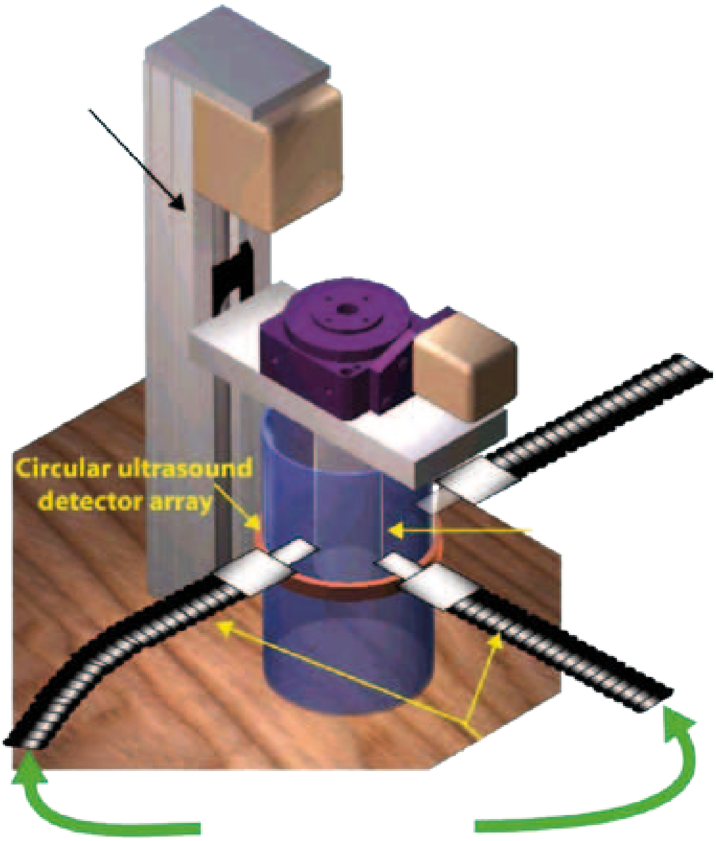
The drastic cooling measures are necessary because an acceptable signal-to-noise ratio is only practicable at an extremely low temperature. "That's why the key to improvement lies with charge-coupled devices (CCDs) or complementary metal-oxide semiconductor (CMOS) sensors that can increase the sensitivity of the camera," Theuwissen explains. "On one hand, the quality of the signal needs to be better, while on the other, the level of noise needs to be reduced." How the solution will ultimately be configured is not yet clear: "The IOP project has been going on since 1 June 2007. Together with the other project partners, we did our best during the preliminary sessions to align the possibilities of the sensors with how the University Medical Centre Utrecht (UMC Utrect) intended to use them."

There is certainly no shortage of ideas, many of which have already been patented. Theuwissen: "Now we need to select the most promising option from some ten possible approaches to a solution. Fortunately, to help us in making the choices, we can use advanced computer simulations, for example to study the noise behaviour of the sensors as a function of the temperature. Once the choices are clear, four PhD students will start developing the ideas further. If we succeed in doing what we are planning to do, we will end up with a more manageable SPECT camera. With that, researchers will be able to determine the effectiveness of new medicines *in vivo*. And for a number of diseases that are difficult to treat, the improved camera could lead to more effective medicine research."

Participants:

- Delft University of Technology
- University Medical Centre in Utrecht
- DALSA BV
- MILabs BV

Contact:
Prof. dr ir A.J.P. Theuwissen
T: +31 (0)15 278 94 64
E: a.j.p.theuwissen@ewi.tudelft.nl



Sketch of the photoacoustic setup for imaging small laboratory animals. This setup will facilitate molecular imaging by means of the absorption of the gold rods in combination with an antibody.

Project number: IPD067771
Project name: PRESMITT: plasmon resonant nanoparticles for molecular imaging and therapy
Goal: diagnostics and therapy with gold nanoparticles and photoacoustics

Going for gold: *Nanoparticles in the fight against cancer*

Imaging technologies and therapy are both important approaches to fighting cancer. Combining those two approaches is one of the goals of the PRESMITT project. In achieving that ambitious goal, tiny gold rods on a nanoscale are playing a crucial role. Antibodies linked to nano-particles attach themselves to the cancer cells. Photoacoustic technology then brings those nanoparticles – and with them the tumour – into view. The generation of heat that is required for this process can also be used to destroy the cancer.

"The choice of gold stems the fact that gold is inert and theoretically non-toxic," says Prof. Dr Ton van Leeuwen of the Clinical Applications of Biomedical Optics research group at the University of Twente. "Moreover, the particles need to be made of metal. Metals characteristically have a very high light-absorption coefficient, and that property is necessary for an optimal contrast effect when it comes to imaging. The contrast effect when using metals nano-particles is far superior to that obtained with the pigments currently used as markers."

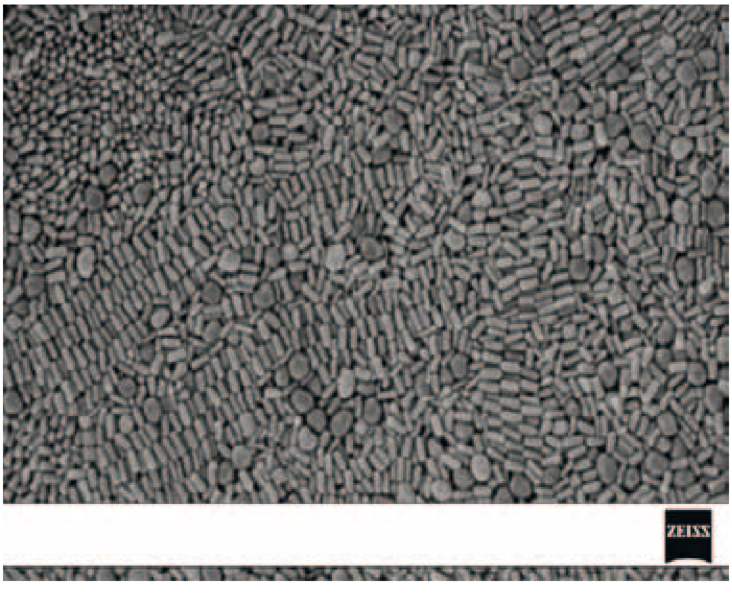
Rod-shaped solution

The advantage of using nanoparticles as markers is that they can be built up to have exactly the required optical properties. Van Leeuwen: "Those properties are an optimal scattering of light and the absorption of the desired colour of light. It's a good thing that we can make the necessary adjustments, since a globe-shaped gold particle would absorb mainly green light. By adjusting the form of the particle, it is possible to achieve an absorption peak in red or infrared. Why is that important? Just try shining a pocket torch into your hand: green and blue light is absorbed; only red goes through. With red light we can penetrate much deeper into the tissue." The choice for rod-shaped particles is what makes that possible. Van Leeuwen explains: "In the interaction between the frequency of the light and the reflection of the nanoparticles, it's all about their resonance. Rod-shaped particles have both a short axis, which means they have a rapid resonance (a high-resonance frequency), and a long axis, which causes a low-resonance frequency. My colleague Srirang Manohar is working on developing nanorods of the right dimensions to ensure an optimal absorption of red light and thus a maximum contrast effect in the imaging."

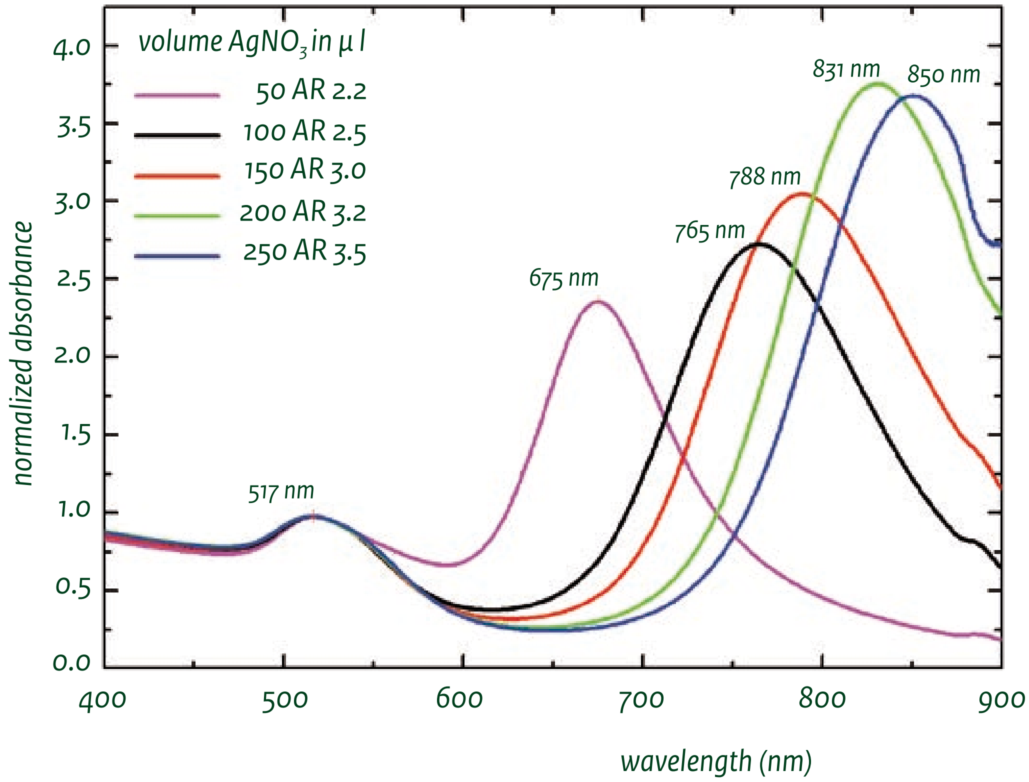
The advantage of using nanoparticles as markers is that they can be built up to have exactly the required optical properties

Photoacoustics

Yet none of this explains how the gold nanorods can find tumours. Van Leeuwen: "In fact, they can't. It's the antibodies to which the nanorod particles are linked that are capable of doing that. That way, you create a marker that remains attached to a specific cell, in this case a cancer cell. To be able to detect those markers, we make use of photoacoustic technology." This technology is already being used for the detection of gases, among other things. It is based on the principle that substances transmit sound waves when they are heated. "We use a light source that penetrates the body as deeply as possible. A laser source takes care of the necessary heating of the particles. We then pick up the reflection of the nanoparticles that are linked to cancer cells by means of antibodies. The reflection is received in the form of sound, which reveals the location of the tumour."



Electron microscopy photo of gold nanorods. The ratio of the long and short axes (aspect ratio, AR) influences the optical properties of those particles.



The figure shows that as the AR increases, the peak of maximal absorption shifts towards the infrared.

The heating of the nanoparticles that is required for the imaging can also play a role in destroying cancer cells

Destroying cancer cells

The heating of the nanoparticles that is required for the imaging can also play a role in destroying cancer cells. Van Leeuwen: "It is a question of heating the particles for a certain period to a temperature above 43°C but well below 100°C. We still need to investigate which strategy will lead to an efficient destruction of the cancer with the least damage to the surrounding tissue."

The parties involved in PRESMITT will also be further developing photoacoustics.To achieve their objective, they will need to further investigate the interaction between the light and the nanoparticles, for example. Van Leeuwen: "We are really only just at the beginning. We still need to determine any influence that the environment might have on the optical properties and to rule out the toxicity of the nanoparticles. But if we succeed in combining imaging with therapy, that would obviously be a very attractive proposition."

Participants:

- University of Twente
- Erasmus Medical Centre
- ESAOTE Europa
- Luminostix BV

Contact:

F.J.M. Damhuis
T: +31 (0)53 489 40 19
E: f.j.m.damhuis@utwente.nla

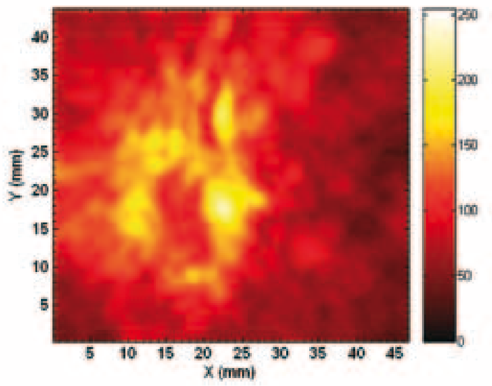
Project number: IPD083374
Project name: Hympact: Hybrid mammography using photoacoustic computed tomography
Goal: accurate detection of breast cancer using photoacoustics

The Twente Photoacoustic Mammoscope PAM 1.

HYMPACT for tumour detection: *Listening to breast cancer*

The existing technologies for detecting breast cancer are not entirely adequate. In the worst case, they can even lead to an incorrect diagnosis. The partners in the HYMPACT project are working on technology that would improve detection. To that end, they are using light, rather than X-rays or ultrasound. In connection with the HYMPACT project, the Biophysical Engineering research group at the University of Twente is doing research that will lead to a second-generation prototype for photoacoustic mammography.

For decades, doctors have been using X-ray photography and echoscopy to look inside the human body. Magnetic resonance imaging (MRI) was later added to that toolkit. Those technologies make it possible to diagnose for instance breast cancer at an early state. But they still have fundamental problems, says Dr ir Srirang Manohar of the Biophysical Engineering research group at the University of Twente: "With each of those technologies it is still very difficult to see the difference between healthy tissue and tumour tissue. As a result, a doctor might overlook a tumour or diagnose cancer where there is none. That could sometimes lead to the death of a patient or to an aggressive treatment being prescribed for someone who is in good health. A additional disadvantage of X-ray mammography is the carcinogenic radiation." Together with other partners, Manohar and his colleagues are developing a device that will be able to localise tumours accurately without harmful radiation. It makes use of both light and ultrasound.



Photoacoustic image showing a ring-shaped surface caused by blood-vessel growth around a breast tumour. This image was made at a depth of 12mm from the breast surface as measured using the PAM 1.

Photoacoustics

"That may sound strange," Manohar admits. But the underlying principles are relatively simple: "The device transmits laser-light pulses of five nanoseconds. When one of those touches a haemoglobin molecule, that molecule will generate heat. If we shoot light pulses at a piece of tissue containing a lot of haemoglobin, thermal expansion will take place. That causes vibrations in the ultrasound spectrum that an echograph can pick up. Human tumours grow relatively quickly and require a considerable amount of oxygen and nutrients. That is why there are always a lot of blood vessels in and around a tumour, which means they contain more haemoglobin than healthy tissue. On that basis, this device will enable us to localise tumours." This principle has been known since 1995 and some laboratory instruments are already making use of it. Manohar: "But we are among the first to be capable of conducting measurements on patients." The researchers tested the first prototype on six breast cancer patients. This resulted in high-resolution images that clearly revealed the tumours. Manohar: "We presented those results to NL Agency with the promise that they could be much better yet in a new device." Photoacoustics works better than normal optical measurements, says Manohar: "Just try shining the beam from a laser pointer through your finger. Human tissue scatters the light such that you can only see a red glow and no image of the bone. The resolution is inadequate. With ultrasound, you get much less scattering, so you can expect high resolutions. That is why photoacoustics makes use of the advantages of both optical imaging and echoscopy."

Developing a device that will be able to localise tumours accurately without harmful radiation

Impression of the instrument under development in the HYMPACT project (image: Heike Faber, University of Twente)

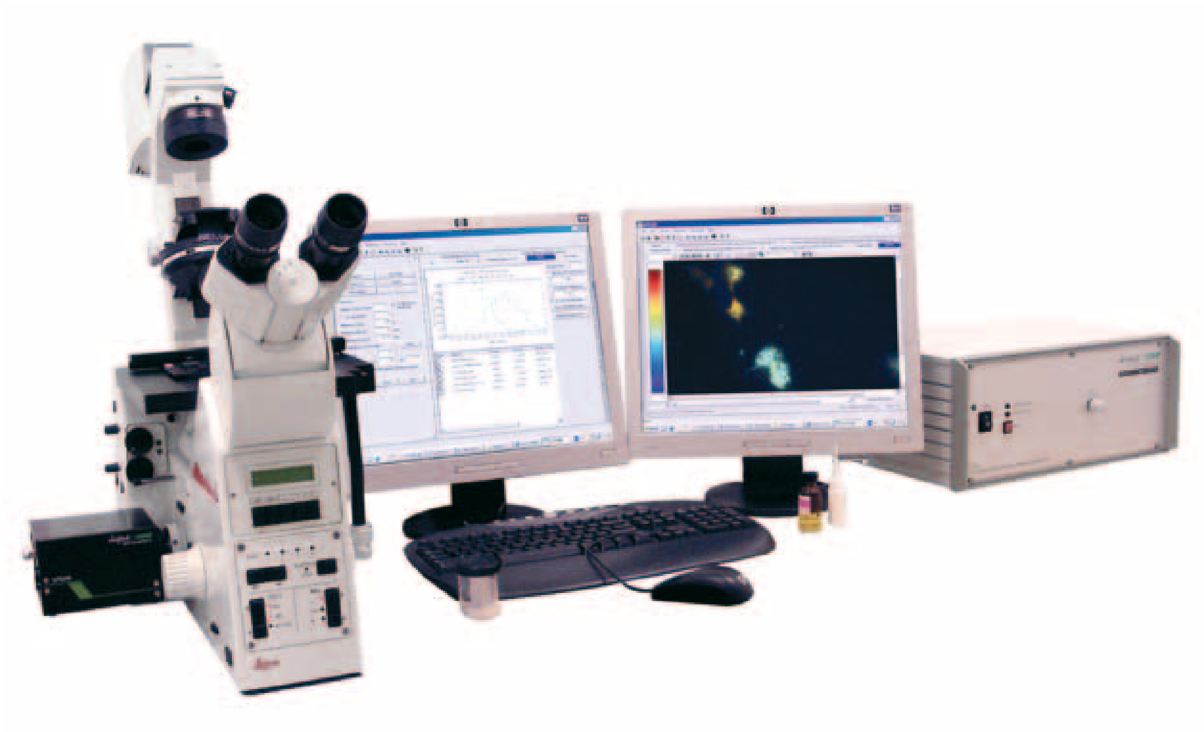
Optical needles

The new device makes use of computed tomography (CT) geometry, which images a slice of the inside of an object using multiple projections encompassing the object. The first prototype could only image one projection. Manohar: "The new device will enable us to achieve higher resolutions. As we still know so little about the optical properties of breast tumours, the optimisation still has a long way to go. Which laser wavelengths will provide the clearest images? What is the bandwidth within which ultrasound signals
will indicate a tumour? We still don't know. To refine this technology, we still need to collect a lot of optical data. Doctors at Medisch Spectrum Twente are now going to be using optical needles. Those are optical fibres within a biopsy needle, developed by project partner Luminostix. Using those needles, the doctors will be measuring the spectrum of breast tumours. That quantitative analysis will result in the data we need to provide our device with an optimised laser." One disadvantage of the first prototype is that patients have to lie still for three-quarters of an hour. Manohar: "We want to reduce that to several minutes by developing a rapid and sensitive ultrasound detector. Our project partner Oldelft is currently working on that. Once the development of the device has been completed, there will be large-scale clinical trials at Medisch Spectrum Twente. We will be testing our device there on breast cancer patients. The more data we collect, the better we can make the device."

Ultimately this should lead to an additional instrument, alongside X-ray and echo equipment. Using those in combination will enable even earlier detection and better diagnoses. Manohar: "Moreover, the ultrasound detector we are developing will be much more sensitive than the current models. The laser will also be more compact and more robust for clinical applications. So this project is leading to a number of nice spin-offs."

Participants:
- University of Twente
- Erasmus Medical Centre
- Oldelft
- Luminostix
- Medisch Spectrum Twente

Contact:
Dr ir S. Manohar
T: +31 (0)53 489 31 64
E: s.manohar@tnw.utwente.nl



Project number: IPD083412
Project name: MEM-FLIM: Modulated electron-multiplied all-solid-state camera for fluorescence lifetime imaging
Goal: to develop a new chip-sized detector for fluorescence lifetime microscopy

FLIM microscope

Better imaging possibilities for cell biologists thanks to FLIM chip

With a fluorescence lifetime imaging microscopy (FLIM) system, researchers can follow in real time the interactions that are taking place between proteins in a living cell. That is particularly useful, says Prof. Dr ir Ian T. Young, chair of the Department of Imaging Sciences and Technology at the Delft University of Technology. But the current systems have certain drawbacks. He wants to resolve those by replacing the complex camera outfitted with an image intensifier in the current FLIM systems by a simple chip.

FLIM is a microscopy technology that is widely used by cell biologists. Like fluorescence microscopy, FLIM takes advantage of the fact that some molecules are fluorescent: when they absorb light, they transmit part of that light back at a longer wavelength. A conventional fluorescence microscope measures the intensity of that radiation. A researcher can add a fluorescent antibody, which will bond with a specific protein, to a biological sample. Using the fluorescence microscope he or she can then determine the concentration and the distribution of that protein.

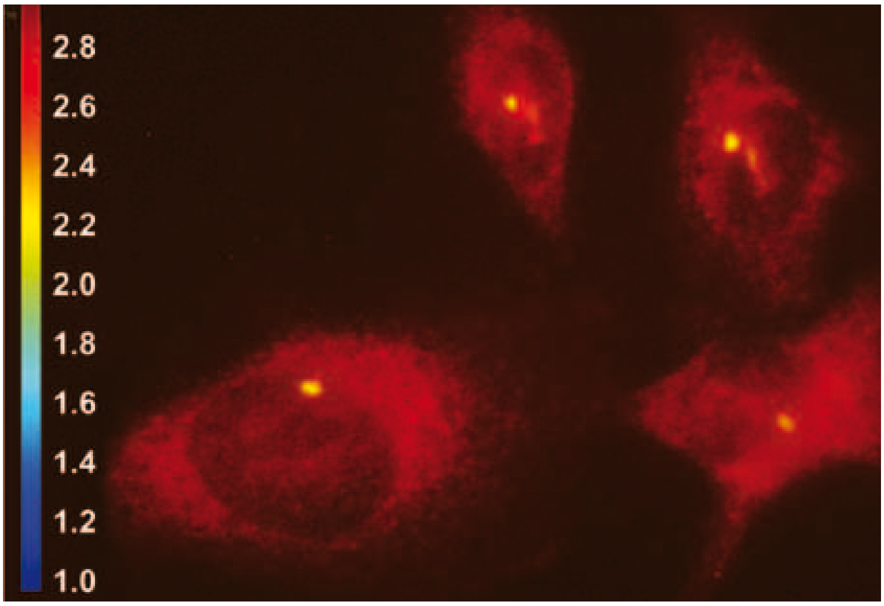
"The aim of the project is to prove that solid-state FLIM technology works"

FLIM goes a step further. The microscope lights up the sample and fluorescent molecules in the cell absorb that light. A molecule that has absorbed a photon will radiate that back after a few nanoseconds as light with a longer wavelength. In that way, the sample under the microscope produces a kind of 'light echo': the fluorescence follows the light source with a small delay. FLIM measures that delay, and the fluorescence lifetime can be derived from that. The latter refers to the time that fluorescent molecules need on average to fall back into their original state when transmitting a photon. In other words, FLIM provides an image of both the intensity of the fluorescent molecules and, for each pixel, their lifetime in nano-seconds. By linking two types of well-chosen fluorescent molecules to two different proteins, you can use FLIM to show whether those two proteins are interacting with each other and where that is taking place in the cell. That is because such an interaction will lead to a change in the lifetime.

All in one go

"The current FLIM microscopes work just fine," Young says, "but there is certainly room for improvement. A FLIM microscope has a camera incorporating CCD technology with an image intensifier tube. The intensified CCD camera has several disadvantages. The system needs high-frequency amplifiers and high-tension cables capable of providing several kilovolts of power, for example. In addition, the image intensifier tube is sensitive to overexposure. What is more, it is expensive: a FLIM system costs over €100,000, not including the microscope. Moreover, the properties of the image intensifier and the way it is linked to the camera's image sensor bring about noise." Anyone who manages to do something about even one of these drawbacks will be improving the FLIM microscope, says Young. "But it is better to resolve all of those problems in one go. And that is what we intend to do." Together with the other project partners, Young is developing a FLIM system in which the intensified CCD camera will be replaced by a chip. Young: "That intensified CCD camera is a complex device with various different optical and electronic components. A chip is solid-state, smaller and lighter, works with low voltage and is only half as expensive." That means the technology will be suitable for other, eventual applications such as endoscopy. Young: "With the current FLIM cameras, that is completely inconceivable."

But the image sensor for a FLIM microscope needs to meet a number of conditions. For instance, it needs to be able to measure at a frequency of 40 MHz or higher with the utmost accuracy. Young: "There can't be too much noise. Heat gives rise to thermal noise, so the chip needs to have a good energy balance. Nor may there be much electronic noise, since that would lead to disturbances in the image." Project partner Dalsa is testing chip designs in a virtual environ-ment to determine which variables are significant in terms of minimising noise.



FLIM image of HeLa cells with FRET

Giant pixels

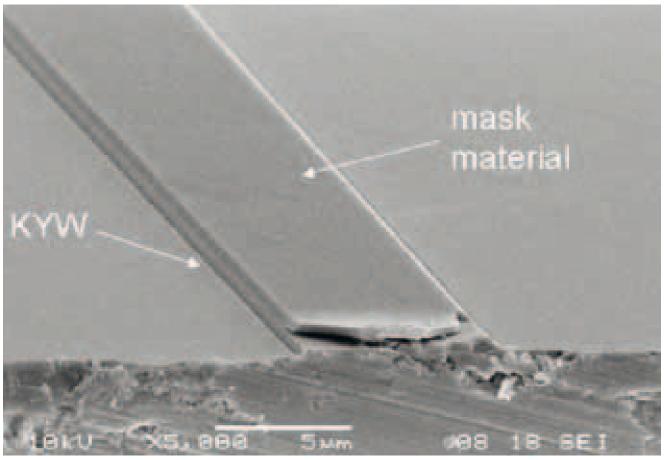
Young's group is primarily concerned with the software and the hardware around the chip. Young: "The hardware consists of the printed circuit board (PCB) on which the chip is integrated together with the power supply and the cables, for example. This hardware layout is also crucial for the prevention of noise and disturbances."In developing software that can analyse the signals from the camera, the researchers start with the algorithms for the current FLIM systems that were developed and produced by Lambert Instruments. They then adjust those to achieve an optimal system. The biggest challenge in that regard is the fact that one pixel is much larger than one molecule, say Young. "A signal that enters a pixel can actually be a combination of different signals. The software needs to be able to unravel those."

The aim of the project is to prove that solid-state FLIM technology works. Young:"We are making a prototype microscope for application in our own lab, but that is not suitable for mass production. We will soon be building a new chip and a conventional camera on one and the same microscope in order to be able to compare them. Proving that our FLIM technology is better will be more convincing than simply claiming that."

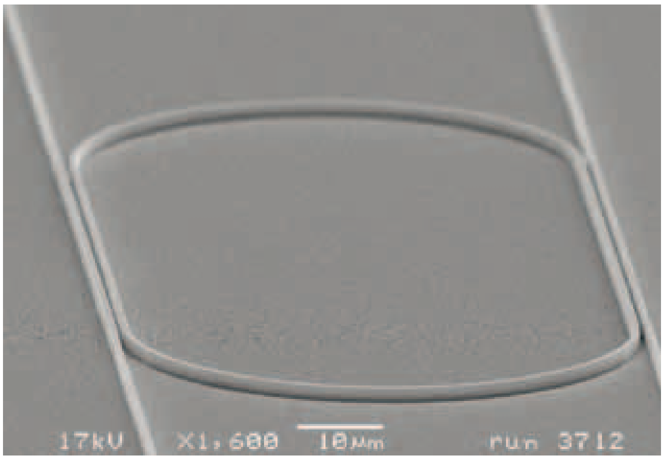
Participants:

- Delft University of Technology
- Dalsa
- Lambert Instruments
- The Netherlands Cancer Institute

Contact:
Prof. dr ir I.T. Young
T: +31 (0)15 278 53 90
E: i.t.young@tudelft.nl



SEM photo of a channel waveguide



On-chip laser cavity based on a ring resonator

Project number: IPD083385
Project name: On chip integrated NH_3 human gas sensor
Goal: to develop a new detector for ammonia gas sensing

Manageable gas detector *thanks to shortwave laser*

Detecting the presence of certain gases in exhaled human breath is a relatively simple way to find indicators for medical disorders. The equipment that doctors use for that purpose is bulky and expensive, however. Prof. Dr Markus Pollnau of the Integrated Optical Microsystems research group at the University of Twente is developing a small and inexpensive detector for ammonia, which can be a sign of kidney problems. What is the secret? A laser integrated on a chip, optical waveguiding and a photoacoustic cell.

More and more often, hospitals are using devices that detect the presence of certain gases in low concentrations in the air that people exhale or that they secrete via their skin. The presence of certain gases indicates such conditions as gastric ulcers, lung cancer and kidney problems. While this method only detects indicators and is not specific enough for making diagnoses, the fact that it is simple and non-invasive is a major advantage. Even so, there is certainly room for improvement, says Pollnau.
"The current devices are quite expensive. A hospital might well be able to afford one of them, but a general practitioner surely cannot. The detector is also bulky and heavy: you need to bring the patient to the device; doing it the other way around is not an option."

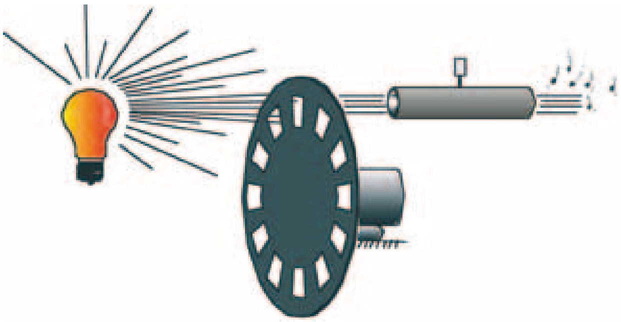
"The detector will be capable of detecting smaller amounts of NH_3 than existing detectors can, and it will come in a manageable size"

Pollnau's research group is developing a detector for ammonia, NH_3. Pollnau: "If the air that someone exhales contains ammonia, that can be an indication that he or she has kidney problems. The lower the concentration of ammonia that you can detect, the greater your chances of detecting kidney problems at an early stage."
The detector will be capable of detecting smaller amounts of NH_3 than existing detectors can, and it will come in a manageable size.

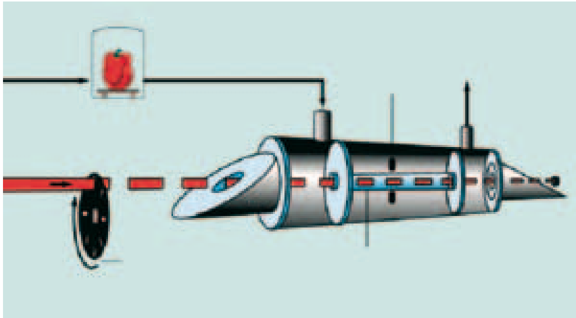
Listening to absorption

The detector that Pollnau's group is developing, together with the other project partners, has two important components. Pollnau: "The first is a solid-state laser. The active medium of the laser we are developing consists of a crystaline base material doped with thulium or holmium. The laser has a wavelength of 2μm. Doping is a method of providing a substance with impurities in order to change its optical properties." Pollnau: "Solid-state lasers are not new, but lasers that make use of these specific materials are. The project partners are aiming at 2μm, since NH_3 easily absorbs light from that wavelength. If the gas absorbs the light, it becomes warmer. That leads to thermal expansion of the gas."

The second most important component of the detector is what does the actual detection. Pollnau: "That component is a photoacoustic cell, a small acoustic space that contains the mixture of gas that we are most interested in. Thermal expansion leads to resonance in that space. By measuring that resonance, we can determine the concentration of the gas that we want to detect." In large part, the project will consist of adjusting the photoacoustic cell to separate the resonance patterns that indicate NH_3 from the inevitable noise in the cell. The laser will be integrated in a chip and optical waveguiding technology will link the light to the photoacoustic cell. Pollnau: "The resulting device will be small, lightweight and manageable."



Photoacoustic detection of gas traces.



Photoacoustic effect > the absorption of light leading to the generation of acoustic waves.

Testing in practice

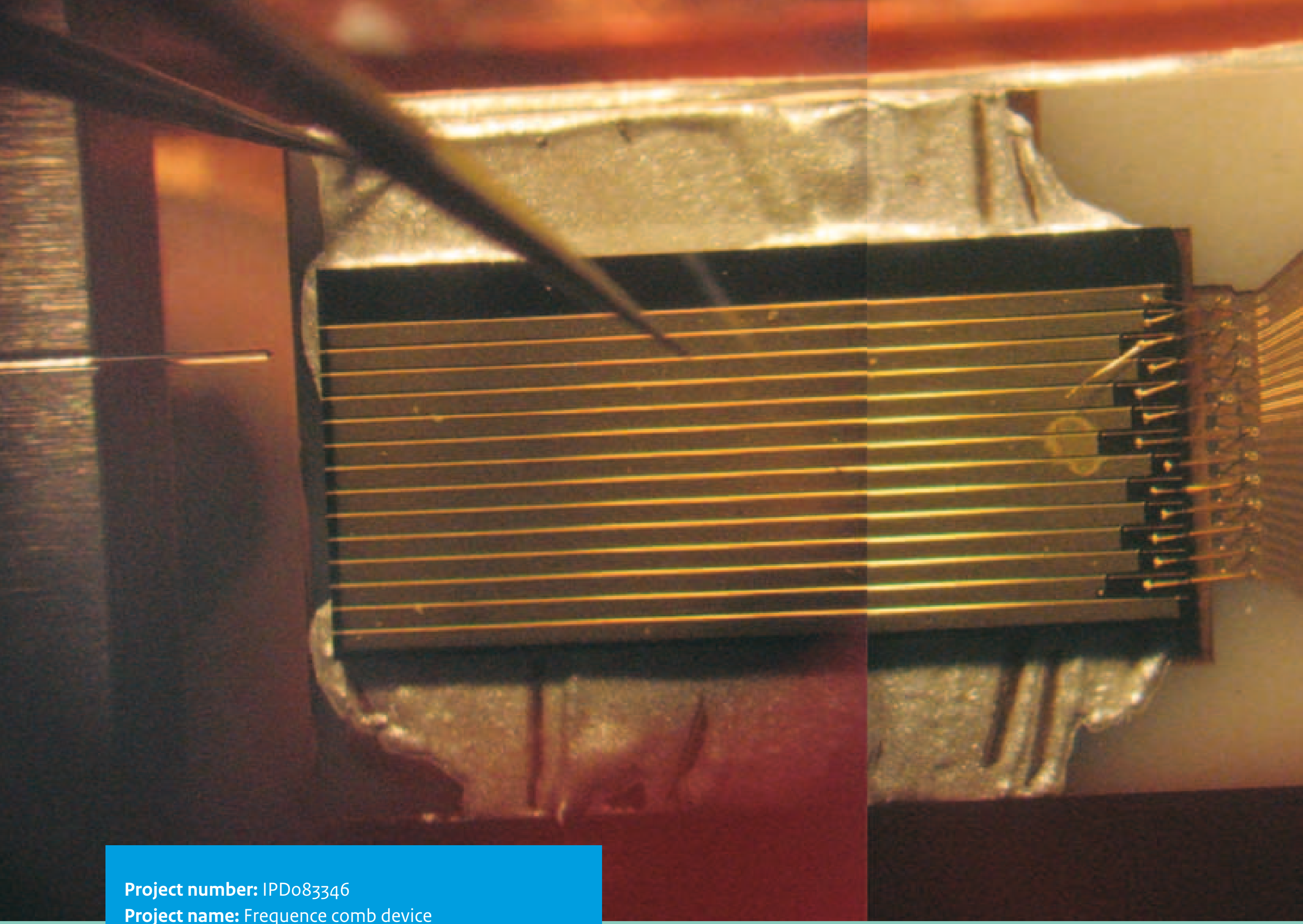
Once a prototype has been developed, it will first need to be tested by using it to measure known concentrations of NH_3. Subsequent clinical tests will need to show the extent to which the detector can be used for making diagnoses. Pollnau: "That will not only depend on the effectiveness of NH3 detection. Physicians already know of the connection between the concentration of NH_3 in someone's breath and certain physical disorders, but we still need to determine exactly what that connection entails." Whether or not the detector will be suitable for use in medical practice will depend on a number of factors.

Pollnau: "It will depend on the ultimate cost of the device, the efficiency with which it detects NH_3 and the usefulness of its detection results for diagnostics. But the project will not only be successful if it results in a marketable detector. Very little is yet known about the photoacoustic detection of low concentrations of gas by means of light with a wavelength of 2 µm. This project will lead to a considerable increase of knowledge in that area. And since this technology could also be used for non-medical applications of gas detection, that knowledge will prove particularly useful."

Participants:

- University of Twente
- Radboud University Nijmegen
- Sensor Sense BV
- Lionix BV
- Utrecht Medical Center

Contact:
Prof. dr M. Pollnau
T: +31 (0)53 489 10 37
E: m.pollnau@ewi.utwente.nl



Project number: IPD083346
Project name: Frequence comb device
Goal: to develop a very stable miniaturised compact pulse laser for metrology and non-linear microscopy

Photo of an indium phosphide chip with 14 quantum-dot lasers, seen here as horizontal lines on the 9mm chip.

Compact pulse laser *for a wide range of applications*

For new space missions, an extremely compact and accurate device for measuring distances in a vacuum is desirable. At the same time, cell biologists long for better microscopy in living cells. They are particularly interested in having the capability to distinguish specific substances in order to observe processes – without having to use potentially disrupting tracers and markers. Both of these highly divergent ideal applications will require the same basis: a very compact source for short-pulse lasers.

Over the past few years, short-pulse lasers with a highly stable output have undergone a spectacular development. So-called mode-locked lasers emit light pulses with a highly constant frequency. The time between the short pulses can be regulated so accurately – stabilised – that they are even better at measuring time than an atomic clock. The regularity of the pulses over the passage of time means that the optical spectrum of the laser consists of a large series of wavelengths that together have an accurately determined distance in light frequency: the 'frequency comb'.
Dr Erwin Bente of the Opto-Electronic Devices group within the Electrical Engineering Department at the Eindhoven University of Technology: "This creates possibilities for measuring distances in a vacuum. The extremely accurate time measurements form the basis for measuring distances.

The Eindhoven University of Technology hopes to have the core of an extremely small and light-weight telemeter for space travel

The essence is simple: the object upon which a laser pulse is emitted will bounce back a reflection. The duration of the reflection determines the distance to the object. The actual application now under development is more complex, however. For that, we are working with a split bundle. One of the two split signals goes directly to the object, while the other reaches it via a reference arm. Both pulses come together again after reflection. By analysing both the overlap and the difference, we can determine the time – and thus also the distance – to a fraction of the pulse length."

Aside from the potential benefits for space travel, this accurate way of measuring distance is also promising for the growing number of high-tech processes that take place in a vacuum, such as EUV lithography. Bente: "Unfortunately, the current short-pulse laser sources still consist of 19-inch racks, supplemented by racks full of electronics for stabilisation. That is fine for lab setups, but not for space travel; every kilo that is sent into the universe costs a fortune. But aside from that, the lasers would never survive the launch."

That is why miniaturising through optical integration is the motto. In close collaboration with the Laser Centre at Amsterdam's Vrije Universiteit, which is specialised in extremely accurately stabilised lasers, the group in Eindhoven has begun developing lasers for that purpose. An indium phosphide chip holding 14 short-pulse lasers of 9mm is proof that the project is already well on its way. With this laser source, the Eindhoven University of Technology hopes to have the core of an extremely small and light-weight telemeter for space travel.

Microscopy

Such a laser source is equally as interesting for microscopy, but its application in that field will require the development of a more extensive optical circuit behind the laser. In the 'Frequency Comb Laser Devices' project, the University of Twente is involved as both a developer and a user of microscopic technologies, partly to be able to indicate how the university's own researchers would eventually like to apply the laser. Toptica GmbH in Germany is in the project as a laser manufacturer. For certain studies, biologists currently use confocal laser scanning microscopes (CLSM), which focus a laser source continuously on a sample, to which special markers have often been added. The sample absorbs the laser light entirely, and only part it is bounced back to the microscope. To get a sharp image of the desired selection of the sample the CLSM makes use of a pinhole – a tiny diaphragm – that only allows the reflection from that part of the sample that is in focus. Bente: "This has a number of drawbacks. Since the entire sample absorbs light and the detection is inefficient, the procedure requires a lot of laser light. The required amount of laser light makes the sample so warm that it precludes research on living cells. The necessary markers form another disadvantage."

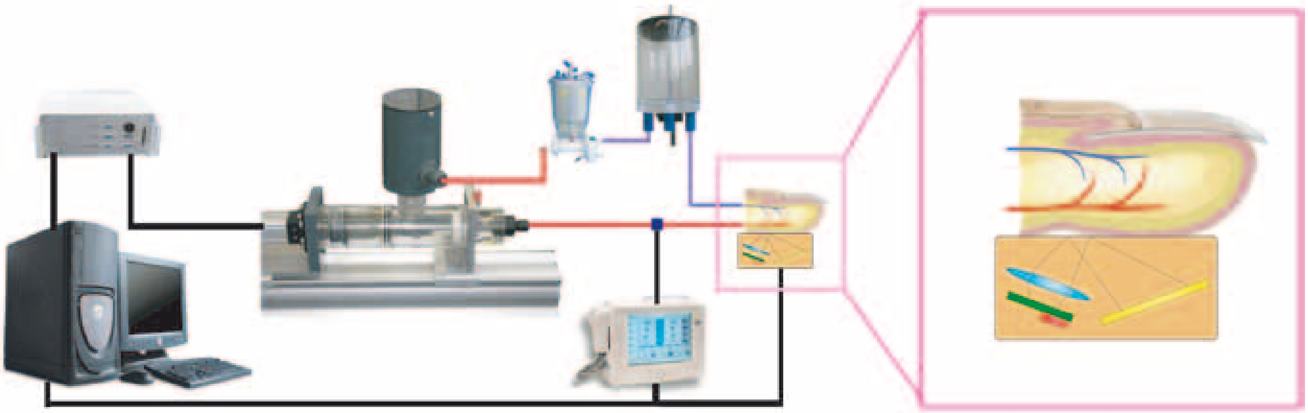
The alternative is a nonlinear microscope. With such a device, the laser source only generates light at the focal point, and the sample only absorbs light at that point, which means little heat is generated. That brings working with living cells within reach. And by varying the sample over three axes with regard to the lens, it is possible to make a 3D image. Bente: "Only the short pulses from a 'mode-locked' laser have sufficient intensity in the focus to light up the sample. However, both the microscope and the sample itself distort the laser pulses. To form an optimal image of a certain point, a so-called pulse former needs to correct the pulses. And for a 3D image, that entails constantly adjusting the correction. Such a pulse former separates the laser light into individual frequency lines: the 'teeth' of the frequency comb. The pulse former monitors and corrects the phase and amplitude of each of the fifty lines separately, after which all of the corrected lines come together again. Normally speaking, this requires a bulky piece of optical equipment. With this project we intend to enable the same process using two semiconductor chips." The Enschede-based company Xio-Photonics is developing one of those: a chip using silicon technology that will separate all wavelengths from the laser light into different channels. The Eindhoven University of Technology and the Eindhoven-based company Cedova have taken it upon themselves to develop the second chip, made of indium phosphide. That chip will intensify the light by wavelength and set the desired phase. Bente: "One thing we still need to find a solution for is the transfer of the fifty separate light signals from one chip to the other. That has never been done in practice and it will demand a robust and stable positioning."

Favourable perspectives

Not only will the version with two chips be smaller, but thanks to the infinitesimal distances on a chip, the modulation will also be faster than you could achieve with optics. The modulation speed is in the order of nanoseconds, which makes it possible to give each pulse a distinct phase setting. The variation in wavelength difference between laser pulses creates interesting possibilities and the University of Twente is studying those now. Bente: "Certain molecules in a sample will react to a certain pulse form. This means that substances or processes in a sample can be imaged selectively, without any need for marker substances for tracing. This is a major advantage, since such marker substances can disturb the sample. If we manage to meet the challenges, there will be even more advantages. For our technology you will be able to apply optics in the 1500nm to 1600nm range, which is already widely used in telecommunications. That means, for example, that objectives would be available for that at a reasonable price."

Participants:
- Eindhoven University of Technology
- VU University Amsterdam
- Lionix BV
- University of Twente
- Toptica Photonics AG
- Cedova BV

Contact:
Dr E.A.J.M. Bente
T: +31 (0)40 247 51 06
E: e.a.j.m.bente@tue.nl



Schematic diagram of biospeckle interferometry research

Project number: IPD083359
Project name: HIP: Hemodynamics by interferometric photonics
Goal: a new technique based on biospeckle interferometry for ambulant monitoring of blood values

Ambulant monitoring of blood values *using biospeckle interferometry*

By now, the ageing population is no longer a vague notion; it has become a visible reality. Robust ambulant medical measuring instruments can contribute towards keeping the growing need for care affordable – and improving that care at the same time. In that connection, the parties within the Hemodynamics by Interferometric Photonics (HIP) project are working on a compact device for robust ambulant oxygen-saturation measurement. An interesting byproduct of their work is a hybrid software-and-hardware testing platform that can serve as a model of part of the human vascular system. The idea is that this platform can be used for a broader range of applications.

Among other consequences of the demographic development is a growing need for care. As society ages – assuming nothing changes – cardiovascular diseases, among others, will take an even larger human and financial toll than they already do. So something certainly needs to change. Not only is the demand for care increasing, but the care being given also needs to be both better and less expensive. This list of demands is weighty, but in many cases not unfeasible. One of the keys will be to turn care that currently requires costly hospitalisation into ambulant care. While blood pressure and pulse can easily be monitored at home nowadays, that is not yet the case when it comes to things like tissue perfusion and blood oxygen saturation. Other kinds of readings even require invasive interventions.

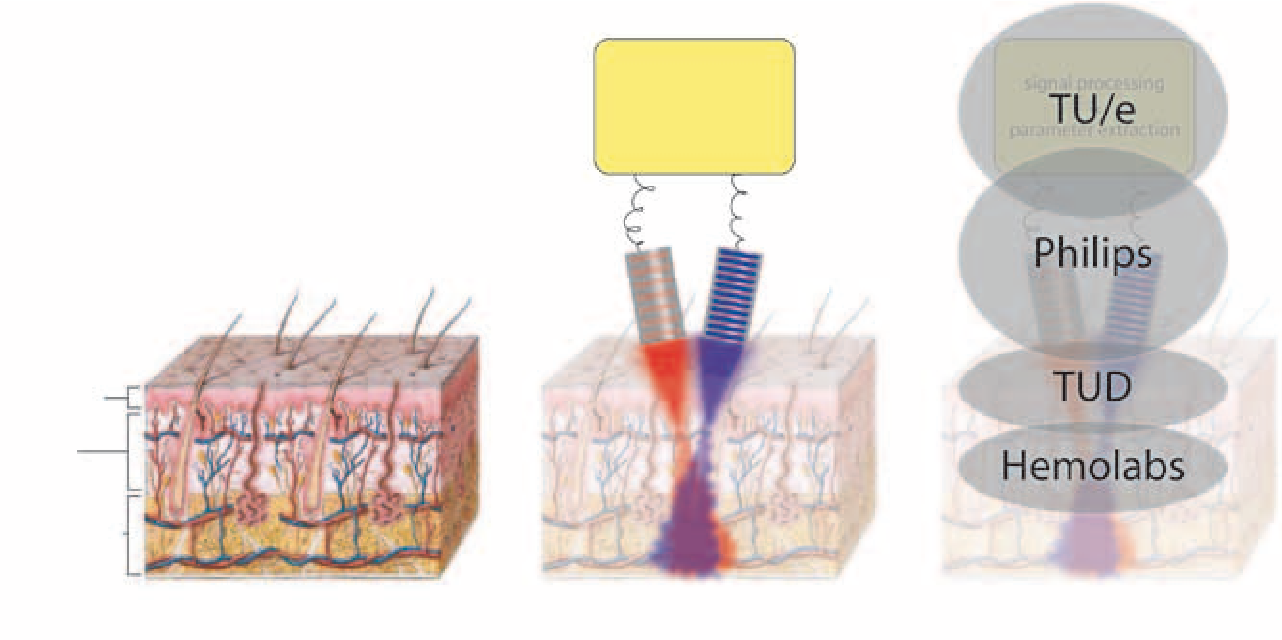
The equipment for measuring oxygen intake (= saturation = pulse oximetry = SpO_2) is still too large, too delicate, too expensive and too sensitive to interference. Moreover, it requires too much energy for ambulant application. The HIP project wants to demonstrate that reliable ambulant saturation measurement is possible in principle. One of the most important tasks in that respect is to minimise the occurence of motion artefacts. Those are disturbances in the measuring signal resulting from patient movements. To reach that goal, the HIP project will start by adding laser Doppler technology – more precisely: biospeckle interferometry (BSI) – to the current sensor systems. A coherent (laser) light bundle is shone on a surface, in this case skin or tissue. Interference from the emitted light waves onto and into the skin causes a speckled pattern. The reflection, which can be detected by a CMOS image sensor, thus forms the basis for useful information about the area that the laser source shines on. That information might include the fact that the data being measured by the pulse oximeter at a given moment is incorrect due to movements. BSI is used in that way to filter out motion artefacts from the saturation measurements. In the definitive application, a little clip containing both sensor systems, SpO_2 and BSI, could be slid onto a fingertip, for example.

Demonstrating the principle

"The basic technical principle is already known," says Dr Jeroen Veen of Philips Research in Eindhoven. "Laser diodes and CMOS sensors are both available in cost-effective designs." But putting together a practicable combination of SpO_2 and BSI is no easy task, he adds: "At this early stage, for example, we are still working with two separate, sizable instruments. We need to manage to unite both of those within a compact, robustly working combination device. The first goal of the project is to demonstrate that the principle of this sensor integration will work. Everything depends on our capability of integrating everything into a small, finger sensor, which could then be supplemented by a small case that you could place on a bedside table, or even by a watch-like device. It will mean developing and testing various different configurations with a laser diode and a CMOS until we have a reliable point of departure."

The second task is to develop software with algorithms that will translate the sensor signals into meaningful medical information. Veen: "The BSI signal forms the input, but the software-based translation of that can make a significant contribution to the robustness of the application with regard to motion and disruption. Two PhD students will be working in those areas this year to make that happen."

The HIP project wants to demonstrate that reliable ambulant saturation measurement is possible



The BSI project is a nice example of open innovation

Testing platform

Once an application has been developed, it will still need to be extensively tested. To that end, Hemolab, an Eindhoven University of Technology spin-off, is developing a testing platform within the HIP project, which will be an independent product component of the valorisation plan. “It's very difficult to define a standard way of measuring subjects for crucial physiological values,” Veen clarifies. “That is why, to complement the testing of humans, Hemolab is developing a hardware-and-software model of a part of the human vascular system.” It concerns a microvascular structure with little pumps and channels in a tissue phantom. Veen: “We hope it will stimulate a number of aspects of light propagation thanks to the added software. You install the sensor on the model, simulate motion and then systematically work out what kind of influence the motion of the sensor in relation to the skin has on the quality of the SpO2 sensor measurements. That will help us better understand the role of motion disruption. And that knowledge will allow us to finetune the BSI as a correction of that, with the help of algorithms.”

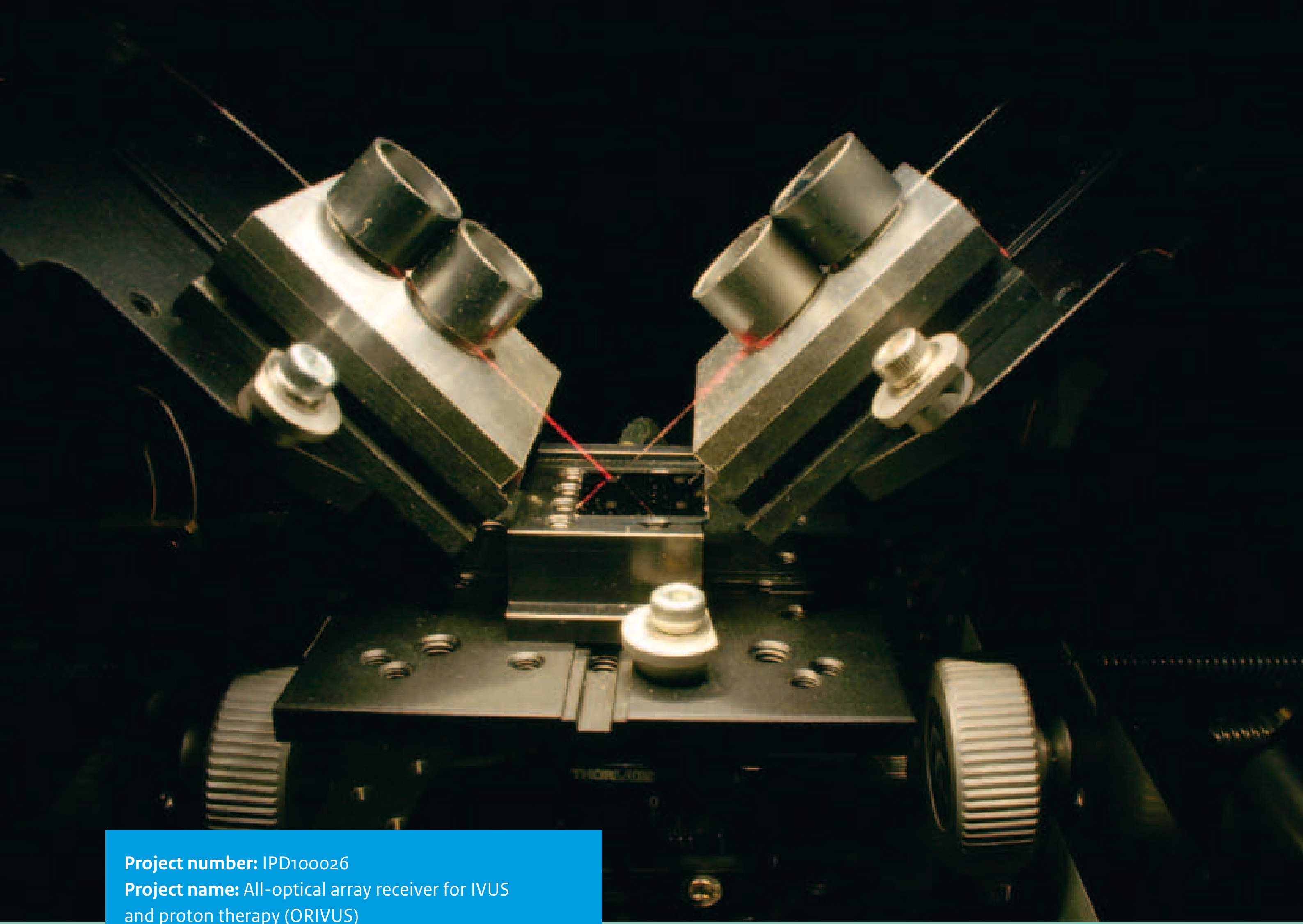
Adding functionality

As a prospect for the future, according to cautious expectations, BSI should also be able to add functionality. Veen: “The current saturation measurements indicate which percentage of the red blood cells are carrying oxygen. Moreover, pulse oximeters also determine the patient's pulse, and the amplitude gives an indication of the saturation of the tissue. We think the combination of SpO_2 and BSI, which maps out the local circulation, will eventually provide a more conclusive perfusion index than the current combination of pulse and saturation.” But that is something for later. Veen: “First we need to demonstrate the effect. If we can succeed in developing a sound correction methodology, we will already be well on our way. That would lay the basis for miniaturisation to a portable little device and, after continued development, for an application that would provide more and better information than the current institutional equipment.”

Participants:

- Delft University of Technology
- Eindhoven University of Technology
- HemoLab
- Philips Research

Contact:
Prof. dr H.P. Urbach
T: +31 (0)15 278 94 06
E: h.p.urbach@tudelft.nl



Project number: IPD100026
Project name: All-optical array receiver for IVUS and proton therapy (ORIVUS)
Goal: to develop a small all-optical array receiver - a photonic NanoPhone - based on integrated nanophotonics

Setup for optical characterisation of the acoustic sensor

Photonic NanoPhone
for proton therapy and IVUS

The photonic NanoPhone, an all-optical array receiver containing several hundreds of small and sensitive yet inexpensive acoustic sensors, will be beneficial to at least two important medical applications. In proton therapy, the NanoPhone will enable the monitoring and adjustment of both the trajectory and the strength of the proton beam during treatment. In intravascular ultrasound imaging, it will afford a much higher lateral resolution than conventional piezo-based sensors do. Moreover, since the NanoPhone will be insensitive to electromagnetic interference (EMI), it will also be suitable for use in an MRI environment. This research project will focus primarily on its application in proton therapy.

With the aim of stopping tumour growth, more than 50% of all cancer patients receive electromagnetic radiation therapy. However, estimates show that about 10–15% of the cancer patients in the Netherlands would benefit from proton therapy, since charged particles such as protons can be directed more accurately and with a more carefully regulated dose. “In the current form of proton therapy, the trajectory and strength of the proton beam are established beforehand, based on images from MRI or CT scans in combination with computer models,” says Paul Urbach, Professor of Optics at the Delft University of Technology and project leader of the IOP project ‘ORIVUS’. “However, since dose control is crucial to avoid damaging healthy tissue, it would be highly preferable to obtain direct feedback and make the adjustments during the treatment itself.”

“The acoustic sensors can be made inexpensively using existing CMOS mass-fabrication technology”

Blurred images

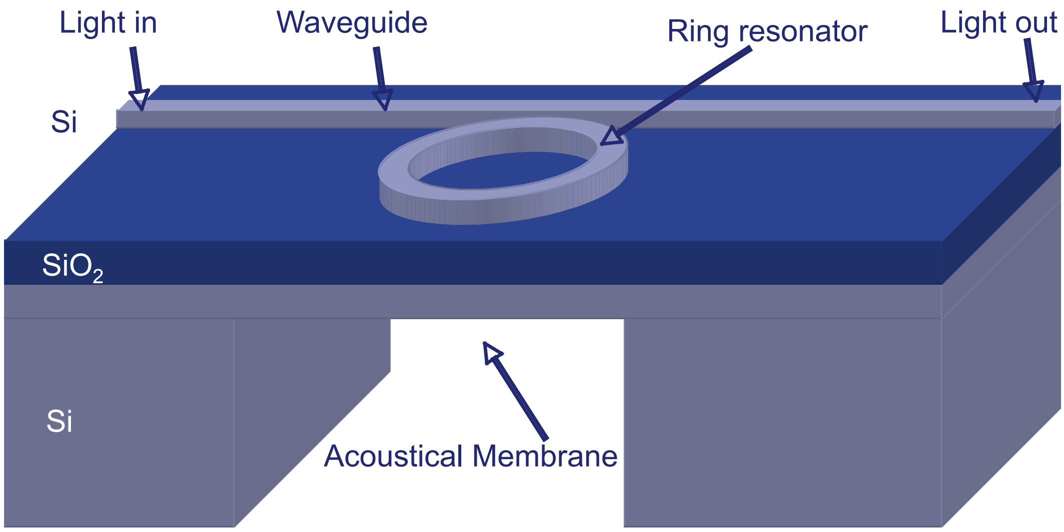
Fortuitously, the deposition of proton energy happens to generate a low-amplitude acoustic wave field. Paul Urbach: “Using an array of small but highly sensitive acoustic sensors, you can detect and measure that acoustic wave field with a high degree of accuracy. On the basis of images derived from the acoustic waves, a medical specialist can deliver the protons very accurately in carefully regulated doses.”

Another medical procedure that could stand to benefit significantly from the photonic NanoPhone is intravascular ultrasound imaging (IVUS). “In current practice, a cylinder-shaped probe is brought through the blood vessel to the heart to localise vulnerable plaque. But the resulting images do not have the desired resolution and are often even heavily blurred. Due to the patient’s breathing and the flow of blood through the vein, the catheter is continuously moving,” Paul Urbach explains. “Using many more sensors - several hundreds as is the case with the NanoPhone - will drastically improve the resolution of the images, since the acoustic waves can then be measured from multiple positions simultaneously.” Moreover, the all-optical system allows read-outs from an array of sensors using a single optical fibre.

Tailoring

The sensors in the NanoPhone are approximately 30 microns each and consist of a thin elastic silicon membrane with an integrated optical ring resonator on top. When hit by an acoustic wave field, both the membrane and the ring resonator will deform, causing a shift in the optical resonance frequency of the ring. That shift in frequency will be monitored by an external interrogator system and can be interpreted as an acoustic signal. “Using a large number of sensors allows you to determine the acoustic wave field much more accurately. Earlier research has shown that the sensitivity of such sensors is very promising,” says Paul Urbach. “On top of that, they can be made inexpensively using existing CMOS mass-fabrication technology. So the production price will not be a problem.”

To understand the influence of the acoustic wave on the deformation of the membrane and thus of the ring resonator, fundamental research is needed. The so-called elasto-optic effect has to be taken into account as well, since that also influences the frequency shift. By tailoring the design of the membrane and the shape, thickness and length of the resonator, the sensitivity of the sensor can be optimised. “It will take a substantial effort to model all these variables, but I have high expectations. Our PhD students are exceptionally qualified for the job.”



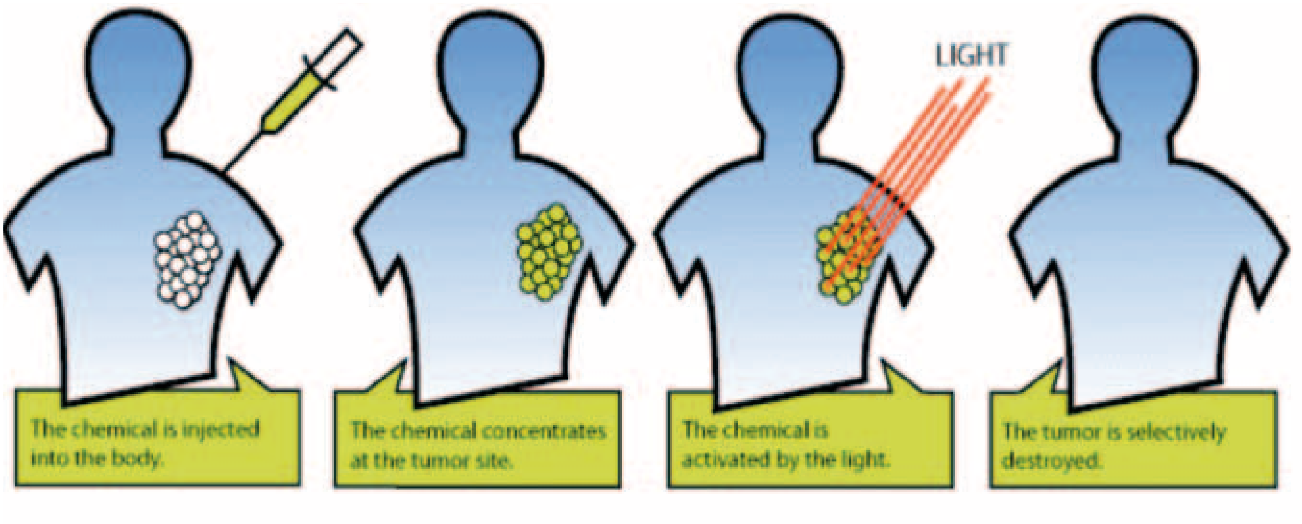
A possible configuration of a ring resonator on top of an acoustic membrane.

Non-destructive testing

The ultimate goal of 'ORIVUS' is to deliver a prototype of the detector, including data acquisition and data processing, and to validate the principle with preliminary tests.
To attain this ambitious goal, the Optics Research Group and the Acoustical Imaging & Sound Control Group of the Delft University of Technology are working together with the Nano-Instrumentation Expertise Group at TNO and the SMEs Technobis and HQSonics. In order to explore and test the possibilities of the NanoPhone in the medical field, the project will cooperate with Erasmus MC.
As TNO has extensive know-how in the field of integrated optical sensor systems, its contribution to the project will be essential. In connection with proton therapy, collaboration has been established with the Holland Proton Centre (HollandPTC). This centre is one of three initiatives that aim to offer proton therapy in the Netherlands. HollandPTC itself brings together the expertise of three highly respected medical centres, including the two largest cancer centres in the Netherlands. If all goes according to plan, the first patients will be able to receive proton therapy treatment in 2013.
The usefulness of the NanoPhone will however not be limited to the medical field, says Paul Urbach.
"The NanoPhone is a general acoustic detector that is both small and highly sensitive. That makes it also very suitable for the non-destructive testing of materials, especially in restricted or hostile environments such as oil and gas pipes."

Participants:
- Delft University of Technology
- TNO
- Technobis
- HQSonics
- HollandPTC

Contact:
Prof. dr H.P. Urbach
T: +31 (0)15 278 94 06
E: h.p.urbach@tudelft.nl



Principle of photodynamic therapy.

Project number: IPD100020
Project name: Image-guided and/or targeted photodynamic therapy using a combination of a new photosensitizer with upconverting nanoparticles (IMPACT)
Goal: to increase the clinical value of photodynamic therapy by ultimately developing a dedicated multispectral-camera platform for detection and treatmentnanophotonics

Selective and sensitive detection and treatment *of tumours with light*

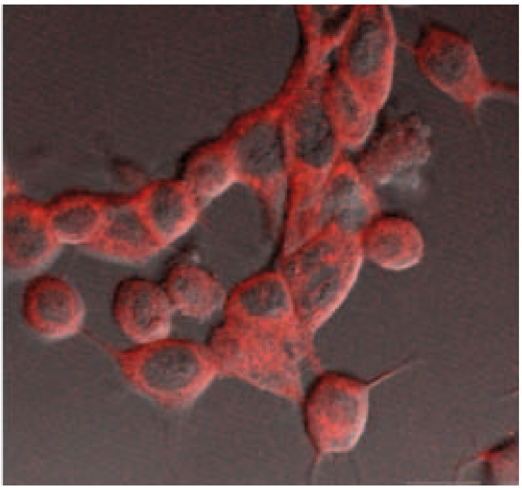
In the fast-developing field of cancer research, a recent and promising technique is photodynamic therapy: killing tumour cells with the aid of laser light. Although already used in clinical settings, photodynamic therapy is not without its side effects and limitations. The IOP project 'IMPACT' is developing techniques to make photodynamic therapy suitable for a wider range of tumours and to reduce its side effects. A major deliverable will be a combined detection and treatment device.

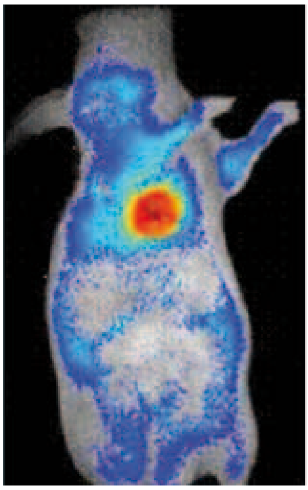
Being able to accurately differentiate between healthy tissue and cancer tissue is key in surgical oncology. The slightest differences in colour and structure can be indicative of diseased tissue. In making that distinction, surgeons depend heavily on their experience, their vision and their tactile sense. Estimations show that approximately 25% of patients have to return for a second operation to remove cancer tissue that was left behind. In the future, surgical procedures can be drastically improved by selectively staining the tumour using a tumour-specific fluorescent dye. That will make the tumour's boundaries clearly visible to the surgeon. "Image-guided surgical treatment will be a big step forward," says Clemens Löwik, Professor of Molecular Endocrinology and Molecular Imaging at the Leiden University Medical Center. "But even better results could be accomplished by killing the cancer cells using light, instead of surgery."

Injected nanoparticles "travel" through the body to the tumour

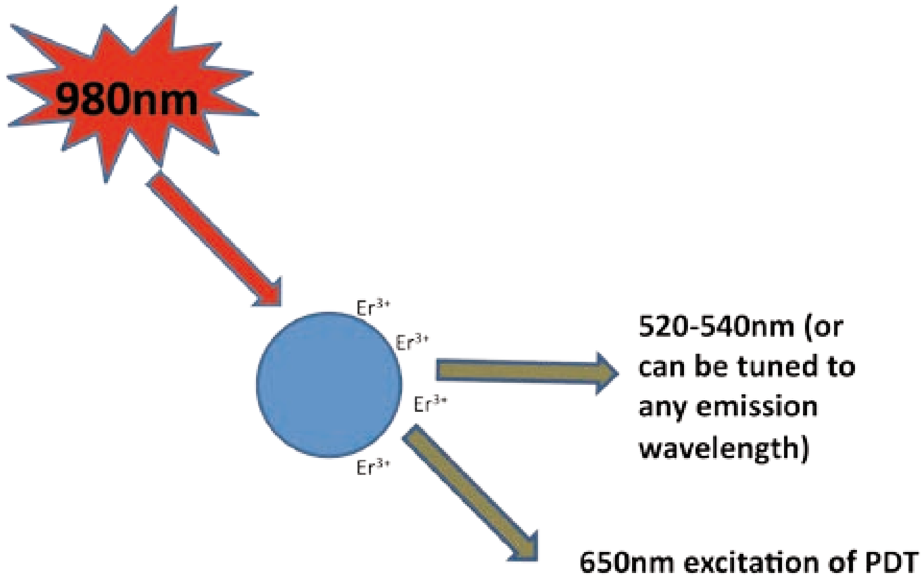
New photosensitizer

The treatment of cancer with light – known as photodynamic therapy – involves injecting the patient with a photosensitizer. The chemical is harmless on its own, but once illuminated it becomes extremely toxic. Tissues containing the photosensitizer will be killed almost instantaneously upon illumination. "In other words, simply shining light on a tumour will destroy it," Löwik says. There are three major issues with the photosensitizers currently being used, such as Foscan. First, the photosensitizer remains in the body for six weeks. "During that period, exposure to light causes severe skin burns," Löwik explains. "It can even result in blindness. To prevent that from happening, patients have to stay inside throughout the entire period." Secondly, the photosensitizer is present in both healthy and cancer tissue. As a result, illumination kills not only the tumour but also the healthy tissue surrounding it. Finally, the visible light that is used to activate the photosensitizer does not penetrate very deeply, since it is effectively absorbed by human tissue. This limits the treatment to small and very superficial tumours.





The photosensitizer Bremachlorin, which is also fluorescent, specifically targets tumour cells (left). On the right, a tumour in a mouse that has accumulated Bremachlorin and is imaged with a near-infrared camera system.



A nanoparticle filled with Bremachlorin is activated with 980nm laser light. This causes the nanoparticle to locally generate a tuneable internal light source. Bremachlorin is activated with a wavelength of 650nm.

Seaweed

The IMPACT project addresses those three issues. Within the project, a new photosensitizer is currently under development that will leave the body within days, if not hours. That photosensitizer accumulates selectively in tumours, thus reducing any collateral damage to healthy tissue during treatment. Moreover, it will use near-infrared light instead of visible light or far-red light. Near-infrared light can travel deeper into tissue, enabling the treatment of larger tumours. As Löwik explains: "The new photosensitizer, Bremachlorin, is derived from the seaweed spirulina and has been shown to target tumour cells specifically.
We don't know why it is so highly selective, but that makes it far easier to detect a tumour's boundaries with exactness. Moreover, it leaves the skin cells within three to four hours and the whole body is clean after 24 hours."
Bremachlorin is put into nanoparticles, which - once injected - "travel" through the body to the tumour. Subsequently, laser light with a wavelength of 980nm, which penetrates deeper into tissue than visible light can, causes the nanoparticles to locally generate an internal light source of a different wavelength. This internally emitted light can be tuned to match the wavelength needed to activate the Bremachlorin, causing the tumour cells to die. The efficient use of this procedure, known as upconversion, will be one of the project's deliverables.

Commercially interesting

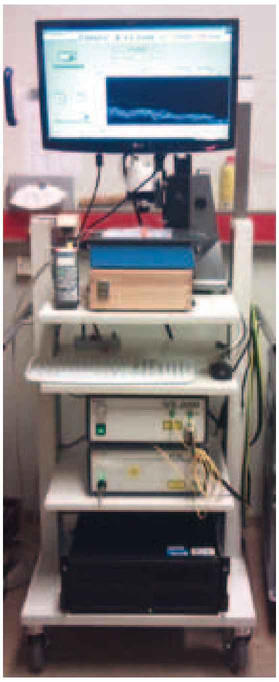
The project will result in a platform that contains all the necessary instrumentation for this kind of photodynamic therapy. The platform will consist of a multispectral camera, software that will automatically determine the exact region that needs to be treated, and an image-guided laser system that will effectively kill the tumour cells. Löwik expects the total package and the underlying intellectual property to be commercially very interesting. The companies O2view and Percuros are engineering and delivering the technology necessary for imaging and laser treatment, while the academic partners of the consortium will focus on optimising the nanoparticles as well as testing the therapy in mice.

Participants:

- Leiden University Medical Center
- Van 't Hoff Institute for Molecular Sciences (University of Amsterdam)
- Academic Medical Center, Amsterdam
- Percuros
- O2View

Contact:
Prof. dr C.W.G.M. Löwik
T: +31 (0)71 526 30 75
E: c.w.g.m.lowik@lumc.nl

The demonstrator will be a pen-like device.



Current OCT devices are expensive and consist of bulky optical components.

Project number: IPD100019
Project name: Low-cost handheld device for optical coherence tomography
Goal: to develop a demonstrator of a low-cost handheld OCT device that will open up new application areas for optical coherence tomography

Low-cost handheld device *for optical coherence tomography*

Optical coherence tomography (OCT) is a relatively new optical imaging modality. It can make high spatial resolution images of tissue up to a few millimetres deep. Currently, OCT devices are expensive and bulky, and their (commercial) application is limited mainly to the area of ophthalmology. In order to open up other application areas, the IOP project 'Low-cost handheld OCT device' is developing a demonstrator to establish the feasibility of cost and size reductions in OCT.

In medicine, imaging modalities such as MRI, CT, X-ray, ultrasound and microscopy each have their own strengths and weaknesses. “OCT is a very useful addition to this range, because it enables cross-sectional imaging of tissue at a resolution of several microns,” says Dr Jeroen Kalkman, a postdoctoral researcher in the Biomedical Engineering & Physics Group at the Academic Medical Center (AMC), in Amsterdam. “Only microscopy can match or surpass that resolution.” OCT and microscopy are based on the principle that tissue reflects light. However, since light scatters and is absorbed when penetrating tissue, microscopy can only image up to one hundred micrometres deep. OCT can extend that range to a few millimetres. “Since the eye is transparent up to the retina, OCT is currently used mainly in ophthalmology to obtain very detailed images of the retina,” adds Ton van Leeuwen, Professor of Biomedical Physics and Biomedical Photonics at the AMC. Another application area for OCT is intravascular imaging.
There, a probe is used to introduce a light source into a vein to check locally whether a stent has been placed correctly or to detect plaque composition and accumulation.

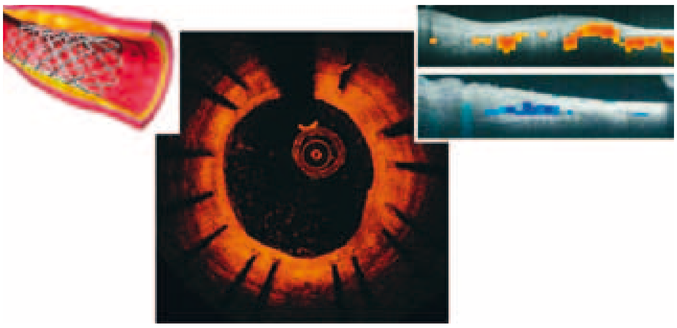
“We hope to achieve a five- to ten-fold drop in the production price”

Best possible system

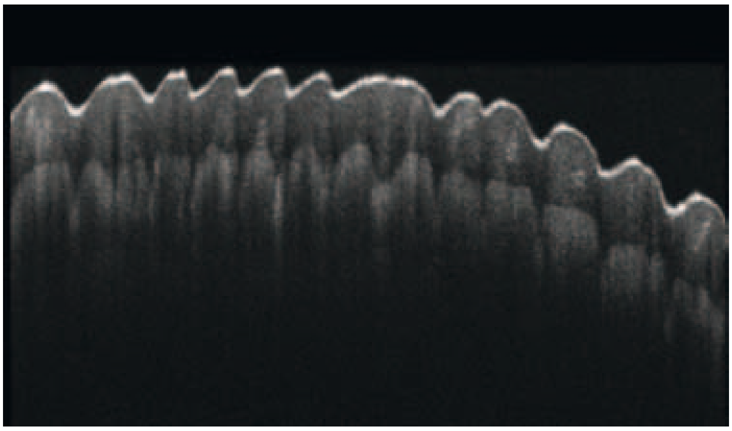
Current OCT devices are expensive and consist of bulky optical components such as light sources, lenses, mirrors and interferometers. With those components, a light bundle with a specific bandwidth is aimed at the tissue and its reflection is captured. Because of the high velocity of light, it is not possible to measure the time difference between sending and capturing, as in the case of depth ranging with ultrasound. Instead, the beam from the light source is split into two bundles. One is aimed at the area to be examined, while the other bundle is diverted in another direction and serves as a reference. “The reflected light is then combined with the reference signal to determine exactly how much light was reflected at a specific depth of the sample. By measuring this reflection for a great number of depths, a complete dataset is built with which we can construct an image,” Kalkman explains. Van Leeuwen: “In this IOP project, we want to reduce both the cost and the size of the components and to increase the functionality of OCT. This will result in a demonstrator of a low-cost handheld OCT device. We have chosen a specific configuration to achieve the best possible and most compact system.”

Pen-like device

The new system will be based on three strategies. The first is to reduce the cost of the optical system of the OCT device by miniaturisation. “This will be achieved using an integrated optics wave-guiding platform,” says Kalkman.
“The necessary components, such as the interferometer and the beam splitter, will be integrated on an optical chip.” This part of the project is being executed by partner LioniX, using their TripleXTM technology. The second strategy involves the use of a tuneable laser. “Instead of sending a mix of near-infrared light with a bandwidth of 100nm, we will use a swept-source OCT laser that can switch the wavelength within that bandwidth extremely rapidly.
In that case, signals are received from different tissue depths at the same time and ‘sorted’ according to depth using a Fourier transformation. That way, we get better signals faster and more efficiently,” Kalkman explains. Partners 2M Engineering and Oclaro Technology will adapt a commercially available laser system to fit the specific requirements of this project.



The use of OCT in intravascular imaging. By means of a probe, light is introduced into a vein to check locally using OCT whether a stent on the wall of the vein (top left inset) has been placed correctly (bottom middle; figure courtesy of G. van Soest). OCT also can be used to investigate the composition of the arterial wall (top right). Calcified lesions are indicated in orange, while lipid lesions are indicated in blue.



In forensics, OCT can be used to analyse fingerprints even when those prints are damaged (figure courtesy of R. H. Bremmer).

"The demonstrator will have the look and feel of a pen, so it can be moved easily over a surface"

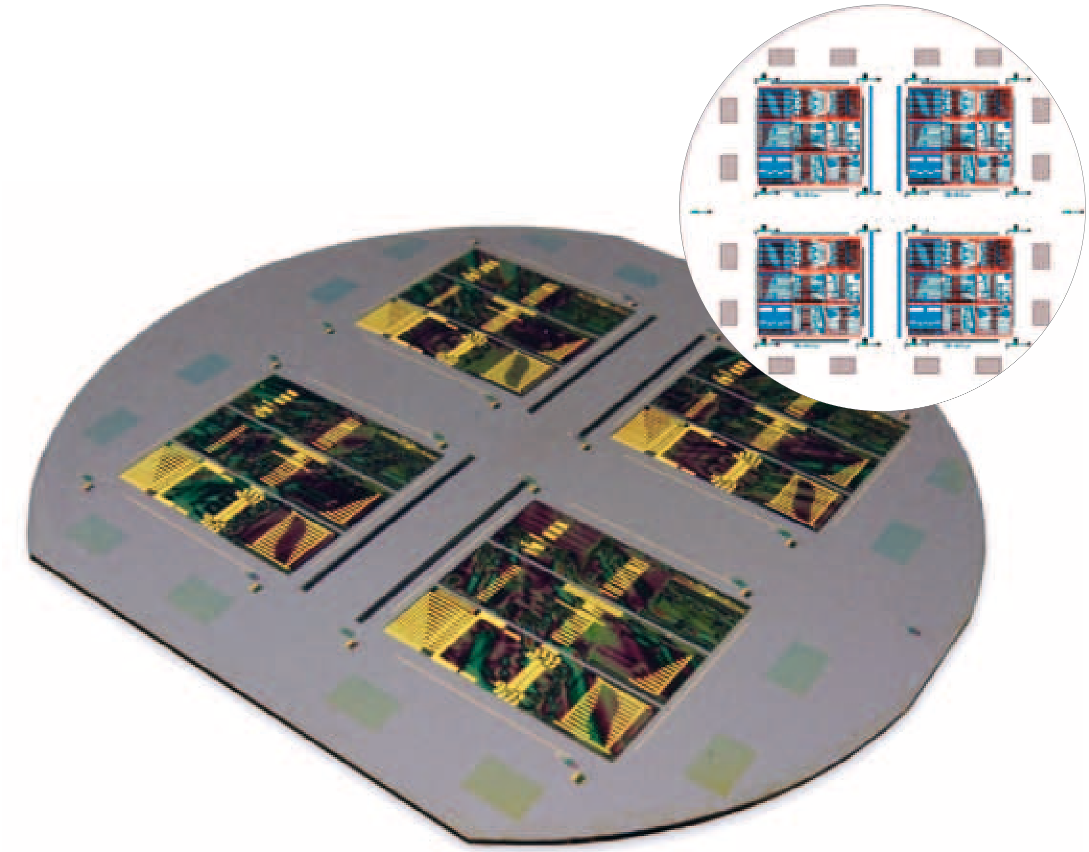
Manual operation of the OCT probe leads to image artefacts, due to the non-constant speed of the probe over the sample. These artefacts can be removed by using motion tracking of the OCT probe and correcting the OCT image after acquisition. For motion tracking of the OCT probe, a Philips Twin-EyeTM laser sensor will be used.
The demonstrator will have the look and feel of a pen, so it can be moved easily over a surface. Fundamental research will be done at both the University of Twente and the AMC. Topics will include signal integration and analysis, the influence of movement in biological tissue on the OCT signals, three-dimensional photonic integration, and the amplification of the light emitted by the swept-source laser.

New applications

The most complex issue in this IOP project will be how to integrate all the components within a manageable, robust and low-cost device. "We hope to achieve a five- to-ten-fold drop in the production price. That will open up other application areas for sure," Van Leeuwen expects. Dermal imaging is one of those he mentions. "For instance in skin cancer diagnostics or when inspecting burns. Surgery and dentistry are other possible application areas, as is forensics. With OCT, fingerprint analysis will be possible even when the prints are damaged."

Participants:
- Academic Medical Center, Amsterdam
- University of Twente
- 2M Engineering
- LioniX
- Oclaro Technology (UK)

Contact:
Dr J. Kalkman
T: +31 (0)20 566 8977
E: j.kalkman@amc.nl



Mask layout and processed wafer containing photonic integrated circuits.

Project number: IPD100025
Project name: Coarsely and finely tuneable laser for gas sensing (TULGAS)
Goal: to develop a gas-sensor demonstrator with a tuneable laser for the wavelength region of 1.8-2.2 microns using generic integration technology

Demonstrator of a gas sensor *based on a tuneable laser*

Gas sensors can detect certain molecules within a sample based on the principle that those molecules have a specific light-absorption peak. By sending light of that particular wavelength through the sample and measuring how much of it arrives at the other end, they can determine the presence and even the number of those molecules. Until now, separate lasers have had to be designed for each specific molecule, however. The IOP project 'TULGAS' will develop a gas-sensor demonstrator with a tuneable laser that can be used for a wide range of gas-sensing applications.

Molecules such as carbon dioxide, ammonia, methane and nitrogen oxides play a role in monitoring greenhouse gases and exhaust gases. Those molecules are also important for measuring the gaseous emissions from livestock buildings, such as pig farms, where the discharge of ammonia is restricted by law. In healthcare, gas analysis offers a promising means of diagnosing certain medical conditions. The presence of ammonia in one's breath can indicate kidney failure, for instance. Using breath tests to monitor patients could reduce dialysis time, potentially leading to a substantial decrease in total dialysis costs.

"Gas analysis offers a promising means of diagnosing certain medical conditions such as kidney failure"

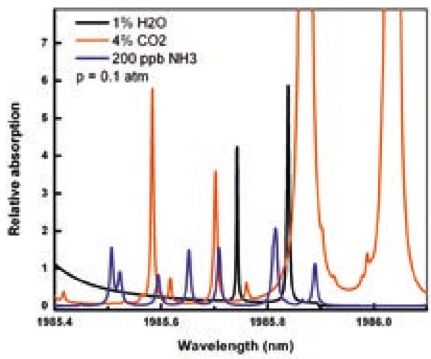
Single generic device

By sending light of a wavelength that approximates the absorption peak of a specific type of molecule through a sample, it is possible to detect those molecules within the sample. The amount of light that reaches a detector at the other end is indicative of the number of those particular molecules present. "The problem with gas sensors, however, is that a laser can only emit a specific wavelength. Consequently, a gas sensor can only be used to detect one type of molecule," says Dr Huub Ambrosius from the Department of Electrical Engineering at the Eindhoven University of Technology (TU/e). "So, based on the expected presence of certain different molecules, you have to use multiple specific lasers to trace them all." To solve this problem, the TULGAS project aims to create a single laser that can be tuned to cover a certain wavelength range, thus replacing the number of different lasers that are currently needed. "More specifically, we want the laser to be wavelength-tuneable at between 1.8 and 2.2 microns. That is the wavelength region in which you will find the absorption bands of carbon dioxide, ammonia, methane and nitrogen oxides." Ultimately, this project should lead to a single generic device that can monitor a multitude of molecules. A demonstrator of such a gas sensor, which should be able to trace molecules in the parts-per-billion range, will be built and tested during this IOP project.

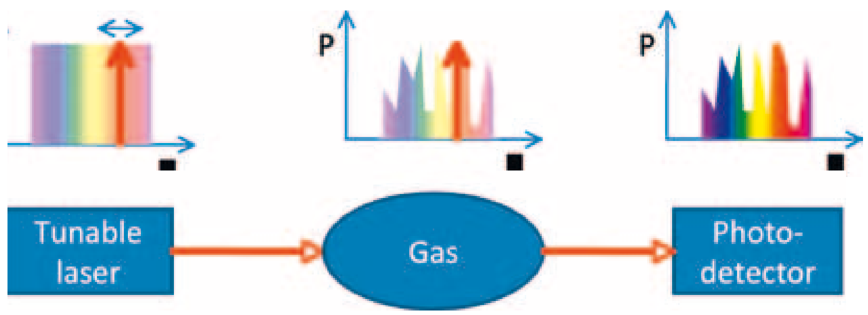
Continuously tuneable

Roughly four steps will be necessary to realise such a demonstrator: conducting the research on the proposed laser, designing and producing an optical chip – a photonic integrated circuit – containing the tuneable laser, the packaging of that chip and, finally, testing the resulting device. The members of the project consortium cover this entire supply chain.

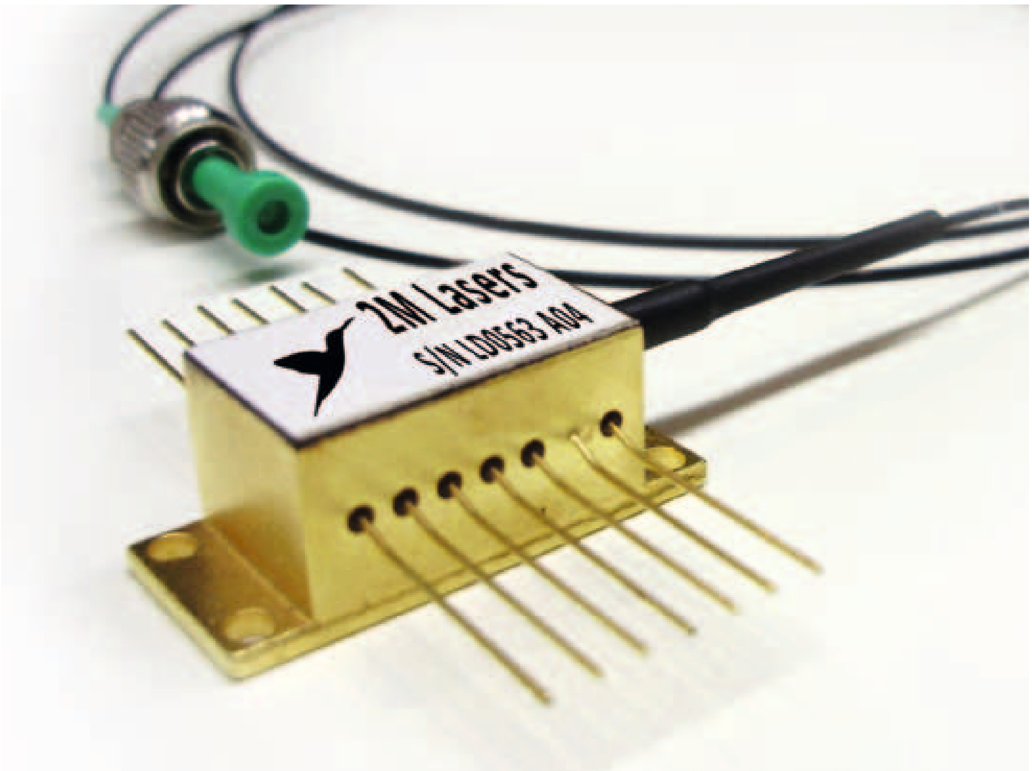
"The proposed laser will be an adaptation of one that was developed at TU/e and that is discreetly tuneable at around 1.5 microns," Ambrosius says. "We want to upgrade this wavelength region to the area around 2 microns and make the laser continuously tuneable so that we can scan the wavelength region several times per second. This will enable the gas sensor to monitor any changes in the sample in real time."



Molecules such as ammonia and carbon dioxide have an absorption peak of around 2 microns (2000 nm).



By sending light of a wavelength that approximates the absorption peak of a specific type of molecule through a sample, it is possible to detect those molecules within the sample. The amount of light that reaches the detector is indicative of the number of molecules.



Example of a packaged photonic device.

This part of the project will be carried out at TU/e. In the second part – the design and production of the optical chip – EFFECT Photonics will be heavily involved. This spin-out from TU/e focuses on the design and prototyping of next-generation optical chips. The company will be using a generic fabrication platform that was developed by COBRA in Eindhoven. "The development and production of optical chips is very much comparable to that of chips in the semiconductor industry," says Ambrosius. "The same steps are followed: the wafer production, the lithography, the slicing of the wafers into chips, and the packaging. In this case, however, the basic material is not silicon but indium phosphide (InP). Our COBRA Photonics and Semiconductor Nanophysics group, which is also participating in the project, is highly experienced in the epitaxial growth of this material." Similarly, the COBRA Photonic Integration group will be adding its expertise in the area of designing and processing optical chips to the project.

Flip-chip bonding

In order to be able to use the optical chip in a device for gas sensing, the chip will need to be packaged together with the necessary electronics. Because this is normally the most expensive part of a semiconductor laser, the design of the package is critical. 2M Engineering will contribute to this part of the project, using a technique called flip-chip bonding. They will also develop the thermal and mechanical package that will enable the fine and coarse tuning of the laser. "Not only do they have specific expertise in those areas, but they will also act as our interface with potential gas-sensor producers and users," Ambrosius explains. Last but not least, the project partner Radboud University Nijmegen will define possible applications for the gas sensor, and its Trace Gas Research group will test a functional prototype.

Participants:
- Eindhoven University of Technology
- Radboud University Nijmegen
- 2M Engineering
- EFFECT Photonics

Contact:
Dr H.P.M.M. Ambrosius
T: +31 (0)40 247 51 16
E: h.p.m.m.ambrosius@tue.nl

Project number: IPD100014
Project name: Integrated UV-RGB Beam Combiner, interconnection technology for ultraviolet (UV) and visible wavelengths (UV-RGB)
Goal: to develop a solution for fiber-chip and fiber-fiber coupling for UV and visible light

The result of an earlier IOP project on ultra-precision alignment for photonic systems, where MEMS actuators in a chip align and fix the position of one fiber with respect to another (TU Delft, IOP Precision Engineering, Henneken/Tichem).

Inter-connection technology for UV *and visible wavelengths*

In health and life science applications such as microscopy and spectroscopy, advances have been made by combining light from different laser sources into a single fiber output. While photonic chips for integrating several light sources are currently available, low-cost, high-quality interconnection technology is lacking, especially for submicron-wavelength photonics. The IOP project 'Integrated UV-RGB Beam Combiner' aims to fill that gap. The envisaged technology would also enable new products such as an image projector as small as a packet of cigarettes.

More and more applications in health and life sciences employ combinations of visible light (RGB – red, green and blue) and ultraviolet light (UV). In confocal microscopy for instance, three-dimensional structures are constructed from images that are obtained with light of different wavelengths. Similarly, flow cytometry – a technique for counting and examining microscopic particles such as cells and chromosomes – is also based on the usage of more than one wavelength. The required wavelengths in those types of applications are produced by numerous different single-laser sources and then combined into one single fiber output. "Combining light of several wavelengths is not a problem in itself," says Dannis Brouwer, Assistant Professor of Engineering Technology at the University of Twente. "Photonic chips that do that are readily available, produced by companies such as LioniX, for example. The issue lies in how to couple the interfacing fibers to one another or to the integrated optical chip. The current solutions are bulky and expensive. The industry is in need of low-cost, highly reliable and accurately aligned pluggable connections. That is why Willem Hoving of XiO Photonics, a University of Twente spinoff, initiated this project."

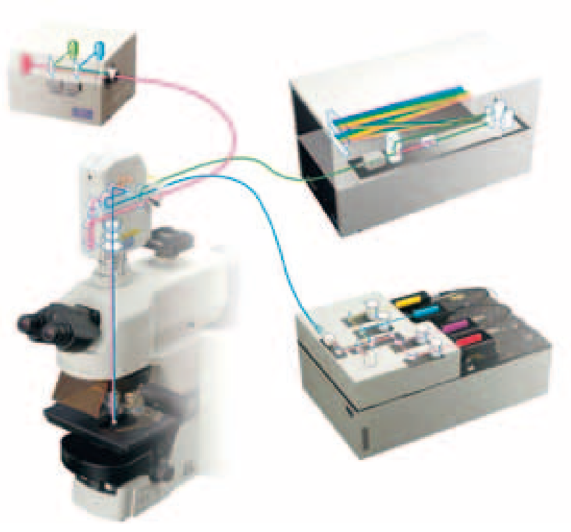
"The industry is in need of low-cost, highly reliable and accurately aligned pluggable connections"

Alignment

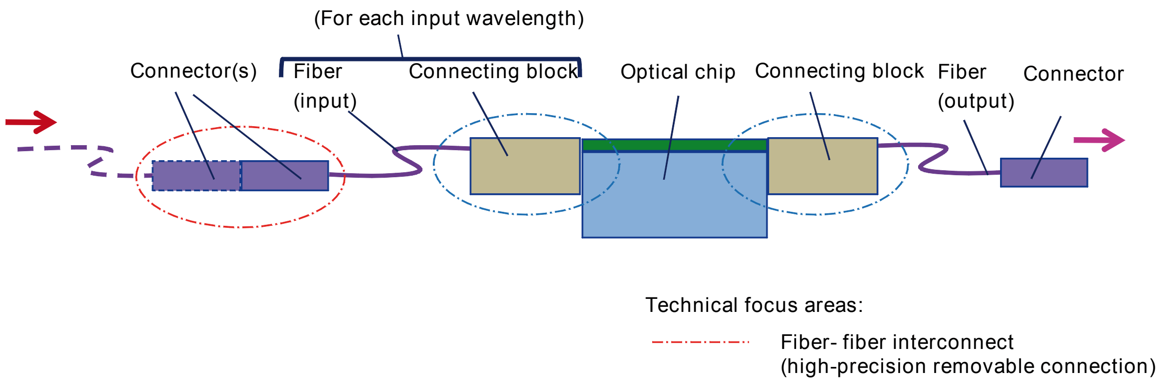
The need to combine visible light with ultraviolet light only complicates matters. The current connectors for coupling fiber to fiber or fiber to chip primarily use adhesive bonding - glue - as an interconnecting technique. "Glue is very sensitive to light with a short wavelength, such as UV light," Dannis Brouwer explains. "When exposed to such short wavelengths, glue degrades rapidly. As a result, first the alignment of the fiber (or fibers) and ultimately also the connection itself are lost."
The sensitivity of glue to UV light is not the only problem, however: the limited capacity for alignment precision of the current interconnection technology is another. During the process of bonding, heat and/or shrinking induces stress on the fibers that need to be connected. That makes it extremely difficult to maintain the required submicron alignment accuracy, which results in a very low yield when producing connectors. "This is currently a real problem in the photonic industry. To solve it, you will need to be able to correct or adjust the alignment of the fibers during the bonding process."

Spot welding

The IOP project 'Integrated UV-RGB Beam Combiner' will research several approaches to tackling the problems with both the bonding and the alignment. Two Dutch universities – the University of Twente and the Delft University of Technology – will each focus on their own area of technological expertise to come up with solutions. The researchers in Delft are specialised in micro- and nano-scale assembly with a focus on ultra-precision alignment for photonic systems. Therefore they will look into the possibility of using silicon-based microfabrication technology and microelectromechanical systems (MEMS) to integrate functions for aligning and fixating the position of the fiber with respect to the optical chip. One proposal is to create a modular system that would be able to fine-align and fixate a single fiber; multiple optical outputs could be realised by placing several of those modules next to each other. The research involves the design of both the total package layout and the functional partitioning (i.e. where to place alignment and fixating functions and features), the design and realisation of suitable MEMS actuators and the development of methods for fixating the chip once it is aligned with respect to the optical chip. The researchers at the University of Twente will study the use of laser energy for bonding and aligning.



System for confocal microscopy using four lasers. (Photo: Nikon)



The proposed interconnection solution contains connecting blocks on either end of an integrated-optical chip, coupling it to input and output fibers, as well as pluggable connections between fibers.

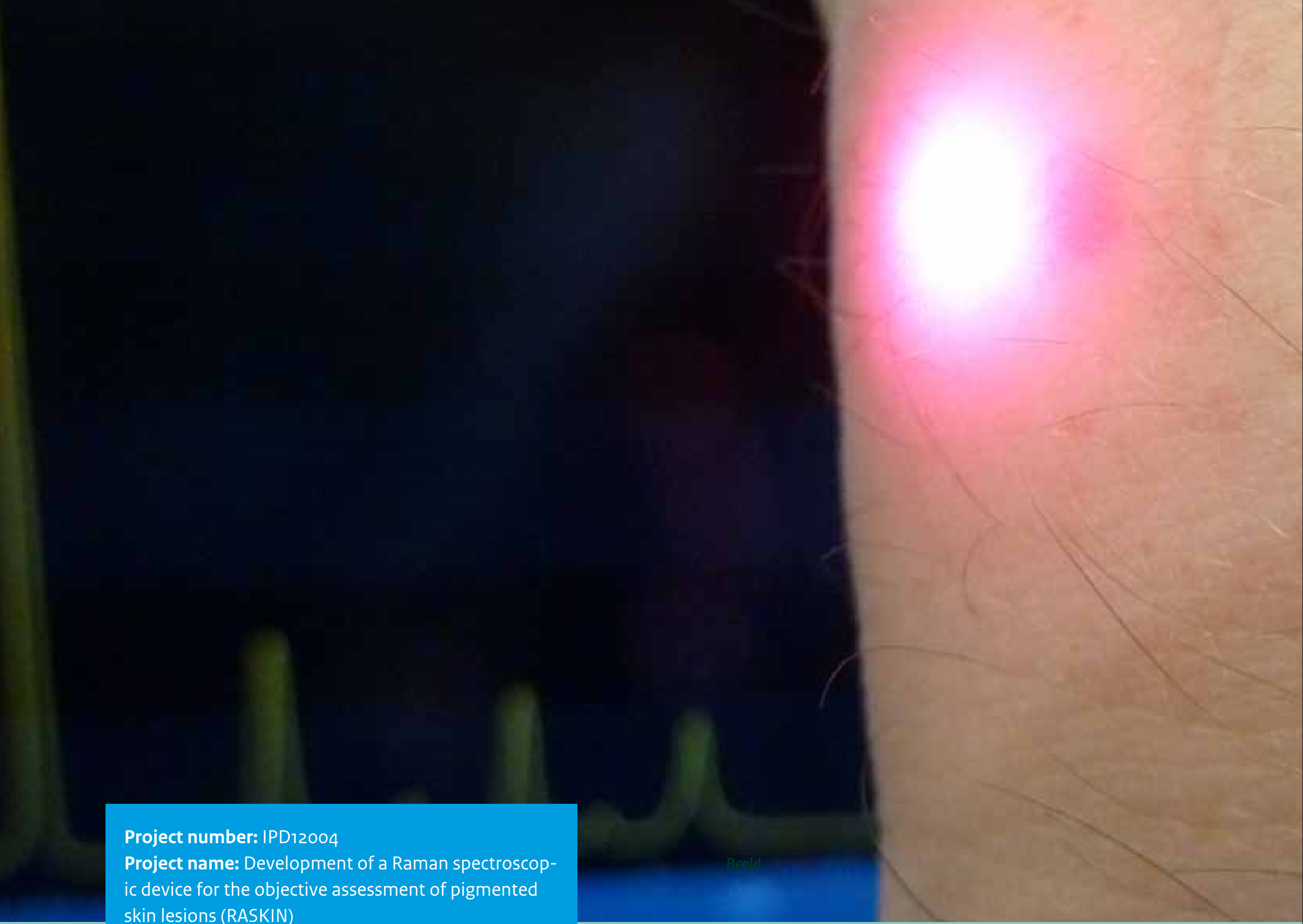
Dannis Brouwer: “Continuous or spot welding based on laser energy is a more reproducible process than adhesive bonding. It allows you to model exactly what will happen to the fiber when it is heated locally. Based on the model, we hope we can anticipate whatever misalignment there will be and then make the necessary adjustments in advance. Since the optical fiber has a certain polarisation that needs to be maintained, we will have to examine the alignment in six degrees of freedom both during and shortly after the welding.” The project will include both the realisation of a measurement setup to check the models and the use of artificial ageing to check the behaviour of the connectors in the long run (over several years).

Direct interest

Four companies are heavily involved in this project: XiO Photonics, Tyco Electronics, IMS and Coherent Europe. Their involvement ensures that the solutions proposed by the universities will target the product-related problems that these industry partners foresee. XiO Photonics designs and fabricates integrated optical products such as integrated laser-beam combiners and spot-size converter chips. Tyco Electronics, a manufacturer of interconnection products for telecom and datacom, is interested in employing combinations of visible and UV light in connection with the new medical division it is setting up. IMS makes industrial mechanised systems for fiber-chip alignment and assembly. Coherent Europe is a world leader in laser products and deeply embedded in the high-end market segment for both UV and visible-light lasers. “They all have a direct interest in the results and plan to implement them into new products,” says Dannis Brouwer. “Apart from using the interconnection technology in health and life science applications, there are also ideas for products such as pocket-sized image projectors and light sensors. We will all be very happy if we can find a way to align and fixate fibers without the need for adjustment afterwards.”

Participants:
- University of Twente
- Delft University of Technology
- XiO Photonics
- Tyco Electronics
- Coherent Europe
- IMS

Contact:
Dr ir D.M. Brouwer
T: +31 (0)53-489 48 45
E: d.m.brouwer@utwente.nl



Project number: IPD12004
Project name: Development of a Raman spectroscopic device for the objective assessment of pigmented skin lesions (RASKIN)
Goal: to develop a low-cost, easy-to-use Raman spectroscopic device for dermatologists and primary-care physicians for a rapid and objective identification of suspicious pigmented skin lesions

Early diagnostics of skin cancer *with Raman spectroscopy*

Melanoma is the most lethal form of skin cancer. Early diagnostics is crucial as it significantly enhances the patient-survival rate. However, the clinical diagnosis of early-stage melanoma remains difficult. The IOP project 'RASKIN' aims to develop a prototype of a low-cost, easy-to-use photonic device that will help dermatologists and primary-care physicians identify suspicious, pigmented skin lesions. The project will also deliver an extensive set of clinical data to verify the effectiveness of the instrument.

Worldwide, the number of patients diagnosed with melanoma is increasing by 4% each year. An estimated 6,000 cases are expected in the Netherlands alone in 2015. While early diagnostics could make a real difference for patients, the clinical diagnosis of early-stage melanoma is difficult even for the most experienced dermatologists. Most assessments are currently made on the basis of visual inspection and are thus highly subjective. Suspicious pigmented skin lesions are then surgically removed and examined by a pathologist. As it is hard to distinguish between malignant and benign tissue, many skin samples are unnecessarily removed for examination, while at the same time a substantial number of early-stage melanomas go unnoticed. Those could very well metastasize to distant organs. As metastatic melanoma is resistant to chemotherapy, the prognosis for patients who have it is very poor: the median survival time is no more than a few months. "It is therefore of the utmost importance to be able to diagnose melanoma accurately at a very early stage, before deadly metastasis has occurred," says Marijn Sandtke, business consultant at TNO. "We have high hopes that we can achieve this with the help of a generic technology called Raman spectroscopy."

"Using a Raman spectroscopic device, sample tissue no longer has to be surgically removed"

Fingerprint

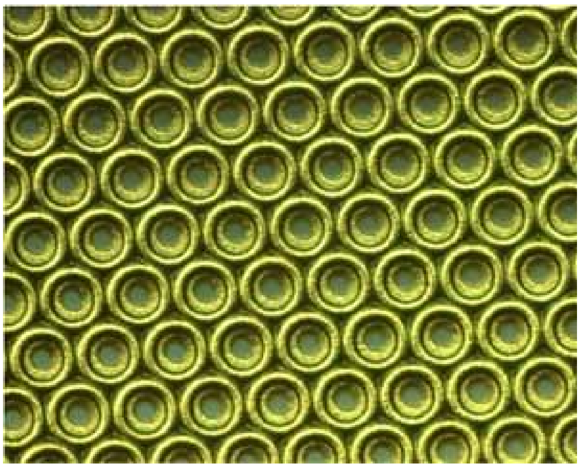
Using a Raman spectroscopic device – Raman spectroscopy was named after the Indian scientist Sir C. V. Raman – sample tissue no longer has to be surgically removed, but merely illuminated with a laser beam. "When laser light reflects on the molecules in the sample, it causes vibrations and rotations of the atoms in the molecules within the illuminated spot," Sandtke explains. "By measuring the differences in the energy levels between the entering and exiting photons, it is possible to determine which molecules are involved. In this way, we can establish the (bio)molecular composition – the signature – of pigmented skin lesions. Since the signatures of melanoma and benign tissue are quite different, this type of analysis would greatly enhance the clinical diagnosis of melanoma in an early stage."

In a previous project, TNO successfully used the Raman technique ex-vivo on liver-tumour tissue. Using it on melanoma presents some difficulties, however. As they are dark brown or even almost black in colour, this type of tissue absorbs most of the laser light, resulting in both an unwanted heating of the tissue and poor signals. Fluorescence is another serious problem. Not only do the molecules in the sample absorb the laser light, but they also generate a strong background signal that makes it harder to detect the molecular fingerprint. By using infrared laser light, this IOP project hopes to circumvent both problems. This type of light – with a wavelength of approximately 1,000 nm – reduces both absorption and the generation of unwanted background fluorescence.

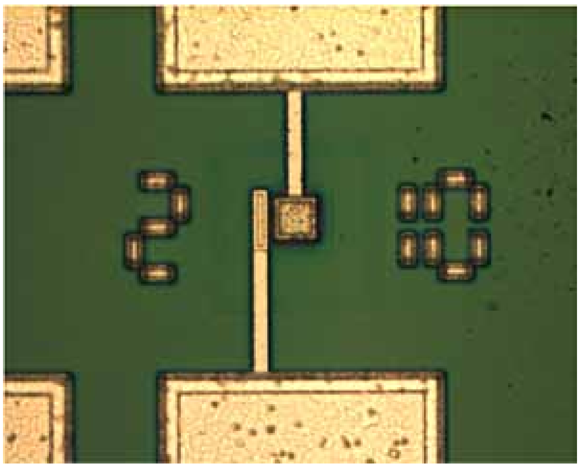
Handheld unit

To develop a photonic device based on infrared Raman spectroscopy, it will be necessary to develop a number of technologies beyond the current state of the art. This will happen during the first two years of the project. "The first technology is the laser itself," says Sandtke. "We will need a compact, low-cost infrared laser with high wavelength

The back of a patient, containing dozens of pigmented skin lesions ('moles') (Source: LUMC)



An array of vertical-cavity surface-emitting lasers (VCSEL), which will be used in the Raman spectroscopic device (Source: Philips Lighting)



Example of a photodiode detector connected to two metal pads. The size of the detector is 10×10 μm2 (Source: Delft University of Technology)

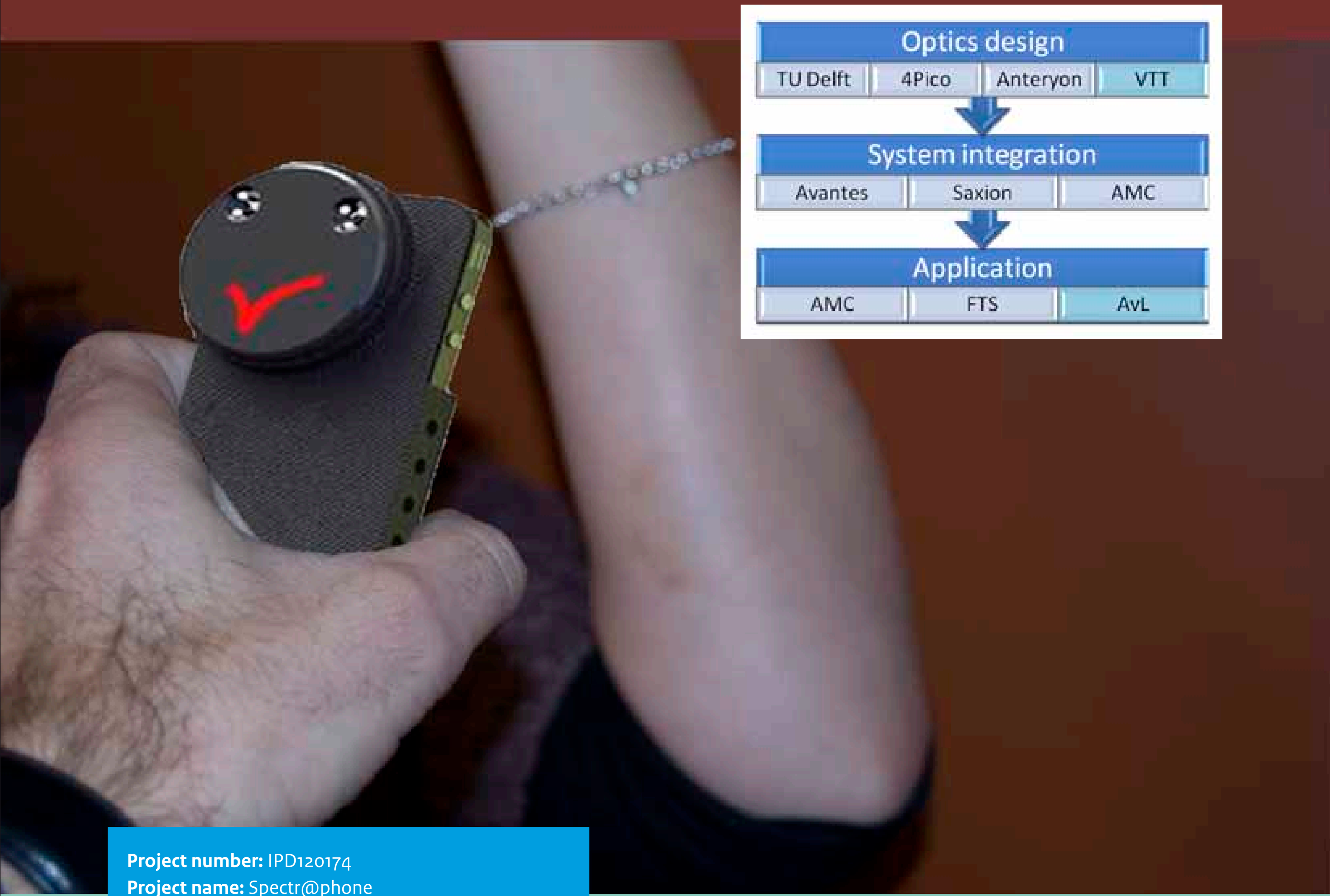
stability. Our project partner Philips Lighting will work on this part of the project." The second technology that needs improvement is the detector. The Delft University of Technology will further develop an existing photodiode process to produce a detector with a sufficiently low noise level (1 kHz dark count rate) for this application. "TNO will be responsible for the opto-mechanical design of both the spectrometer and a handheld measurement unit that can be used by dermatologists and primary-care physicians. This so-called collection probe will need to be able to focus the laser light at the correct position and collect the signals from the lesion. It also needs to be light, small and ergonomic. Erasmus MC – which initiated the project – will help us define the specifications for the spectrometer, probe, laser and detector. For the spectrometer, we can build on TNO's long history of designing infrared spectrometers for space applications." Yet another project partner, Avantes, will incorporate the various techniques into a working prototype.

Data collection

Developing the Raman spectroscopic device is one thing; correctly distinguishing between malignant and benign tissue is another. Sandtke: "To enable the interpretation of the tissue-sample signatures, the Center for Optical Diagnostics and Therapy at Erasmus MC will develop the necessary algorithms. During the last year and a half of the project, once the prototype has become available, clinical data will be collected and tested in order to improve those algorithms." Data collection will take place at the Department of Dermatology at the Leiden University Medical Center. This hospital is the Netherlands' national centre for skin oncology and has the largest pigmented lesion clinic in the country. "There we can compare the results of the Raman device with those from pathological evaluation. At that stage of the project we will also decide on how to present the data from the device to dermatologists and physicians. Will it be enough to show them the test results in green, orange or red, or would they prefer numbers or a graph? By 2016, after having tested the prototype extensively within the Department of Dermatology, we will have a prototype of which both the accuracy and the sensitivity will be known."

Participants:
- TNO
- Delft University of Technology
- Erasmus MC
- Avantes
- Philips Lighting
- Leiden University Medical Center

Contact:
Contact: Dr ir M. Sandtke
T: +31 (0)15 866 64 73
E: marijn.sandtke@tno.nl



Project number: IPD120174
Project name: Spectr@phone
Goal: to develop and test a handheld, multispectral imaging device for (forensic) medical applications

Spectral imaging in *(forensic) medicine*

Combining both optical spectroscopy and digital imaging, spectral imaging holds great promise for forensic medicine and other medical applications. The main drawbacks of the current technology include the high price of commercially available systems, the size and weight of the camera, the long data-acquisition times and the complex data-processing software. All these drawbacks will be solved in the Spectr@phone, a handheld, multi-spectral imaging device that will soon be tested in the Academic Medical Centre (AMC) in Amsterdam.

"Optical spectroscopy is a commonly used method of chemical analysis based on the absorption of light," says Dr Maurice Aalders, a researcher in the Biomedical Photonics group at the AMC. "It enables you to determine the type of structures or pigments in a sample by illuminating it and then measuring the returning colours and their intensity." In medicine, optical spectroscopy is routinely used to measure the composition of blood or, more experimentally, to distinguish cancer tissue from healthy tissue. The resulting absorption spectrum is only relevant for the tiny spot where the light hits the sample, however. "In the fields of application we are interested in – forensic medicine and dermatology – we want to acquire the absorption spectrum for a far larger surface area. We also want to be able to capture it digitally. So-called spectral imaging systems enable us to take such optical biopsies." This is done with a digital camera that takes multiple pictures of an object or sample using a variety of filters, one for each colour (wavelength) ranging from deep blue to near infrared. These pictures are subsequently combined into a multispectral image.

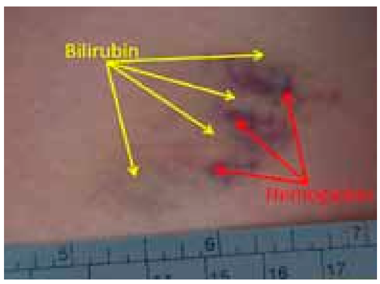
"Spectral imaging systems enable us to take optical biopsies"

Bruises

Two clinical areas in particular stand to benefit greatly from the application of spectral imaging. The first involves the determination of the age of bruises in forensic medicine. "When a paediatrician suspects child abuse, it is very difficult to prove it. Knowing precisely how old the bruises are would be helpful, because that could prove whether multiple bruises were inflicted at the same time and even help identify who had been the caretaker at the time," explains Aalders. Some paediatricians use a colour chart to determine the age of a bruise, but as this method is not very accurate, it is no longer used at the AMC. In an earlier project, AMC researchers discovered that it was possible to determine the age of a bruise to within several hours, based on the area and concentration distribution of the bilirubin and haemoglobin it contains. "Spectral imaging of the bruise enables us to determine these parameters accurately, even in the case of dark skin tissue, where bruises are normally almost invisible." The second clinical area that would benefit from spectral imaging involves the identification of suspicious pigmented skin lesions. "It is important to be able to distinguish a mole from a melanoma as early as possible. Even for experienced dermatologists, that is a difficult task. Spectral images of a skin lesion can give us extra information about the tissue of the lesion and its immediate surroundings, such as blood and melanin content and oxygenation. This would be highly beneficial for diagnostics."

Handheld

Although spectral imaging is a very promising technique, the current systems are unsuited for use in a clinical environment. For one, the acousto-optical or liquid-crystal tunable spectral filters used to scan the required wavelength range are very expensive. Another problem is the camera itself, which is rather large. Also, because of the number of pictures that need to be taken, the images need to be corrected afterwards to compensate for patient movements. Aalders: "In this IOP project, we want to overcome these problems by developing a handheld device using smart-phone camera techniques. The Spectr@phone will be cheap to produce and quick and easy to use." The key element of this compact device will be the camera, which will consist of two elements. The first of those is a very small, potentially cheap, tunable Fabry-Pérot filter that was recently engineered by the VTT Technical Research Centre of Finland. This filter transmits not only the principal wavelength, but also the higher-order wavelengths. VTT has invented a method to combine several transmission bands with an image sensor with pixels that are sensitive to different colours. "By combining this filter with a mosaic filter and four lenses, we can obtain four spectral images in one shot. If we then tune the Fabry-Pérot filter to another wavelength, we can get another four images. This significantly reduces the image acquisition time." The completely new lens



The haemoglobin and bilirubin areas of a bruise (Photo: Drs B. Stam, AMC)

The mosaic filter/lens system that will be combined with the Fabry-Pérot Interferometer

Anteryon's WaferOptics® technology (Photo: Anteryon)

Miniature Fabry-Pérot Interferometer device made with MEMS technology (VTT). The principal transmission wavelength is tuned by changing the amount of space between the mirrors (Photo VTT)

module will be made using the WaferOptics® technology of project partner Anteryon, an industrial supplier of miniature cameras for smartphones.

Design

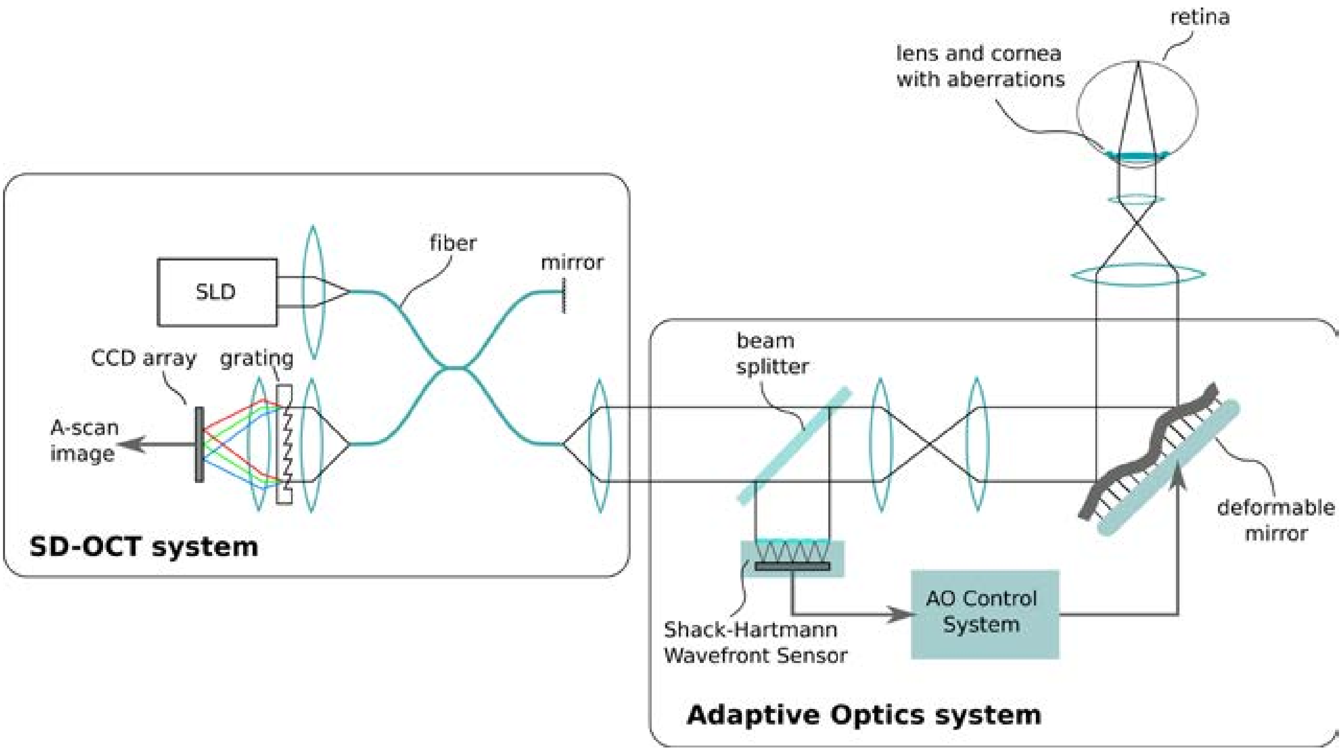
Several partners are working together in the project consortium, representing the total development, engineering and production chain of the Spectr@phone. Avantes, 4PICO, Anteryon and the Delft University of Technology will design, build and test the prototypes of the tuneble Fabry-Pérot filter and mosaic filter lenses. Forensic Technical Solutions, a spin-off of the AMC, will add its expertise on spectral data processing for the two medical applications described above. The design of the prototypes for use with each application will be performed by students of industrial design at the Saxion University of Applied Sciences. The Antoni van Leeuwenhoek Hospital in Amsterdam is involved as an affiliated partner and will facilitate patient measurements in its Dermatology Department. At the AMC, the device will be tested on patients with bruises resulting from trauma, for example. "Besides these two medical applications, there are many others that could benefit from spectral imaging," says Aalders. Examples include the analysis of blood spatters at crime scenes and the monitoring of fruit or food freshness at supermarkets.

Participants:

- Academic Medical Centre (AMC), Amsterdam
- Antoni van Leeuwenhoek Hospital*
- Avantes
- Anteryon
- 4Pico
- Delft University of Technology
- Forensic Technical Solutions
- Saxion University of Applied Sciences
- VTT Technical Research Centre of Finland*

* Antoni van Leeuwenhoek Hospital and VTT Technical Research Centre of Finland are Affiliated Partners of the project

Contact:
Dr Ing Maurice Aalders
T: +31 (0)20 566 38 29
E: m.c.aalders@amc.nl



Project number:IPD12020
Project name: i-OCT (integrated smart optics for low-cost, super-resolution OCT)
Goal: to develop a prototype of a low-cost, high-resolution OCT system for use in ophthalmology

An OCT system extended with an adaptive optics system that compensates for aberrations in the lens and cornea of the eye

Integrated smart optics technology *in ophthalmology*

Optical coherence tomography (OCT) is an imaging modality that produces high-resolution images of tissue up to a few millimetres in depth. Although the axial (depth) resolution of OCT imaging is sufficient for use in ophthalmology, the lateral resolution is hampered by aberrations in the lens and cornea of the eye. While adaptive optics can compensate such irregularities, integrating that with OCT is complex and costly. To overcome these problems, the IOP project 'i-OCT' will develop integrated smart optics technology.

Optical coherence tomography is based on the principle that tissue reflects light. When a light beam is aimed at tissue, OCT provides cross-sectional images in which the contrast is based on differences in the backscattered light. "Compared to other non-invasive, in vivo, contactless imaging modalities such as ultrasound, high-resolution computed tomography (CT) and magnetic resonance imaging (MRI), optical coherence tomography (OCT) has a much better axial resolution: from 2 to 10 microns," says Michel Verhaegen, Professor of Systems and Control at the Delft University of Technology and project leader of i-OCT. As a result, OCT is commonly used to visualise the many thin, functional layers in the top millimetre of retina tissue. "That makes OCT very effective for diagnosing and screening eye diseases such as glaucoma, age-related macular degeneration and diabetic retinopathy. But it is also useful for imaging coronary vessels." In the latter context, a probe is used to introduce the light beam into an artery to check locally for arteriosclerotic plaque. In urology and gynaecology, OCT is used to improve cancer diagnostics, for instance at the Academic Medical Center (AMC) in Amsterdam.

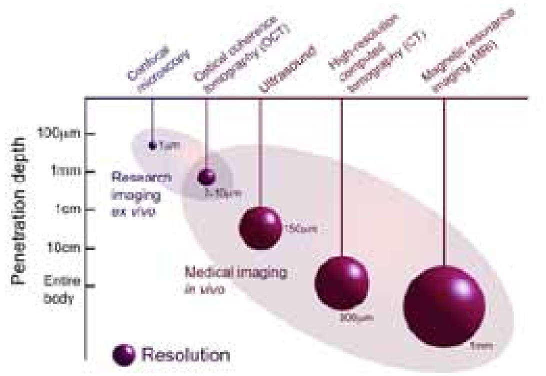
Adaptive optics

In ophthalmic use, the lateral resolution of OCT is determined by the spot size of the light source on the retina, which is approximately 20 microns. "The problem, however, is that organic materials such as an eye's lens and cornea are not homogeneous. Different layers have different refractive indices, and aberrations present in the lens and cornea will influence how the light is focused on the retina. That means that the lateral resolution of the OCT images is not good enough to facilitate the imaging of the most important part of the retina: the cones," explains Verhaegen. "By correcting those aberrations with adaptive optics, it is possible to enhance the lateral resolution. This technology has already been in use for a decade in astronomical telescopes and microscopy." While adaptive optics has also demonstrated its usefulness in ophthalmology, commercial OCT systems have yet to include this technology. "Not only would the necessary add-on hardware double the volume of the OCT system – you would need to include bulky optical components such as light sources, lenses, deformable mirrors and interferometers – but it would also double the cost. Besides that, the use of adaptive optics would require substantial maintenance: you would need specialists for regular calibration of the optical hardware. And on top of all that, you would have to deal with a loss of information, since the Shack-Hartmann wavefront sensors classically used to measure the wavefront aberrations will 'steal' photons from the optical path." To overcome these issues, the IOP project 'i-OCT' will greatly simplify the necessary hardware. It will also integrate active image-resolution enhancement into the OCT system, reducing costs while preserving high-performance resolution.

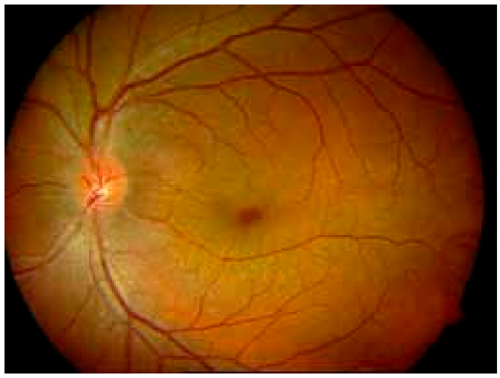
Algorithms

In order to reduce the hardware complexity, the aberrations will be corrected with software instead of using an expen-

> *"Apart from its applications in healthcare, integrated smart optics technology will also be useful in other inspection domains"*



A comparison between the imaging depth and resolution of OCT and those of several other in vivo imaging modalities (Source: University of Illinois)



A retinal image taken with the current low-cost fundus camera of Focal Optical Systems (Photo: Focal Optical Systems)

sive, deformable mirror, which is currently a key element in systems for adaptive optics. Verhaegen: "We know that, in principle, it is possible to make the necessary corrections with model-based algorithms, but this method needs to be improved and accelerated. We need to be able to correct the aberrations in real time. Above all, it is a problem of mathematical optimisation that will be tackled at the Delft University of Technology." Project partner TNO, which has extensive experience and knowledge of adaptive optics, especially in astronomy, lithography and microscopy, is responsible for the system engineering of the new concept. TNO will also develop a technical and commercial roadmap for the i-OCT system. "Apart from its applications in healthcare, integrated smart optics technology will also be useful in other inspection domains, including vegetables and non-organic materials. Hence, TNO will be exploring commercialisation in non-medical markets as well."

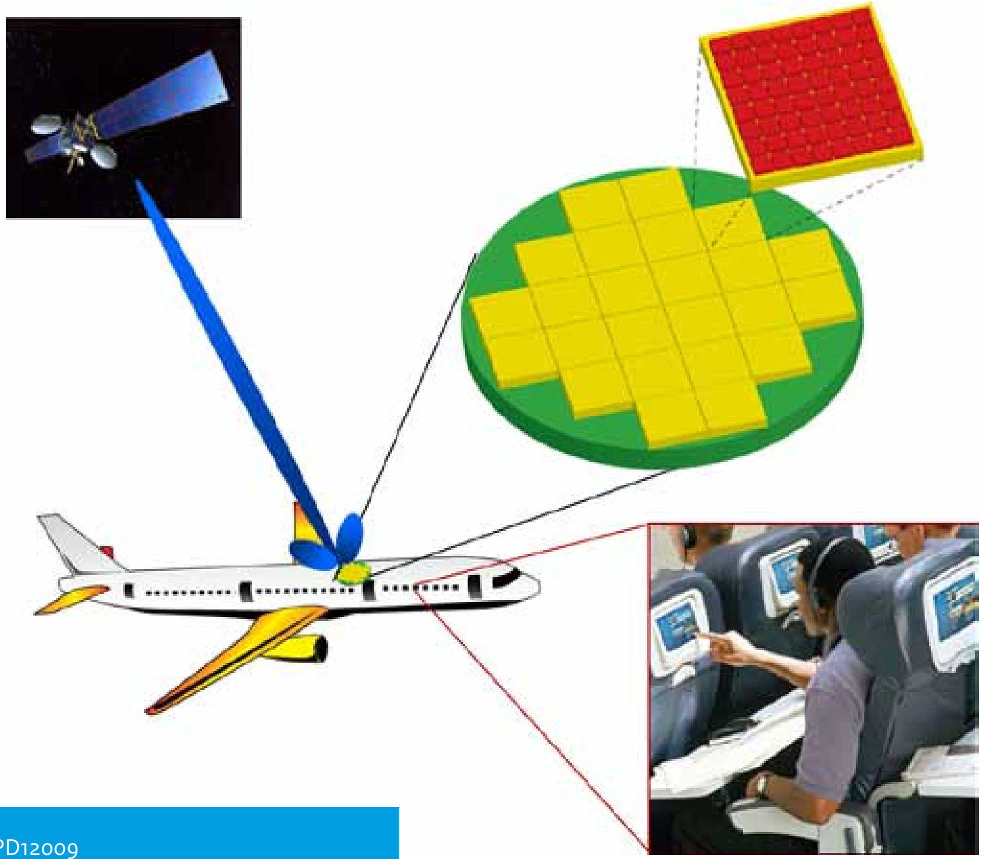
Prototype

Another project partner is Focal Optical Systems, a company that designs and develops optical precision-measurement systems, including diagnostic instruments for ophthalmology. Focal has developed vision-software-enhanced eye-diagnostic devices for pre-screening eye-related diseases in developing countries. "In this project, Focal will develop pre-diagnostic software tools to automate the use of the i-OCT system in clinical environments. It will also develop a prototype of the i-OCT module that will incorporate the designs from TNO and the algorithms developed by the Delft University of Technology. At the end of this project, Focal envisions having put another smart diagnostic retinal-screening device on the market. The Department of Biomedical Engineering and Physics at the AMC will work on several theoretical and experimental aspects of the interaction between light and tissue to find out more about image formation of the retina. With the i-OCT technology developed in this project, it will be possible, for the first time, to quantitatively measure the light-absorption and light-scattering properties of the very thin retinal layers – something that has been a major challenge until now. This will allow doctors access to important physiological parameters such as perfusion, blood-oxygen saturation and the way in which cells are organised – all factors describing the state of health (or disease) of the imaged tissue.

Participants:

- Academic Medical Center (AMC), Amsterdam
- Delft University of Technology
- Focal Optical Systems
- TNO

Contact:
Prof Dr Ir M. Verhaegen
T: +31 (0)15 278 5204
E: m.verhaegen@tudelft.nl



Project number: IPD12009
Project name: Photonic and RF Integration of Optical Beamforming Modules in Smart Antennas for Today (Promis2Day)
Goal: to produce an integrated optical beamforming module for an antenna array to be used in nautical and avionics satellite communication

High-speed broadband connectivity on an aircraft through satellite communication using an ultra flat antenna module

Photonic chip for *fast satellite communication*

To realise broadband connectivity on board commercial aircraft, trains or ships, a satellite antenna is required that can steer itself toward the signal source. The existing dish-based solutions are obviously unsuitable for use on moving vehicles, and the flat antenna systems currently on the market have several drawbacks as well. By developing a novel photonic chip, the IOP project 'Promis2Day' will produce a prototype of an ultra flat antenna module that will be smaller, more intelligent and less expensive to produce.

"Consumers expect high-speed broadband connectivity anywhere, any time," says Chris Roeloffzen, a researcher at the University of Twente and project leader of the IOP project 'Promis2Day'. "Yet whenever we board a plane, ship or train, live TV and fast Internet access are out of our reach. The main inhibitor is the lack of an ultra flat antenna system that can be built into the vehicle's roof for accurate satellite tracking."

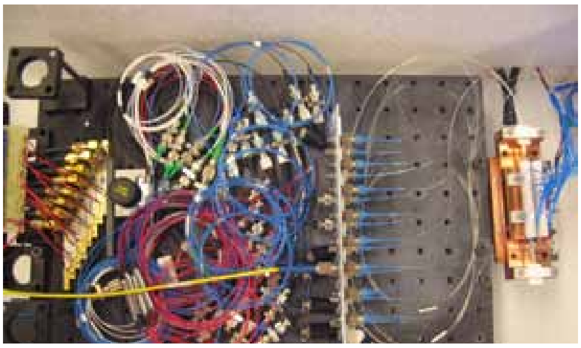
"The international response to this revolutionary technique has been very positive, but further integration is required to realise a cost-efficient and compact module"

Beamforming

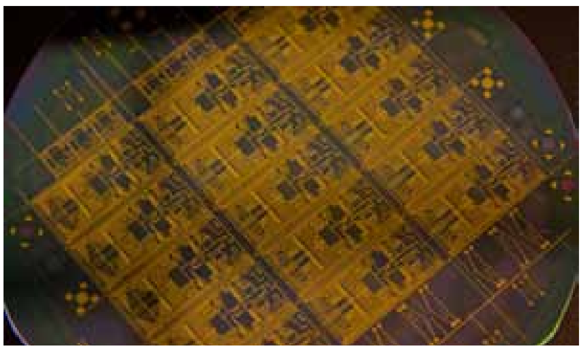
Existing flat antenna systems consist of multiple antenna elements arranged in a neat, rectangular grid. These elements can receive and amplify radio signals from a particular direction, while suppressing signals from other, unwanted directions. This is possible by means of beam-forming techniques. "But if the signals from the satellite reach the surface of the antenna elements diagonally rather than at a right angle, they will be out of phase when they reach the beamformer located behind the antennas," explains Roeloffzen. "This results in a signal with poor quality, since those signals cancel each other out."
Until recently, there were two ways to correct this problem: using directed-beam antennas or using a phase shifter-based beamformer. Directed-beam antennas are directed mechanically towards the signal source. But mechanical components always come with maintenance issues and are rather big. To avoid using them, flat phased-array antennas are used to electronically steer or 'shift' the beam. These antennas, too, have a disadvantage: correcting the phase differences with a phase shifter reduces the strength of the signal for different frequencies, resulting in insufficient bandwidth. "On top of that, neither type of system is still flat enough to be built directly into the fuselage of an aircraft. Instead, they are mounted on top of the aircraft inside a protective radar dome or 'radome'."

Penalty loops

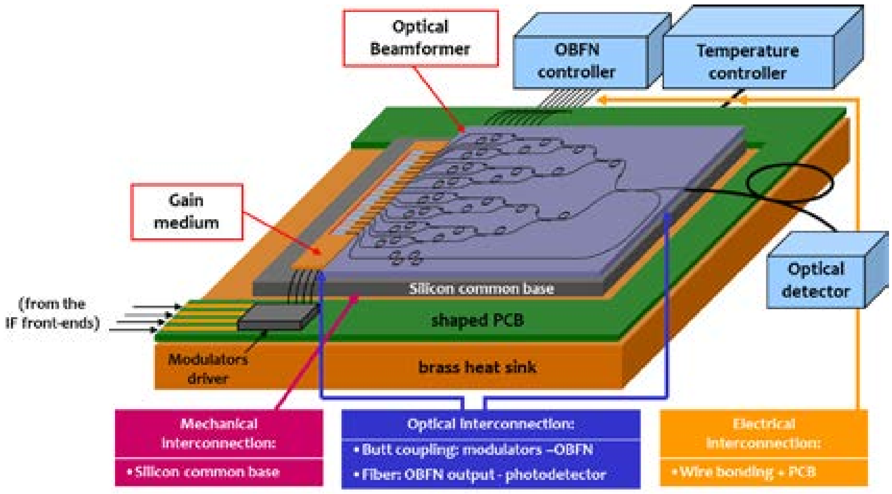
In earlier projects, researchers at the University of Twente developed a demonstrator for a new type of antenna system that cancels out these drawbacks. This system can not only track satellites during the flight of the aircraft without any mechanical movement but is also smaller, cheaper to produce and more intelligent. Last but not least, it is more environmentally friendly because it is ultra flat. "Because of the radome, the current systems consume significantly more kerosene. Since the aerodynamic drag of a flat antenna system is zero, that can save an aircraft approximately 2 to 3% on fuel consumption compared to other systems for airborne satellite communications."
The demonstrator of the special antenna, which was developed and successfully tested by Roeloffzen's Telecommunication Engineering group, contains an Optical Beam Forming Network (OBFN) as its core technology. Roeloffzen explains: "In the OBFN, the high-frequency radio signals are first converted into optical signals so they can be processed. Then we delay these light signals by making the signal path longer or shorter, as necessary, using optical ring resonators. In these resonators, the light signals can be made to do additional 'penalty loops' to delay their arrival." This functionality is integrated on a single photonic chip using regular CMOS production techniques. Finally, the resulting signal is converted back to radio-frequency



The existing demonstrator, containing an older version of the optical chip (right) and off-the-shelf components with bulky glass-fibre cables (left). 'Promis2Day' will integrate all these components on a single photonic chip



Wafer containing the current version of the photonic chip (Photo: LioniX)



The design of the integrated optical beamforming system

signals. “The international response to this revolutionary technique has been very positive, but further integration is required to realise a cost-efficient and compact module. We want to get all the necessary steps onto a single chip. For instance, the converters we are using in the current demonstrator are expensive, off-the-shelf components with bulky glass-fibre cables. Our aim is to reduce the size of the demonstrator from 30 x 40cm to a tile the size of a beer coaster containing 64 elements. Ultimately, one antenna system will consist of 32 such tiles and will be able to establish a satellite broadband connection with a speed of 3 Gb/s. That is the maximum speed that current satellites offer.”

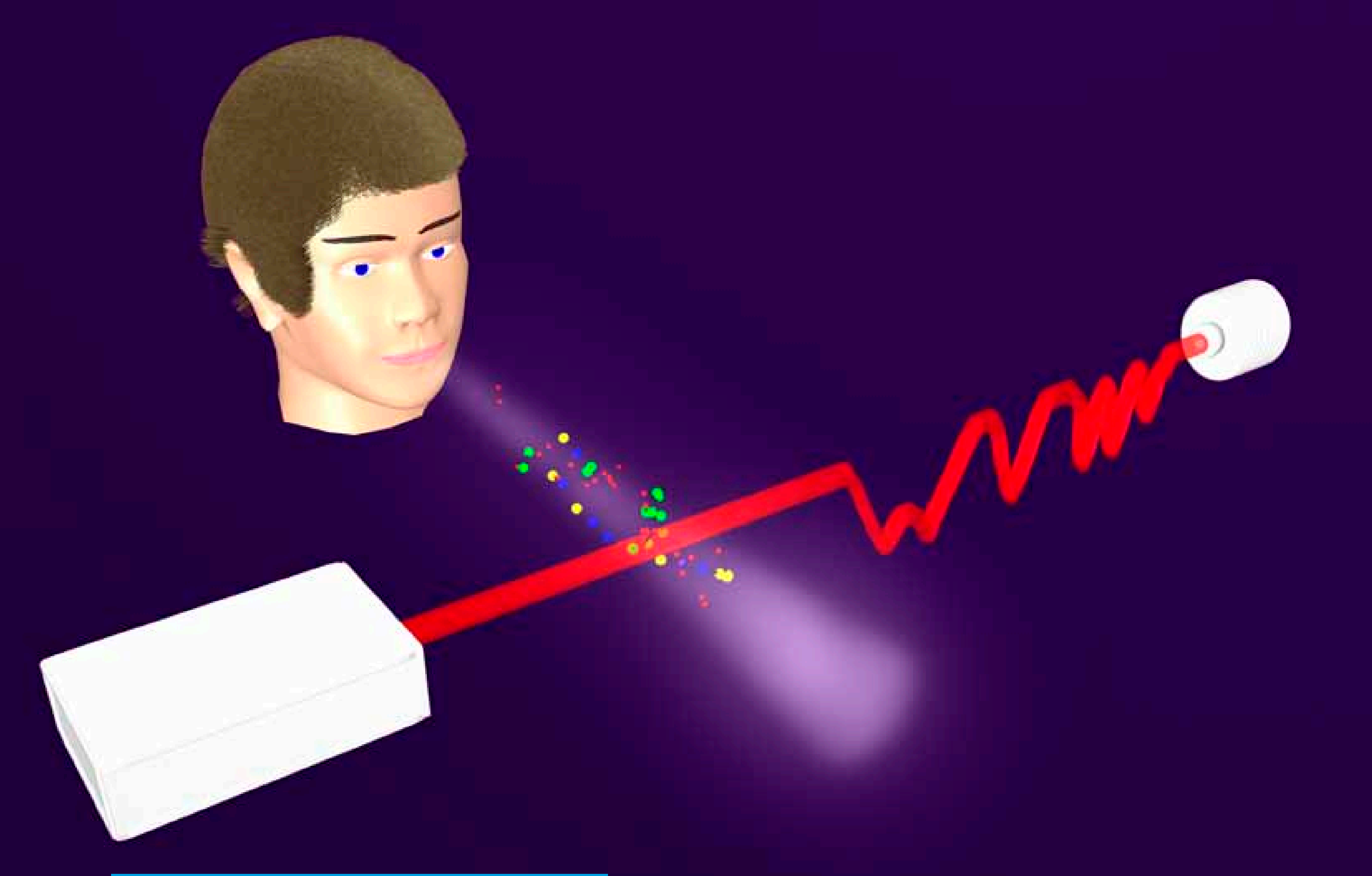
Market potential

Roeloffzen’s group is responsible for the system architecture in this project. His researchers are working closely together with the Laser Physics and Nonlinear Optics group, also of the University of Twente, which will design and optimise the necessary laser and converters. Several industrial partners are involved as well. The university’s spin-off company LioniX will design and produce the optical chips using their TriPleX optical waveguide technology. This technology can process the light signals on the chip with minimal energy loss. Neways Micro Electronics is responsible for developing the packaging. Last but not least, SATRAX, another spin-off of the university, will commercialise the resulting smart antenna array. “I am convinced that there is great market potential for this solution,” says Roeloffzen. “That is why I founded SATRAX in 2009. Airlines, producers of antenna systems and ultimately the automotive market all want to offer broadband connectivity to their customers. But to be able to do that, it is essential to miniaturise the components on a single optical chip and to lower the costs significantly. In this project, we will prove that this can be done.”

Participants:

- LioniX
- Neways Micro Electronics
- SATRAX
- University of Twente

Contact:
Dr ir Chris Roeloffzen
T: +31 (0)53 489 28 04
E: c.g.h.roeloffzen@utwente.nl



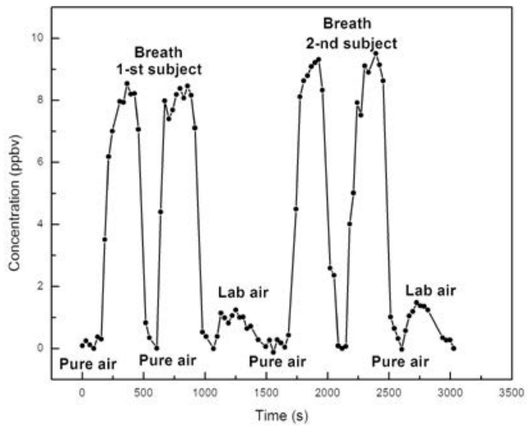
Project number: IPD12015
Project name: Integrated FTS
Goal: to develop an integrated Fourier transform spectrometer (FTS) for chemical sensing based on multiple mode-locked lasers

Breath analysis using trace gas analysis techniques based on absorption spectroscopy

Integrated gas sensor

Patients suffering from the lung disease cystic fibrosis are prone to respiratory infections with Pseudomonas aeruginosa. Such bacterial infections cause progressive damage to the lungs and airways and are the most important cause of mortality. A quick, patient-friendly, reliable and sensitive method is needed to detect infections in an early stage. The IOP project 'Integrated FTS' will develop a gas sensor based on absorption spectroscopy that meets these requirements. Other application areas will also benefit from the sensor.

Currently, monitoring infections with Pseudomonas aeruginosa is not feasible, since samples for cultures can only be reliably obtained through bronchoscopy. Most cystic fibrosis patients are young children or adolescents, and their condition makes this procedure unsuitable for routine screening. "Trace gas analysis techniques based on absorption spectroscopy can provide a very good solution to this problem, because you can detect P. aeruginosa bacteria by looking for the presence of hydrogen cyanide in breath," says Dr Frans Harren of the Institute for Molecules and Materials at Radboud University Nijmegen. "Doctors would only need a sample of exhaled breath from the patient to perform the analysis."



Examples of HCN concentration levels in human breath

Absorption spectroscopy

Gas sensors based on absorption spectroscopy can detect certain chemical substances in a breath sample by sending light of a wavelength that approximates the absorption peak of a specific type of molecule through the sample. The amount of light that reaches a detector at the other end is indicative of the number of those particular molecules present, in this case hydrogen cyanide (HCN).

The current industrial standard for absorption spectroscopy is Michelson-based Fourier transform spectroscopy (FTS). In FTS, light from a broadband light source is passed through a sample and analysed by a Michelson interferometer. The output of the interferometer is sent to a photodiode, where all the spectral features are recorded at once. The signal is then Fourier transformed to calculate the exact frequencies at which absorption takes place.

Doctors would only need a sample of exhaled breath from the patient to detect P. aeruginosa infections

Nobel Prize winners

Although FTS has unique advantages and is relatively simple, it lacks sensitivity, comes with a large footprint and is very expensive. "For the real-time detection of molecules at a high resolution and with a high sensitivity – a concentration level in the parts-per-billion range – it is simply not suitable," says Harren. Promising new strategies for the next generation of spectroscopic instruments have emerged from research on laser-based precision spectroscopy, including the work done on the optical frequency comb technique by Theodor Hänsch and John Hall, winners of the 2005 Nobel Prize in Physics. "Frequency combs will replace both the light source and the Michelson interferometer that are used in traditional Michelson-based FTS. They are a very promising solution because one frequency comb is equivalent to hundreds of thousands of single-mode lasers emitting at perfectly well-known frequencies. This makes it possible to cover a large spectral bandwidth without the complex FTS setup."

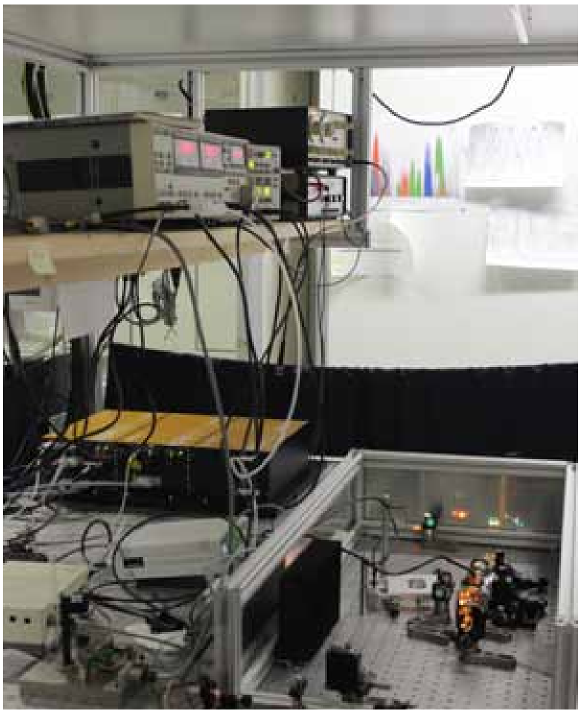
Semiconductor lasers

However, the frequency comb setups currently used in metrology and physics research laboratories have several drawbacks. They are bulky because they use solid-state lasers or fibre lasers, but they are also expensive: a typical setup costs €100,000. They also require experts to maintain and stabilise the lasers. To solve these problems, this IOP project will take advantage of the integrated technology of femtosecond mode-locked semiconductor lasers. Harren: "Such lasers are very small and the optical chips that contain them can be mass produced. This will make it possible to develop a compact gas sensor that is potentially much cheaper, at approximately €10,000 to 15,000 per sensor."

By using two mode-locked lasers in the same integrated design, multiple gaseous molecular compounds can be analysed in real time. This will widen the applicability of gas sensing to include other gases such as H_2O, CO_2 and its isotopes, and ammonia (NH_3).

Expertise

The project consortium brings together expertise in laser engineering, high-resolution spectroscopy, digital signal processing and trace gas sensing and its applications. "The consortium partners have been carefully chosen to cover all these areas," explains Harren. The Photonic Integration



The current frequency comb setup at the Life Science Trace Gas Facility at Radboud University Nijmegen

Life Science Trace Gas Facility at Radboud University Nijmegen

group of the Eindhoven University of Technology (TU/e) will conduct the research on the proposed mode-locked lasers and the necessary electronics. SMART Photonics, a spin-out company of Philips and TU/e, will design and produce the optical chips containing the lasers. The packaging of that chip and the electronics will be done by EFFECT Photonics, another spin-off of the TU/e. Sensor Sense, a Nijmegen-based developer and manufacturer of trace gas detectors based on optical techniques and itself a spin-off company of Radboud University Nijmegen, will provide a proof-of-principle system and develop a valorisation plan. Last but not least, Radboud University Nijmegen will provide the requirements for the integrated system and be responsible for the first demonstrations of the gas sensor in three healthcare trace gas sensing applications.

Kidney diseases

In one demonstration, a compact test setup specifically for HCN monitoring will be used at the Radboud University Nijmegen Medical Centre to detect infections with P. aeruginosa bacteria. “The possibility of rapidly analysing complex gas mixtures is also relevant for monitoring patients with kidney and/or liver diseases, as we will show in the second demonstration,” says Harren. “Using breath tests to detect NH3 – an indicator for such diseases – could reduce dialysis time. The third medical demonstration involves the detection of Helicobacter pylori infections in the stomach by looking for the presence of isotopes of CO_2.” The latter two proofs of concepts will be conducted in collaboration with the UMC Utrecht.

Agrotechnology is another interesting application area for real-time gas sensing. “Take the real-time monitoring of food-storage conditions and especially the amount of CO_2 in the air, for instance. By maintaining optimal conditions for fruit and vegetables, you can protect the crops against moisture loss, decay and ageing.”

Participants:

- Radboud University Nijmegen
- EFFECT Photonics
- Eindhoven University of Technology
- Sensor Sense
- SMART Photonics

Contact:
Dr Frans Harren
T: +31 (0)24 365 21 28
E: f.harren@science.ru.nl

The IOP Photonic Devices is being carried out by NL Agency. For queries regarding the IOP Photonic Devices, please contact one of the following NL Agency programme coordinators:

Programmacoördinatoren Agentschap NL:
Dr ir Eddy Schipper
T +31 (0)88 602 53 43
E eddy.schipper@agentschapnl.nl

www.agentschapnl.nl/iopphotonicdevices

The following individuals are members of the advisory committee for the IOP Photonic Devices:

This is a publication of:

NL Agency
NL Innovation
Juliana van Stolberglaan 3
P.O.box 93144 | 2509 AC The Hague
www.agentschapnl.nl

E infoiop@agentschapnl.nl
T +31 (0)88 602 53 41

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The division NL Innovation helps Dutch businesses to innovate, by providing finance, advice and contacts.