TECHNOLOGY LEADERSHIP
IN TRANSFORMATIONAL TIMES

Executive Report 2021 - 2022

Holst Centre

We are living in transformational times with unprecedented, global challenges on health, climate, energy and supply chain. Technology leadership is becoming a critical asset to address these challenges in a sustainable manner.

Holst Centre has continued its innovation efforts, including spinning off new companies during the pandemic of the past 2 years. We have started new innovation areas and, together with our partners, introduced quite a few new technologies to the market. Our aim remains to jointly develop technologies with those partners to support people in having a healthy life, resulting in a resilient society.

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Technology leadership in transformational times

Global transitions are taking place at an unprecedented speed, fuelled by major health, political and environmental challenges. Holst Centre's directors, Kathleen Philips and Ton van Mol, describe how this creates unique innovation opportunities for their partners.

How do you reflect on 2021?

Kathleen Philips: “What stood out for me was the historic success of the semiconductor industry, which not only withstood the effects of the pandemic, but also flourished. Supply chain shortages have demonstrated the need to become less dependent on foreign trade. Governments have invested in tech and the semiconductor industry on an unprecedented scale, acknowledging the importance of technology to overcome today’s societal challenges.”

Ton van Mol: “I fully agree. The research and innovations that Holst Centre is working on are at the heart of what is important for the future of the Netherlands. The fact that Holst Centre is going to play a role in two projects of the National Growth Fund shows that we are working on socially relevant themes.”

What emerging technologies will soon change our lives?

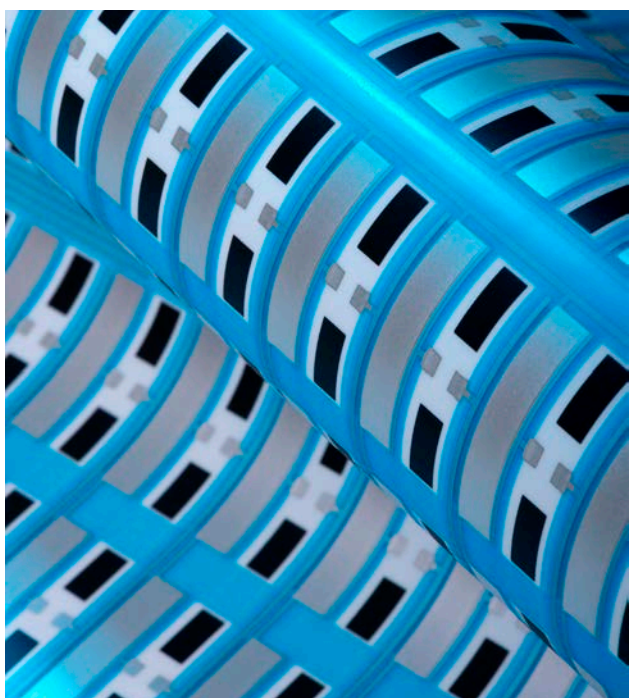
KP: “We are seeing the comeback of Ultra Wide Band (UWB). Where GPS can give you meter-level accuracy, UWB is going to bring that down to centimetre-level accuracy. Imagine the wealth of new applications for positioning this technology sparks for any IoT device, and adding Edge AI intelligence will further enrich the use cases. Plus integrated photonics I would say, which is right in the middle of the hype curve.”

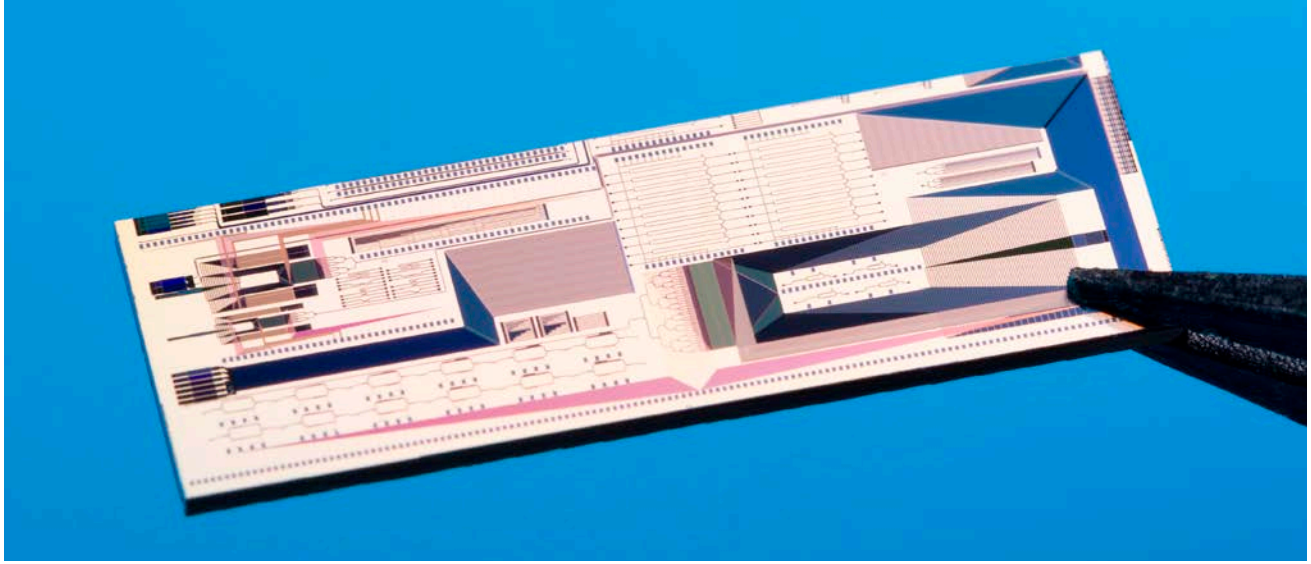
TvM: “Yes, for sure integrated photonics is one of the most promising emerging technologies for our industry and region, and PhotonDelta is one of the two National Growth Fund projects on which we collaborate with the high-tech industry. The potential of this technology is huge, because you can apply it in multiple markets. Photonic chips support the sustainable and energy-efficient solutions needed for applications that include the exponential growth of data traffic, safer autonomous cars, more efficient food production, and health monitoring. Together with our partners we want to further develop this technology and expand production facilities in the Netherlands and Europe to strengthen our global position in photonics.”

How can partners benefit from Holst Centre’s expertise?

KP: “Particularly in this development stage of photonics, the technology benefits from Holst Centre’s open R&D model, our eco-system thinking, and pre-competitive support. The joint knowhow of TNO and imec are exactly what this industry needs to create the missing links and overcome risks that are not per se core business for the companies

Holst Centre remains at the forefront in **health tech**





The potential of integrated **photonics** is huge

involved. We have the assets and knowledge in this region to become world-leading in photonics, but it's important to make profound choices. Either you're all-in, or you're going to find yourself out."

We are faced with several fast-paced major global changes. Where do you see opportunities for your partners?

TvM: "At Holst Centre we are working in close collaboration with the Dutch high-tech manufacturing industry on a future generation of machines to address societal challenges. Energy storage is one of them. That's why we are setting up research facilities for the sustainable production of hydrogen through water electrolysis. We are working on a new generation of batteries that will enable electric cars to travel up to 1,000 kilometres without recharging. Furthermore, Holst Centre remains at the forefront in health tech, with our state-of-the-art health-patch platform and our work on implantable artificial organs. We have the knowledge and expertise to develop these techniques further and share them with other partners."

What are your hopes and expectations for next year?

KP: "We have witnessed a significant increase in tech investments from governments, and we feel supported by our stakeholders who acknowledge the importance and added value of technology to help overcome society's biggest challenges. Therefore we feel confident to continue on this path of joint innovation to keep up with the increasing speeds of global transitions, in health, mobility, energy and other key areas of our society."

TvM: "Absolutely. And I'm also looking forward to bring back the joy of working and building together within Holst Centre. It's a delight to be able to physically work together again, and find new ways and opportunities to collaborate."

Celebrating 15 years of open innovation

Founded 15 years ago as an open innovation research institute by imec and TNO, Holst Centre now boasts over 170 employees from 28 nations who, together with 56 industrial partners, innovate and connect, in answer to today's and tomorrow's societal challenges.

Back in 2005, Philips contacted the R&D centres of imec and TNO to set up an external research lab that would accelerate innovations by way of collaborative research programs with the industry. Based on this visionary foresight Holst Centre was established in 2006. Since then, the disruptive technologies that were developed have been enormously impacting.

Right from the start Holst Centre research proved valuable for tomorrow's electronics, accelerating OLED and flexible display technology for use in future smartphones. Pioneering work in the field of hybrid printed electronics has resulted in advanced IoT sensors, flexible LED foils and wearables. Holst Centre's partnerships allow the industry to apply these disruptive technologies in successful, market-ready products, like Onera's sleep monitoring device and the Philips Healthdot for unobtrusive vital sign measuring.

Freedom to explore

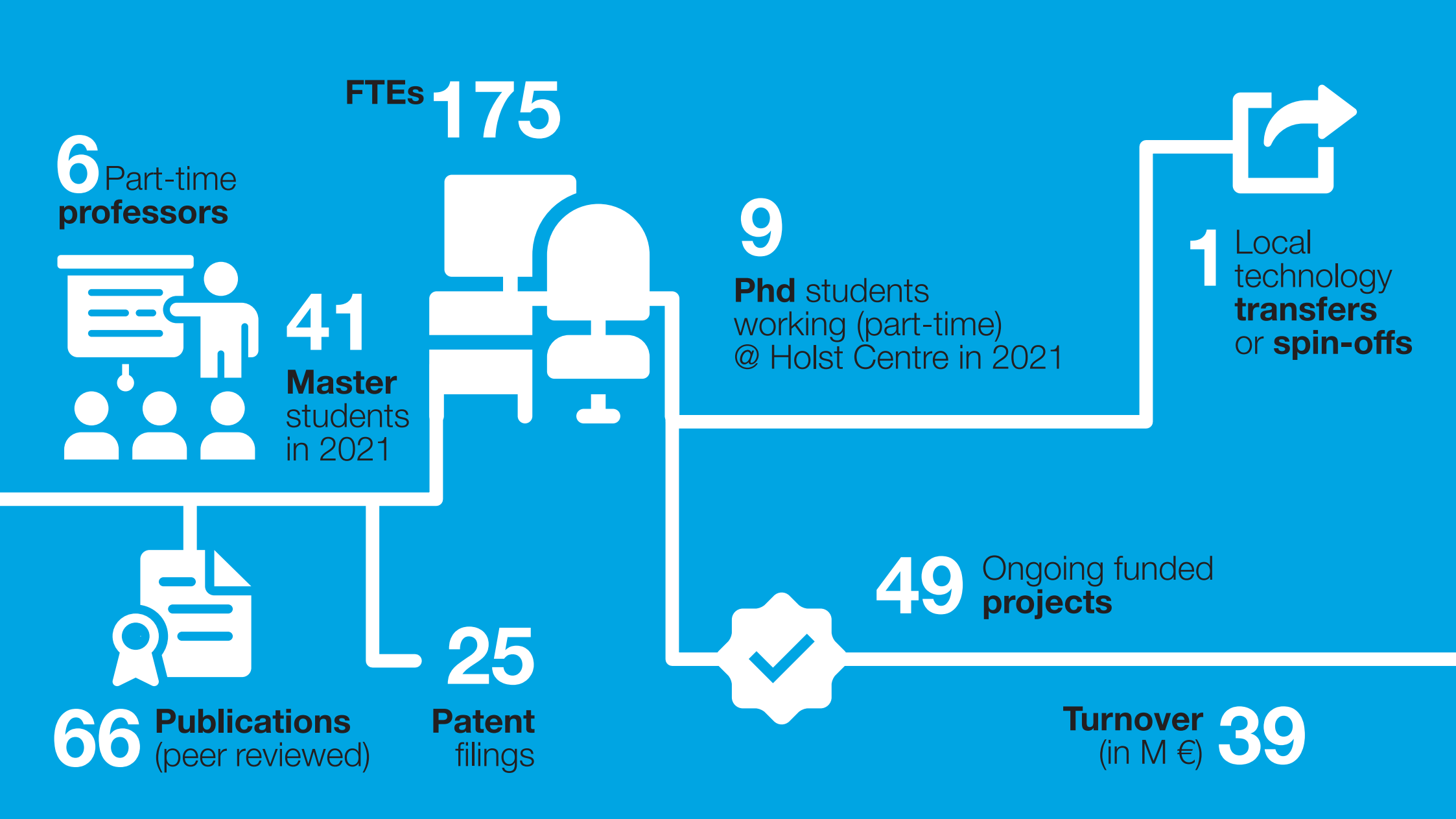
When we reflect on the past 15 years, what have been the key success factors for Holst Centre, we asked both directors. "A long-term vision combined with persistence and focus", says Kathleen Philips, director for imec. "But also our approach to R&D. We believe in the power of having the freedom to explore, while working closely with our industrial partners. At the same time ensuring we learn fast and continuously move forward. In this way, we have become an innovation leader." For Ton van Mol, director for TNO, the strength of Holst Centre lies in innovation with a disruptive character. "By jointly carrying the risk for and with the industry, we are enabling future value-adding technologies. Our challenge – and it's something we are successful in doing – is to continually check if our vision still fits with societal needs and industry priority."
Kathleen Philips concludes: "What we have learned over the past 15 years, is that success is something that cannot be predicted. Nevertheless, we have a proud and proven track record in designing many ground-breaking innovations, enabling business success for our industrial partners, our start-ups and society."

Facts & Figures 2021

Regional NL **collaborations** **16**

(Total number of) **partnerships** **58**

Dutch partners within funded projects (EU and national) **94**


FTEs 175
6 Part-time professors
41 Master students in 2021
9 Phd students working (part-time) @ Holst Centre in 2021
1 Local technology transfers or spin-offs
49 Ongoing funded projects
66 Publications (peer reviewed)
25 Patent filings
Turnover (in M €) 39

Start-ups & spin-offs

Holst Centre start-ups

For imec: Bloom, LifeSense, Onera, launch of imec.istart.nl in The Netherlands

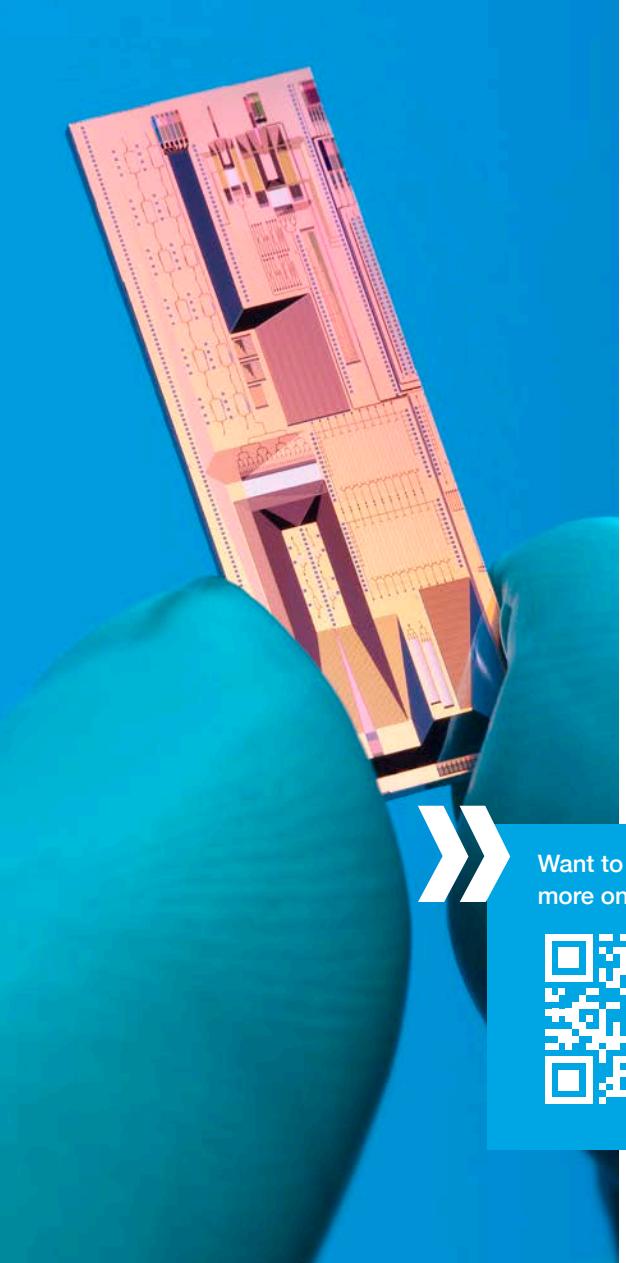
For TNO: Saldtech, Keiron, LionVolt, BeinginTouch, TracXon

Holst Centre's battery start-up LionVolt has successfully closed a seed round of €4 million, bringing its total funding to more than €5 million. Sleep monitoring start-up Onera Health received €10.5 million in Series B funding.

Holst Centre is successfully launching start-ups and accelerator programs to fill in gaps in the value chain and to kick-start new ecosystems. Ton van Mol, director of TNO at Holst Centre: "Parties are interested in our technologies, but prefer product-based collaborations to knowledge-based partnerships. At the same time the innovation ecosystem of industry partners has shifted, from in-house R&D towards start-ups. And with new deep-tech funds on the rise, the investment climate for start-ups has improved significantly." Kathleen Philips, director of imec at Holst Centre: "Next to launching our own start-ups, we are also stimulating partnerships with other start-ups, who are in need of specific expertise, that's a business model for us as well. They prefer working with us because of our track record in maturing technology, and because of our ecosystem with many valuable future partners. Moreover, in 2021 we launched imec.istart.nl; this is an expansion of the successful Belgian venturing program with the aim of further strengthening the Dutch innovation landscape."

The innovation ecosystem of industry partners has shifted, from in-house R&D towards start-ups

Accelerating the commercialisation of Integrated Photonics



Want to learn more on PITC?

In our data-driven society integrated photonics will be a key enabling technology for a wide spectrum of communication and sensing applications. The founding of the Photonic Integration Technology Center (PITC) and the €1.1 billion grant of the Dutch National Growth Fund to PhotonDelta, will enable the Dutch photonics ecosystem to further grow into a world-leading industry.

Integrated Photonics represents a revolutionary technology that allows the development of energy-efficient chips that can sense, capture and process huge amounts of data using light instead of electricity. Photonics expert of imec at Holst Centre, Ruud Oldenbeuving: “We are currently seeing the development of multiple optical platforms. For Integrated Photonics to become successful we will ultimately need various combinations and a seamless integration of these platforms with electronics. Current electronic chips have reached their bandwidth limits. Photonics will open up new perspectives for developing energy-efficient digital solutions.” TNO and imec at Holst Centre join forces to accelerate this technology, by focusing on the integration of photonics with electronics. The importance of our ambition was recently acknowledged and awarded by the Dutch National Growth Fund’s grant to photonics accelerator PhotonDelta.

Bridging the gap

In 2021, PhotonDelta together with TNO, Eindhoven University of Technology and University of Twente launched PITC. Jan-Laurens van der Steen, Business Development Manager for TNO at Holst Centre: “This initiative will speed up the industrial uptake and commercial adoption of integrated photonics. With PITC we have copied the successful Holst Centre collaboration model in which program partners jointly tackle technology challenges, thereby reducing the cost and risk of new technology development. PITC aims to become the leading center of excellence in Integrated Photonics.”

Workplace Vitality Hub

Office environments contribute to a sedentary lifestyle and a whole range of chronic diseases. In the search for improved vitality, the work floor becomes a focus area. To raise awareness, gain knowledge, and demonstrate the added value of technology for a healthy workplace, Holst Centre and partners TU/e, Fontys, High Tech Campus Eindhoven (HTCE) and Twice, have founded the Workplace Vitality Hub at HTCE.

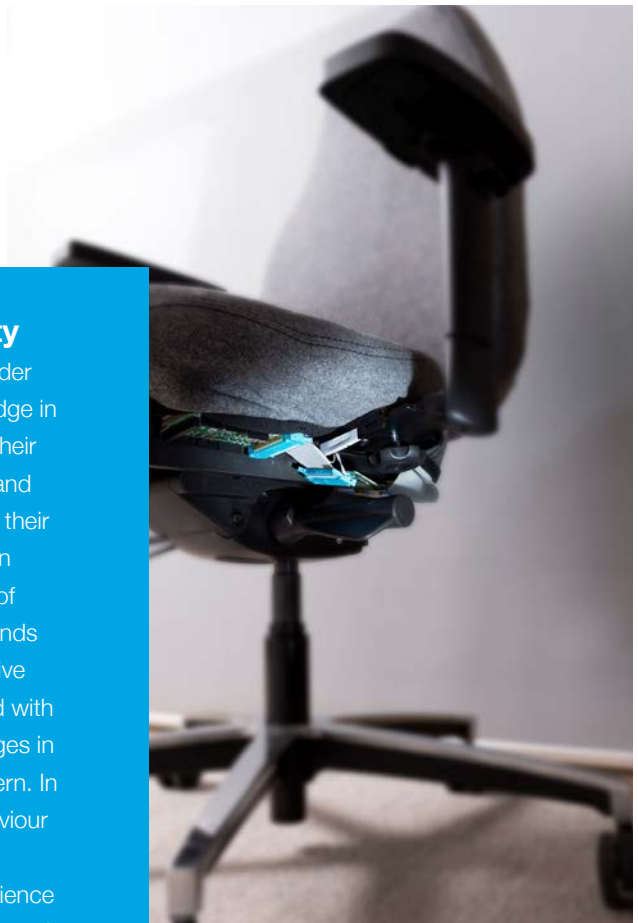
The opening during a pandemic was challenging but also valuable, explains Sywert Bongersma, Director Strategic Partnerships at Holst Centre. “The pandemic has helped tremendously to put the vitality topic on the agenda, underlining the importance of working in a safe and healthy environment. Employers ask themselves: how do I get my people to return to the office? Additionally, the battle for talent has convinced companies to invest in optimised working environments. They’ve come to realize that vitality and joy at work have a bigger impact on productivity than

People should return from their work **more energised** than when they arrived in the morning – that's the dream we have

squeezing an extra per cent of efficiency from a square meter of office space. People should return from their work more energised than when they arrive in the morning – that's the dream we have."

Contributing to that dream is a vast knowledge base on sensors, data technology and the physical work environment. Together with business partners and solution providers a broad innovation network has been set up. The Vitality Hub is a living lab where technological, design and social innovations are developed to be validated. It is also a place where employees and employers can experience what workplace vitality entails, and where an active ecosystem is built around office vitality.

Want to learn more about Vitality Hub?



Take a seat and learn about vitality

At Holst Centre, innovative chairs are currently under development to provide a vast amount of knowledge in how to support people to improve their vitality in their working environment. Collaborating parties TNO and imec are looking into ways to adapt and combine their existing technologies. Imec, for instance, has been looking into ECG measurements without the use of patches and direct skin contact. TNO uses two kinds of sensors in a so-called vitality chair. Piezo-resistive sensors measure pressure to assess posture, and with piezo-electric sensors you can detect small changes in pressure, indicating a heartbeat or breathing pattern. In addition to gaining knowledge on our sitting behaviour at work to combat lower back pain, still the most common ailment for office workers, we can experience how technology can contribute to a more active lifestyle.

Organ on Chip

Boosting the OoC-ecosystem with proven electronics manufacturing techniques

Organ on Chip (OoC) technology holds promise to reduce animal testing and establish more efficient drug-discovery processes. Recent breakthroughs by TNO at Holst Centre include the successful demonstration of cost-effective and scalable fabrication technology for OoC platforms using biocompatible materials and processes.

With our flexible electronics and large-area manufacturing expertise, TNO at Holst Centre is able to accelerate OoC technology and stimulate the development of new medicines such as those for neurodegenerative and cardiovascular diseases.

Within the realm of pharmaceutical research, more human-specific compounds are being developed, which are not suitable for traditional preclinical models, such as murine and other animal models. To close the gap between preclinical and clinical studies, in-vitro devices like organ- and lab-on-chip, plus smart multiwell plates (microplates) are used.

Biocompatible and low-cost solution

TNO at Holst Centre uses industry-proven manufacturing techniques from the world of flexible, printed circuit boards and flat panel displays to design smart multiwell plates that contain microfluidics, and possess integrated electrodes. Albert van Breemen, Senior Scientist of TNO at Holst Centre: “Using our scalable technology we recently have managed to create electrode arrays and microfluidics on one substrate that are biocompatible, which means we can use them for monitoring living cells. By enlarging the substrate, we can upscale production volumes and significantly reduce production costs. Future developments are directed towards the development and integration of additional sensors, such as oxygen, pH and glucose sensors, to further increase the precision and capabilities of in-vitro monitoring.” Ultimately these innovations help to reduce animal testing and promote faster and more efficient drug development.

Fokko Wieringa, Principal Scientist of imec at Holst Centre adds: “Exactly in this context we welcomed Stichting Proefdiervrij on board of the NXTGEN HighTech Growth Fund project. Also, we helped the Dutch National Standardization Institute (NEN) to become the Secretariat of the CEN/CENELEC European Standardization committee for Organs on Chip. In parallel, together with the Dutch Kidney Foundation, European Kidney Health Alliance and American Kidney Patients Association, we are shaping the international roadmap for artificial kidneys. And the same innovation model can also be applied for other Artificial Organs.”

Human-centric Wearables

Validated technology for comfortable long-term home monitoring

Human-centric wearables developed by Holst Centre have the potential to greatly improve patients' lives and accelerate preventive care, while significantly reducing healthcare costs.

Holst Centre

Effective health management relies on accurate, long-term monitoring of physiological parameters. Imagine the added quality of life for a patient who is able to perform his daily routine while being monitored remotely, instead of being hospitalised. Consider the advantages for people in high-risk groups in terms of patient treatments and healthcare costs with unobtrusive medical-grade monitoring devices that accurately detect health risks. Add to that the positive impact on the workload of hospital staff of home monitoring solutions, and it's easy to understand the great potential of Holst Centre's human-centric wearables.

Pre-clinical validation

Ranging from health patches applied directly to the body, to smart fashion, combining the electronics with desirable clothing, over the years Holst Centre has successfully developed a complete range of human-centric wearables.

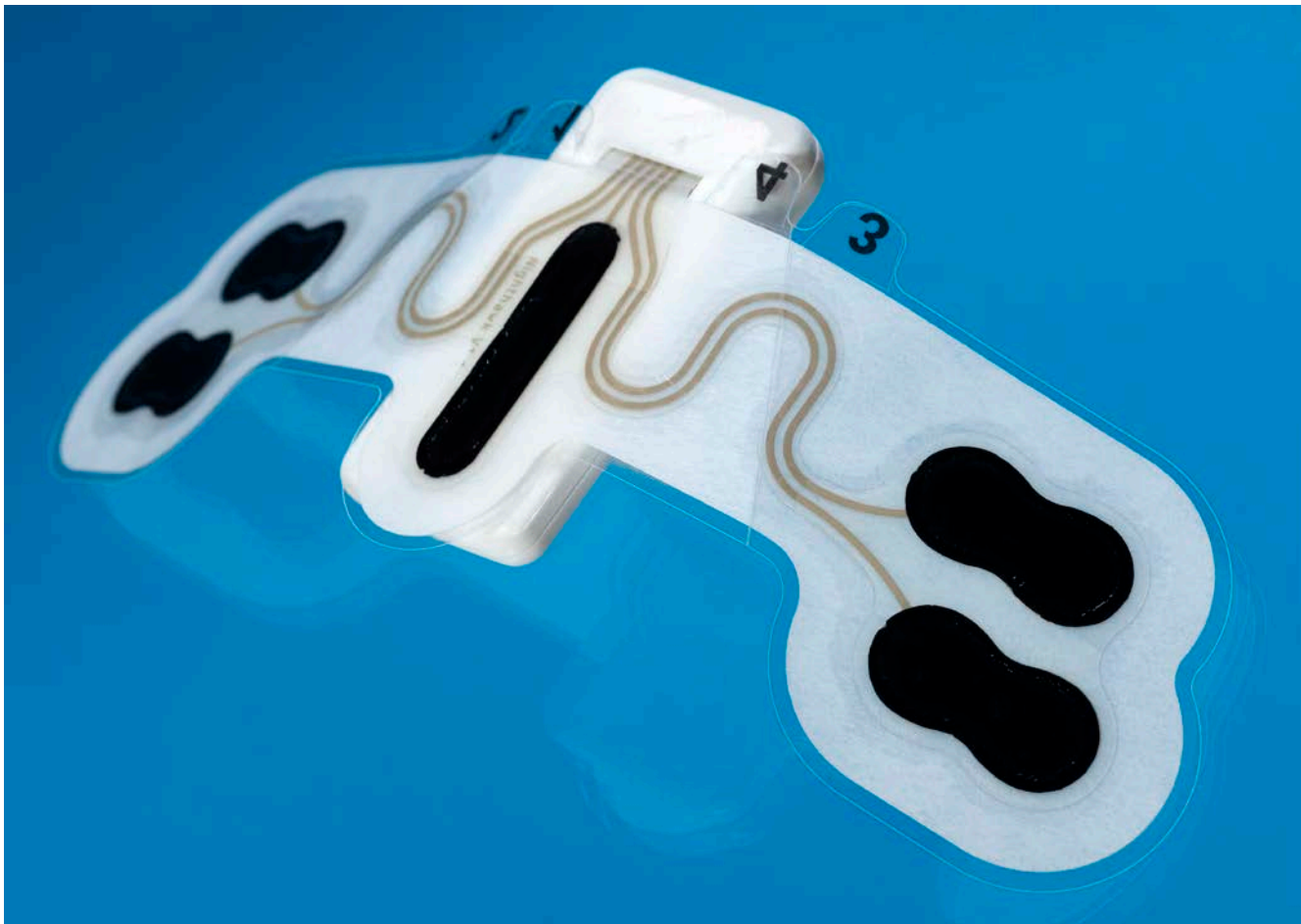
At the heart of all these devices is the multi-sensor health patch platform that is customizable for the home monitoring of a wide range of medical conditions and ailments. Charlotte Kjellander, Senior Scientist Integrator from TNO at Holst Centre: "Our most recent milestone in the development of our patch platform was the validation in pre-clinical trials. These trials proved that the patches are comfortable and reliable to be worn on the human body for up to five consecutive days. At Holst Centre we are experienced in setting up these extensive pre-clinical trials, which follow strict ethical protocols. Our partners benefit from a large network of academic hospitals and medical specialists in the field to start the validation process at an early stage."

Unique building blocks

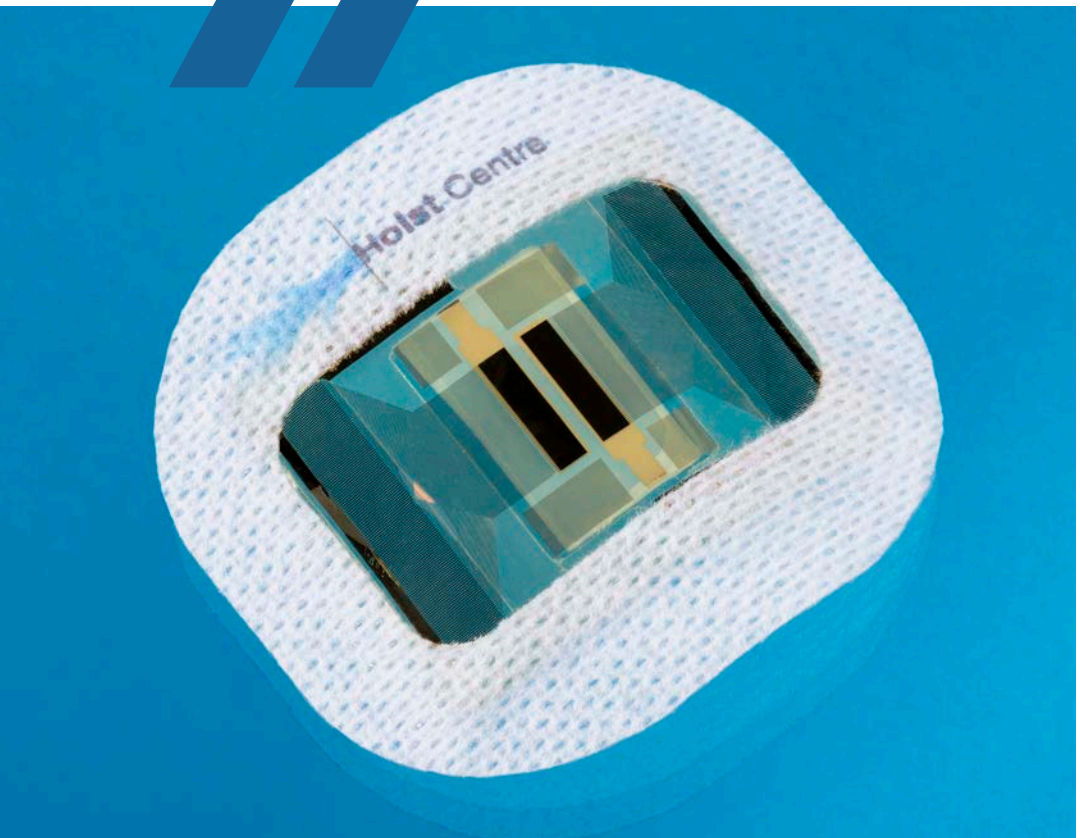
The key differentiator of our patch technology is the combination of tried and tested building blocks with unique

Together with our partners we will continue to innovate our patch platform »

properties. The stretchable, water-resistant circuitry enables an ultrathin and conformal form factor, in combination with skin-contact electrodes, offering a more skin-friendly solution for comfortable long-term monitoring compared to conventional gel-electrodes. Connection to wearable, low-powered and Bluetooth wireless communication chips, all-in-one, is another unique selling proposition of our health-patch platform. Ashok Sridhar, Business Developer from TNO at Holst Centre: “Together with our partners we will continue to innovate our patch platform with new functionalities and sensors, such as near-infrared and ultrasound, because there’s great demand for such applications. Moreover, we want to use these patches not only for diagnostic purposes, but in the end also to close the loop for treatment. So it’s safe to say that the potential for wearables is significant, and we are continuously looking for partners to discover new application fields.”



Ultrasound patch offers unique wearable large-area imaging solution



“Ultrasound gives you the opportunity to take a closer look inside your body, up to 30 centimetres under the skin,” explains Gerwin Gelinck, CTO of TNO at Holst Centre. “Our patch solution offers two major benefits over current ultrasound probes. First is the opportunity to have a large-area image, where current probes only offer a key-hole view. This is particularly vital for monitoring large organs, such as the heart and lungs. The second advantage is the direct contact of the patch with the skin, required for ultrasound imaging. The flexibility of the patch makes it ideal to apply on larger areas because it follows the curvature of the human body.”

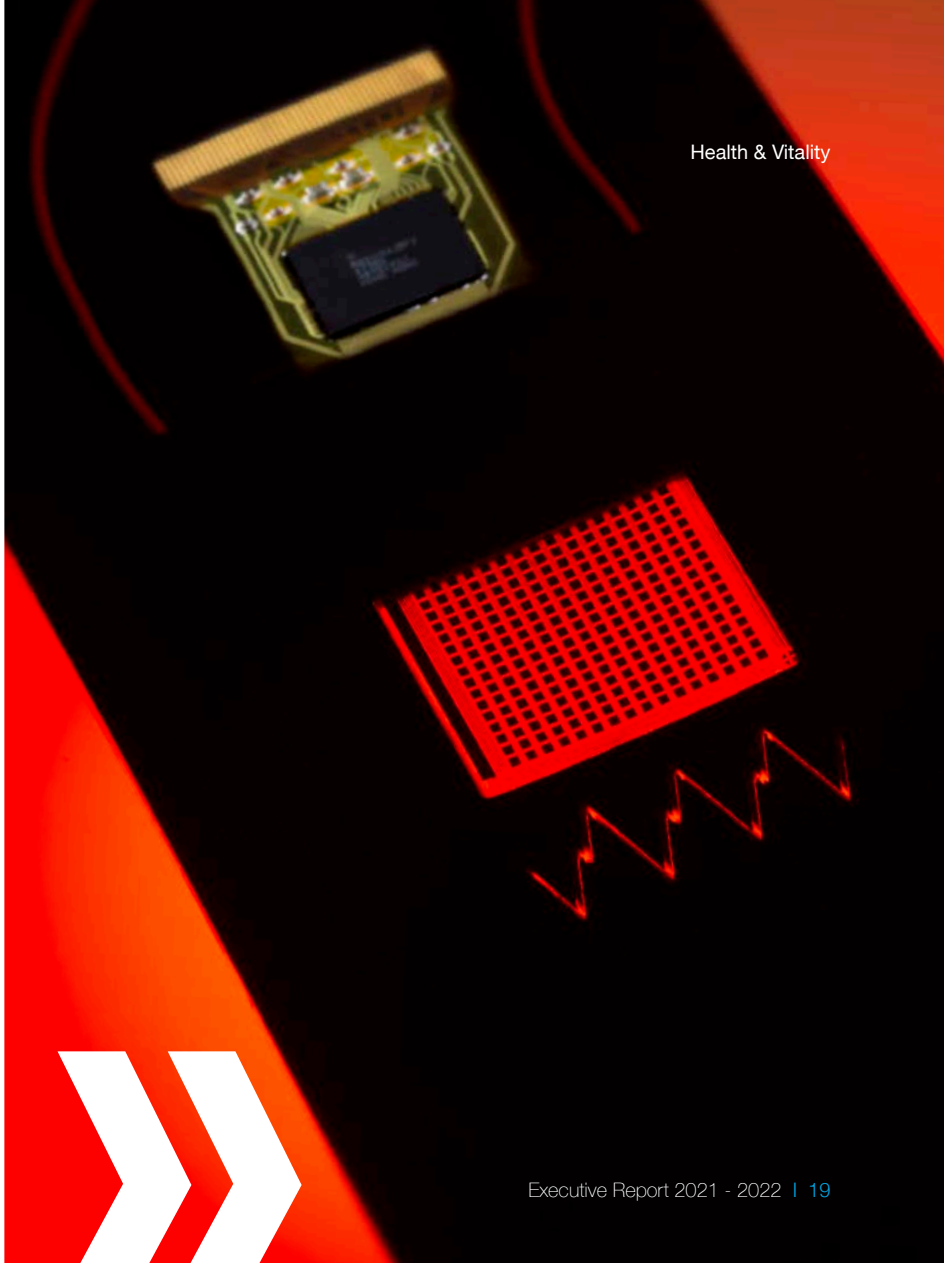
Especially in preventive care the ultrasound patch proves promising. We can for instance remotely monitor the baby’s condition for women with pregnancy health risks.

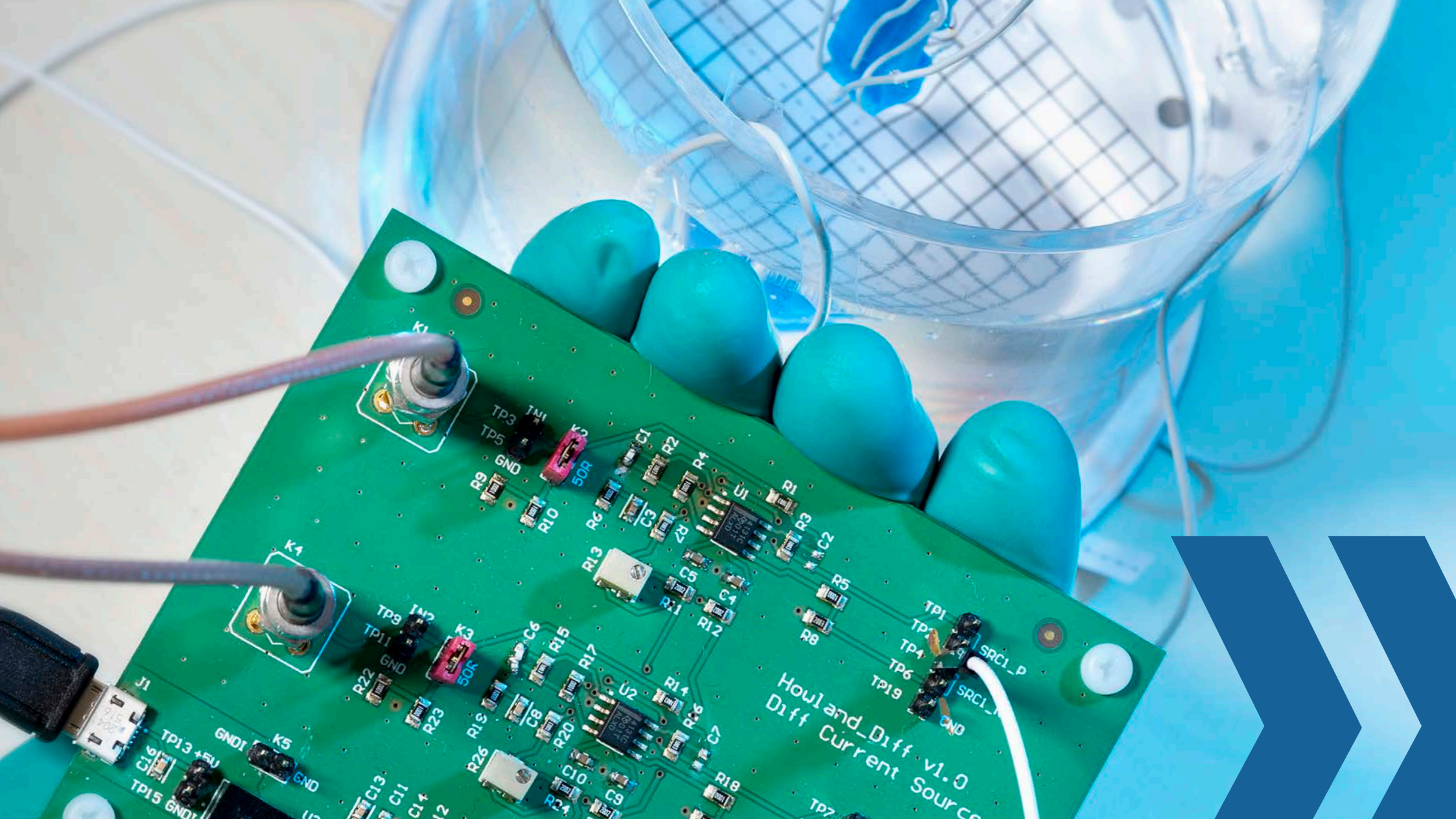
With a patch positioned in the neck you can image the carotid artery and monitor blood flow close to the brain, which helps to diagnose people at risk of a stroke. Another -military- use case for this application is to continuously measure blood pressure to accurately assess the physiological status of fighter pilots.

Wearable optical sensor arrays for accurate cardiovascular monitoring

Cardiovascular diseases (CVDs) are the leading cause of death globally, taking an estimated 17.9 million lives every year. With accurate and comfortable home monitoring devices we can improve patients' lives and detect cardiovascular diseases at an earlier stage. As TNO at Holst Centre, we have developed ultra-thin large-area optical imaging and sensing technology using photo-active layers with a wavelength sensitivity in the near-infrared (NIR). This allows for a deeper penetration of the light underneath the skin, showing differences in oxygen absorption of the hemoglobin. By integrating the photodetector arrays into a wearable and in parallel developing signal-processing algorithms, high-quality PPG signals are obtained in reflection on any part of the human body.

The arrays are very thin and flexible, resulting in intimate skin contact and an optimal signal quality. Numerous medically relevant parameters are extracted, such as heart rate, respiration rate, saturated oxygenation, perfusion and cardiac output. Next steps in research will focus on mapping of various biomarkers and local pulse-wave-velocity measurements (PWV) for continuous cuffless blood pressure monitoring.

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Autonomous Therapeutics

Taking significant steps towards bioelectronic medicine through implantables

Imec at Holst Centre develops next-generation Autonomous Therapeutics applications by means of artificial organs, focused on returning the quality of life to chronic patients. This was explored in the contexts of electrical peripheral nerve stimulation, artificial kidney technologies, surgical tools and photonics. Research in this domain will benefit from the recent acknowledgement and funding by the Dutch National Growth Fund.

The transition from wearable health solutions towards implantable therapy has seen significant breakthroughs. Autonomous Therapeutic systems do not only help monitor our health, but also administer the right (personalized) therapy. This could greatly reduce the load on healthcare, and also provide the opportunity for patients to live normal lives, without having to deal with chronic treatment or lifestyle modifications.To explore the possibilities to adapt and target therapy systems towards sensing and actuation, imec at Holst Centre is working on four promising applications:

1. Pelvic nerves play an important role in bladder, sexual and bowel functions, and movement and sensation in the legs. Peripheral nerve stimulation is used to overcome pelvic nerve disorders. At Holst Centre we have designed a prototype architecture for the Neurogyn pelvic nerve stimulator. Building blocks for more specific stimulation and read-out of nerves are being developed as an in-house research project, which will result in a dedicated silicon chip in 2022.
2. The prestigious KidneyX Prize has been awarded to research team MI-TRAM. The prize allows the team to develop chips that will enable dialysis devices to purify blood much more efficiently (see artifical kidney article on page 27).
3. Surgical tools are developed for specific partners where there is a demand for smart tools and active feedback towards the surgeon to increase the success rate of surgical operations. This project will also provide valuable knowledge for our implantables.
4. Opto-electrical measurement techniques for monitoring heart rate and blood oxygenation have been one of the core competences of Holst Centre's health team for many years. In 2021 we developed an innovative and reliable measuring technique using light. This "Speckle" method is an important stepping-stone for a full-fledged program on photonics.

With two projects approved by the National Growth Fund we can now grow our multimodal research for new biomarkers, photonic actuation (PhotonDelta) and building blocks for bioelectronics medicine and artificial organs (NXTGEN HIGHTECH).

Bioimpedance

Innovative, non-invasive home monitoring using wearable bioimpedance devices

Inflammation is a key characteristic of most chronic diseases, and with imec at Holst Centre's wearable bioimpedance devices, these conditions can be monitored unobtrusively outside the hospital.

As imec at Holst Centre we combine our technological knowhow of designing small, low-power devices with our extensive biomedical expertise to create wearables and, ultimately, implantables that will change the lives of chronic patients forever.

One of the key research areas is bioimpedance, a technique that is already being used to measure fluid accumulation in patients with heart and/or kidney failure. By taking that technology to the next level and integrating it into a small chip for use in a wearable device, patients no longer need to frequently visit hospitals and undergo unpleasant and invasive diagnostic procedures.

"Applying the technology in a very small chip is unique," says Lucas Lindeboom, Biomedical Engineer of imec at Holst Centre. "The technology is non-invasive, widely applicable, and extremely suitable for monitoring all kinds of diseases and conditions. While measurements are becoming increasingly detailed, the technology is getting smaller and smaller. Looking further into the future, we will see that, in addition to wearables, implantables will become the norm."

The technology is **extremely suitable** for monitoring all kinds of diseases and conditions

Promising applications

One of the current applications for bioimpedance wearables is the monitoring of (chronic) inflammation. Fluid accumulation in the lungs of patients with heart failure can also be monitored. The use of bioimpedance in patients with kidney failure to effectively monitor patients' fluid levels is another promising application. Although still in the prototype phase, wearable bioimpedance devices are already being tested in practice. Imec at Holst Centre collaborates with the Future Health department of the Oost-Limburg Hospital in Genk to test and improve the chips, prototypes and algorithms that have been developed.

High-resolution radiation therapy

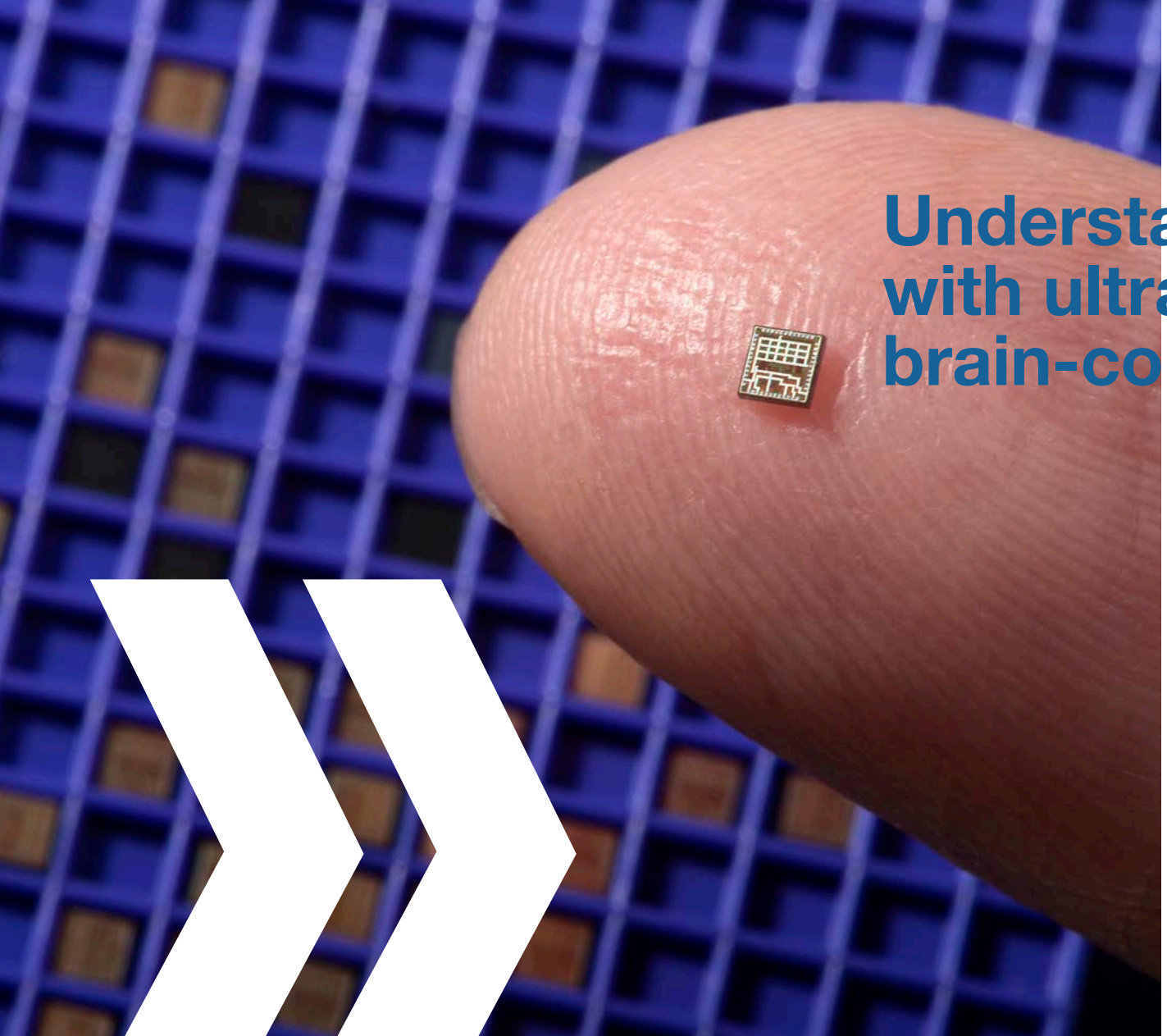
Improving cancer treatment with large-area radiation detectors

TNO at Holst Centre is innovating radiation therapy for treating cancer by developing innovative large-area, high-resolution detector technology that enables a very accurate dose delivery. This technology will greatly improve the effectiveness of radiation therapy, and help save patient lives.

With over 10 million deaths worldwide per year cancer is a leading cause of death. Moreover, from 2020 to 2040 the projected total cancer incidence will increase by almost 30 per cent. Radiotherapy is commonly used to cure cancer by destroying the cancer cells and reducing the size of tumors. According to the National Cancer Institute, about 50 per cent of cancer patients receive some type of radiation therapy during their treatment. During traditional radiation therapy, using X-rays or gamma rays, healthy tissue is also affected. These adverse effects are strongly reduced in hadron radiation therapy, in which high-energy protons and carbon ions can deliver their destructive energy at exactly the right spot inside the tumor. For both modalities, more accurate positioning of the beam spot on the cancer tissue is key.

High spatial and dosimetric accuracy

Currently used detectors for beam positioning have a moderate spatial resolution. Therefore, TNO at Holst Centre has developed a large-area, high-resolution detector that offers a significant step-up in resolution by a factor of 14 -going from 7 to 0.5 mm- allowing for a much more accurate dose delivery. Our high-resolution detectors can save healthy tissue while enabling treatment of smaller lesions at an earlier stage, resulting in better patient outcomes.



Intranet of Neurons

Understanding our brain with ultra-fast wireless brain-computer interface

“We probably know more about the universe and the planets than about our brain.” Scientific Director of imec at Holst Centre, Yao-Hong Liu, is leading the Intranet of Neurons project focused on developing an extremely fast and minimally invasive wireless brain-computer interface. “This could lead to major breakthroughs in research and treatment of all kinds of neurological disorders and psychiatric syndromes.”

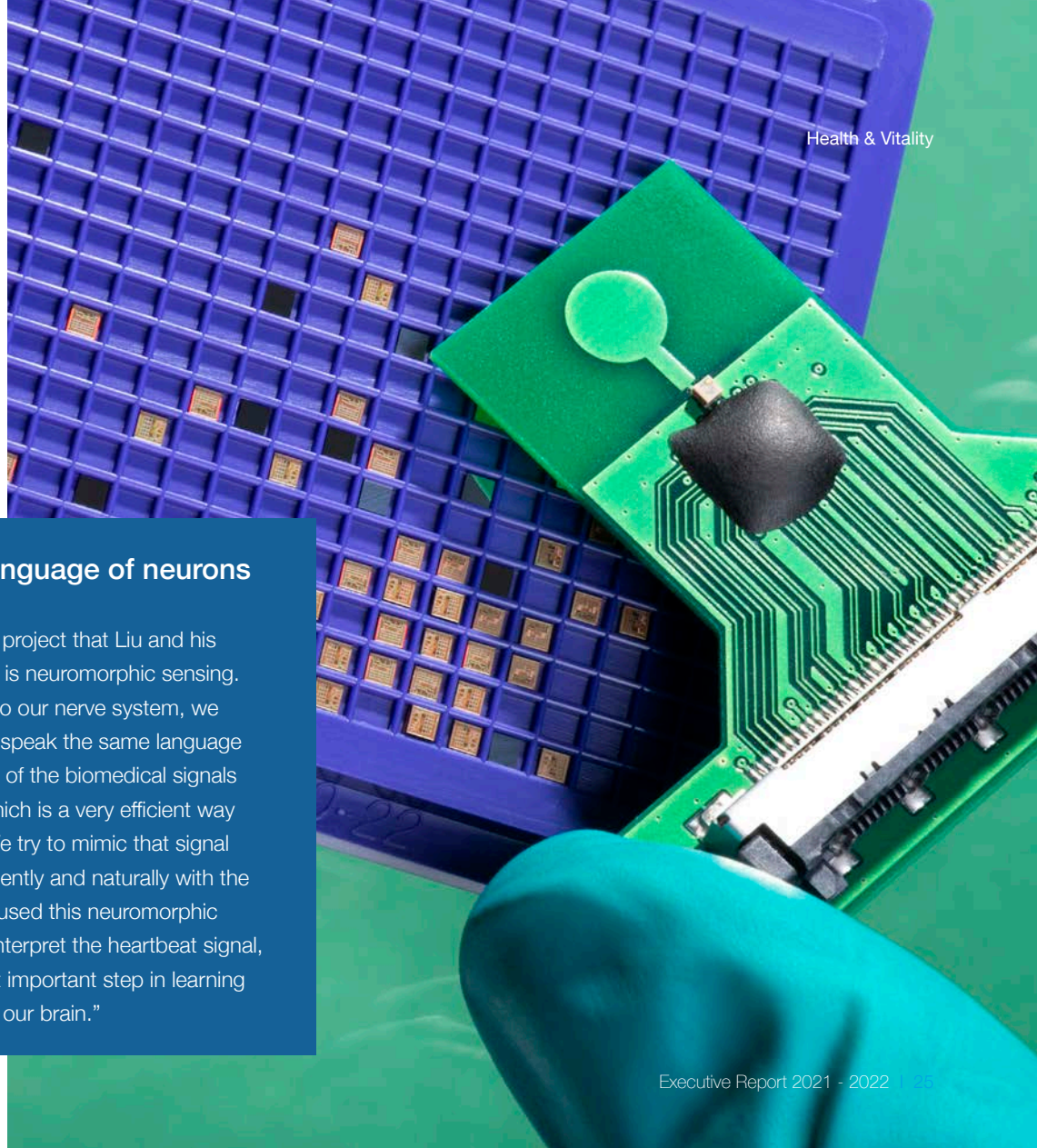
At the International Solid-State Circuits Conference (ISSCC), imec at Holst Centre launched a revolutionary wireless technology suitable for brain-computer interfaces that can access large amounts of neuron activity. Liu: “We managed to push the data-rate up to 1.6 Gigabit per second, roughly 100 times the current state-of-the-art. The low-energy technology makes the wireless interface very well suited for implantables, and its miniaturised design greatly reduces the risk of surgical complications.” The wireless interface is an important building block to eventually build a monitoring device to unobtrusively measure brain activity for longer periods of time.

Robotic limbs and exoskeletons

Ultimately, Liu predicts that within ten years, it will be possible to also stimulate the brain via this wireless connection. “That could mean that we can help patients who are suffering from the consequences of a stroke or other illness, to give back control of their limbs, or let them communicate again.” At the same time, disabled people will be able to control robotic limbs or exoskeletons with this technology. But also, for optimising the function of artificial organs, like a kidney, it’s important to closely mimic real organs and decode their neural communication. Liu: “With this technology, we will eventually be able to give back quality of life to so many patients, that’s an important motivation for our team.”

Learning the language of neurons

Another fundamental project that Liu and his team are working on, is neuromorphic sensing. “In order to connect to our nerve system, we need to learn how to speak the same language as our neurons. Most of the biomedical signals work with a pulse, which is a very efficient way of communicating. We try to mimic that signal to communicate efficiently and naturally with the nervous system. We used this neuromorphic sensing interface to interpret the heartbeat signal, or ECG. It’s a first but important step in learning to communicate with our brain.”



Artificial Kidney

Improving kidney patients' lives using nanotechnology

Smaller, more intelligent and portable dialysis equipment as a prelude to a wearable or even implantable artificial kidney; together with the Dutch Kidney Foundation, imec at Holst Centre continues to innovate, aiming to drastically improve kidney patients' lives.

The dialysis equipment used for people with kidney failure essentially hasn't changed much in the last 50 years. For patients normal life is virtually impossible; in addition to the constant discomfort and fatigue, there is the need to spend long dialysis hours in the hospital several times a week. Together with the Dutch Kidney Foundation, the Swiss firm NextKidney and Dialyss from Singapore, researchers from imec at Holst Centre contribute to the development of a portable artificial kidney: a home-hemodialysis machine, small enough to take along on an airplane in a carry-on trolley. Unlike classic dialysis equipment, it does not require 70-120 liters of dialysis fluid per treatment, but only 6 liters; a major breakthrough in terms of sustainability. This compact device, which works both on 230V/50Hz and 115V/60Hz, could soon make the lives of kidney patients around the world a lot more bearable.

Life-saving technology

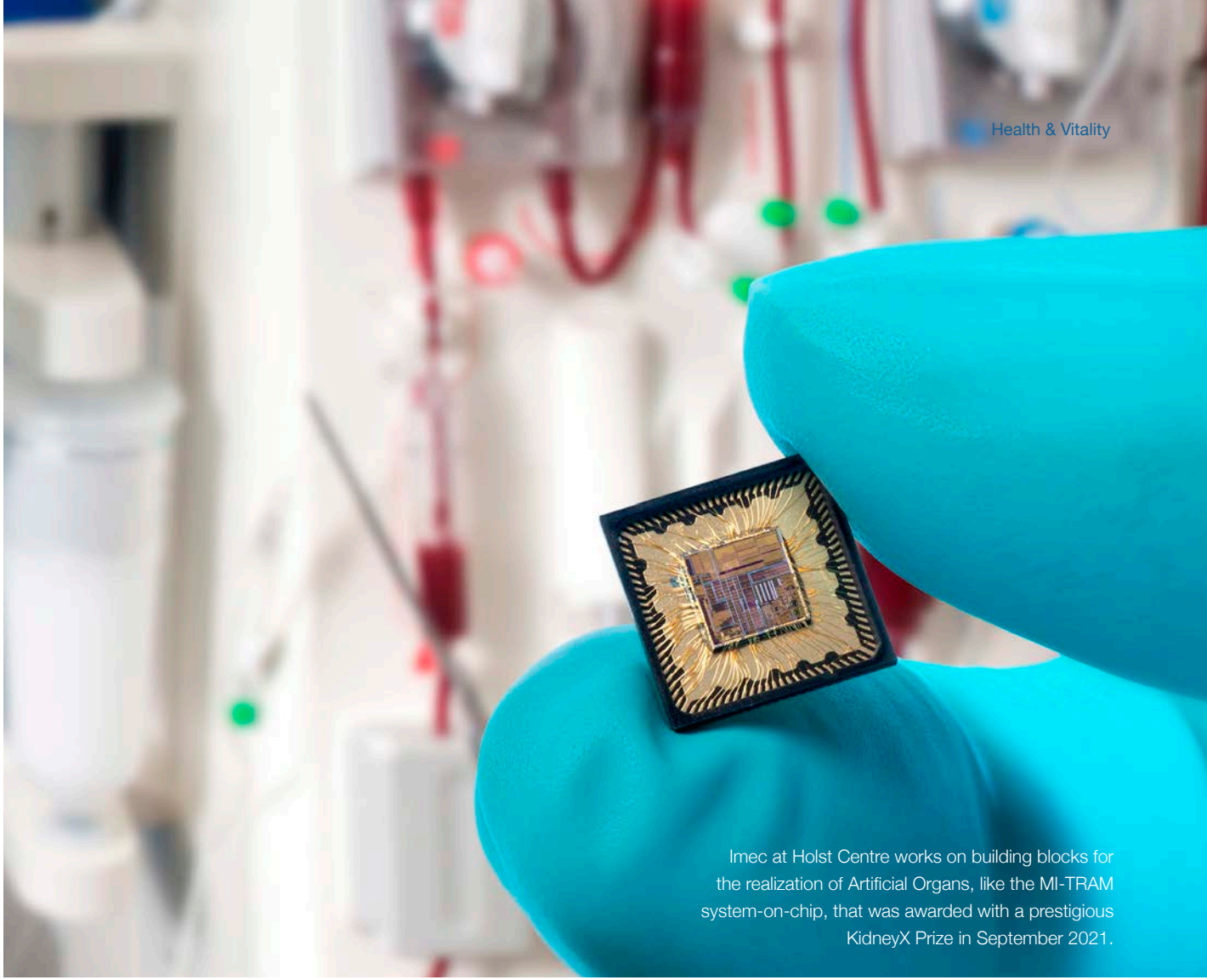
Still, the ultimate goal is to develop an implantable artificial kidney that could eventually make the invasive blood-access needed for hemodialysis completely redundant. With our combined expertise in nanoelectronics and organs-on-a-chip, imec at Holst Centre is at the global forefront for developing artificial organs. Fokko Wieringa, Principal Scientist of imec at Holst Centre, has been shaping the worldwide roadmap to drastically improve dialysis equipment for years. The portable artificial kidney could already turn an entire industry upside down, Wieringa says. "This technology has the potential to improve and save many lives, especially in third-world countries with poor infrastructure. And once we're able to push further with an implantable artificial kidney, the beneficial social and economic impact becomes even greater."

MI-TRAM wins KidneyX Prize

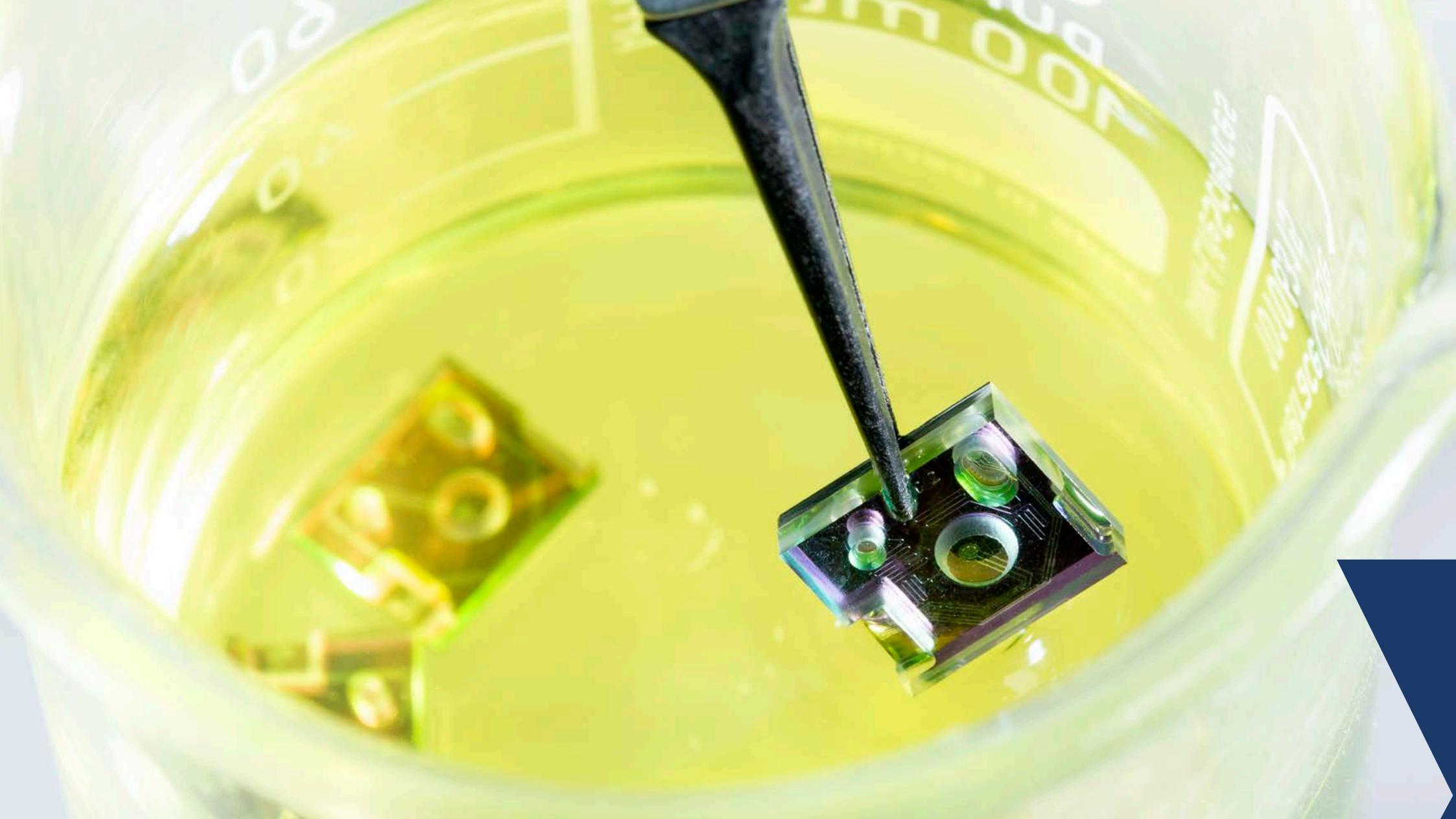
Another recent and very promising innovation for kidney patients that Holst Centre was involved in, is the MI-TRAM project, winner of a prestigious 2021 KidneyX Prize. Fokko Wieringa explains the importance of this ground-breaking technology: "Hemodialysis can keep patients alive, but poorly replaces the natural kidney. Only toxic waste particles

This technology has the potential to improve and **save many lives**

that fit through the dialysis filter pores can be washed out, but some toxins ‘hide’ by electrostatically ‘sticking’ to albumin: useful big protein-particles that must not leak away through the filter pores. This ‘sticky’ type of toxins is bad for the heart, blood vessels, brain, and nerves. Luckily, German professor Joachim Jankowski discovered that focused radio waves can ‘shake’ these toxins loose so they can be removed.” Imec at Holst Centre is working with Jankowski and UMC Utrecht to shrink his lab-table of equipment into a patented tiny 5x5mm chip that can work with all existing bedside hemodialysis machines, but also with new portable, wearable or even implantable artificial kidneys. “Furthermore, our MI-TRAM project will make evaluation kits available for all interested innovators looking to ‘turbocharge’ their artificial kidney solutions via a patent license,” Fokko Wieringa concludes.



Imec at Holst Centre works on building blocks for the realization of Artificial Organs, like the MI-TRAM system-on-chip, that was awarded with a prestigious KidneyX Prize in September 2021.



Process Analytical Technologies

Using nanoelectronics to revolutionise process analytics for immunotherapy

As imec at Holst Centre we effectively develop novel Process Analytical Technologies (PAT) to revolutionise biomanufacturing. Our compact and cost-effective lab-on-chip fluid sensor technology greatly contributes to the process analytics and development of personalised immunotherapies such as CAR T-cell therapy.

One of the essential steps in the CAR T manufacturing process is to effectively modify T-cells using a compact bioreactor. All cells must be contained in single-use (miniature) reactors and facilities with perfectly controlled conditions. This requires very precise measurements of key parameters in tiny volumes of liquids, that meet the same strict regulations and standards that are applicable for high-volume biochemical manufacturing processes with large volumes of liquids. Semiconductor technology makes it possible to shrink the required sensing functionalities into small lab-on-chips. On top of that, tighter process control enables faster lab-to-market times and cost-efficient manufacturing of personalized therapies.

Mass production at low cost

Imec at Holst Centre developed a continuous and real-time lab-on-chip for measuring essential (bio) process parameters (like pH, EC, T, dissolved oxygen, nitrate a.o.), whereas most current fluid sensors are expensive, large and restricted to measuring just one parameter. Long-term stability is achieved by incorporating microfluidics on the chip, while microfabrication enables mass production at low cost. Our on-chip fluid sensor is sterilizable and forms the perfect technology to enable a continuous liquid monitoring system.

This revolutionary fluid sensor is robust, low-maintenance technology that offers cost-effective system-on-chip integration. For the development of sensing solutions for new parameters, such as proteins, and the assessment of bioburden, we closely collaborate with imec's Life Science team in Leuven. In the near future we aim for a seamless integration of all these sensing technologies in small form factors.

Internet of Water

Successful demonstration of a smart water-quality management system

With the Internet of Water project imec at Holst Centre has successfully demonstrated the use of on-chip sensing technology to create a durable, accurate and cost-effective water-quality monitoring system that will prove invaluable to overcome the negative effects of climate change and water contamination.

Processes such as climate change, leading to drought and salination, as well as regulatory drivers, are pushing us to manage water supplies in a more intelligent way, based on smart technologies. Severe droughts during Summer increase the negative effects of salination. Heavy rainfall causes sewers to overflow, polluting surface water. To quantify these influences, water authorities need a close-knit network of low-cost probes to create a smart water-quality management system that gives you the right information to effectively redesign waterways and sewages.

First promising results

With the Internet of Water project we are seeing the first promising results of such a system. “The long-term deployment of 40 probes in surface waters has demonstrated its durability, and the measurements by our liquid sensing technology and algorithms have proven to be very reliable and effective,” says Marcel Zevenbergen, program manager gas & liquid sensing solutions of imec at Holst Centre. “Our sensor technology offers real-time insight into the precise levels of environmental threats such as salination, sewage overflow, and acidification. By leveraging big data, artificial intelligence, and the Internet of Things (IoT) we can help to effectively solve issues of surface water quality. This will provide the water industry the key to taking action based on real-time and context-driven data”.

The successful application of our on-chip fluid sensor technology opens up new opportunities in different fields of Process Analytical Technologies, such as biomanufacturing (read the article on page 30).

OnePlanet challenges nitrogen crisis

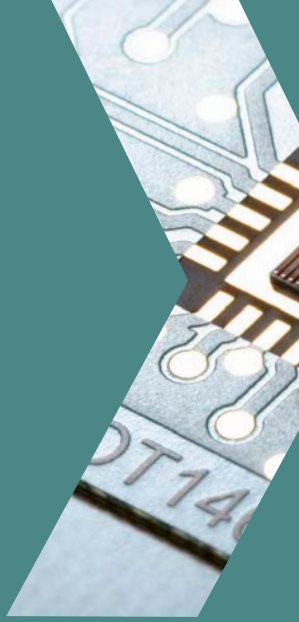
All the accumulated knowledge on the subject of air-quality management of imec at Holst Centre has been successfully transferred from Eindhoven to the OnePlanet Research Center in Wageningen. The multidisciplinary collaboration between Wageningen University & Research, Radboud University, Radboudumc and imec at Holst Centre combines specialisms from the fields of agriculture, food and health. The purpose is to jointly address the nitrogen emissions issue, especially in the Province of Gelderland, and to create local impact with successful solutions that reduce these emissions.

The application of our on-chip fluid sensor technology opens up new **opportunities**

Want to learn more on OnePlanet?

Chip assembly and packaging

Exploring new domains with innovative manufacturing technologies



Driven by the need for miniaturisation and high-speed precision production of electronics, TNO at Holst Centre's innovative manufacturing technologies are now in demand in new domains, as these promising cases clearly demonstrate.

High-speed assembly of micro-components using laser printing

With the growing demand for ever-smaller devices and wearables and displays with higher resolution rates, there's an unstoppable trend towards miniaturisation of components. High-speed, mass-production of these electronics is getting more and more difficult, because the handling and accurate placement of these tiny components is very challenging. Each component needs to be carefully selected, transferred and then accurately placed and assembled with interconnects – all at lightning speeds. "Our advanced laser-printing technology was originally developed for the precision manufacturing of optical sensors for health applications," says Gari Arutinov, Program Manager for TNO at Holst Centre. "Now we use the same technology for the fine printing of interconnects, including an innovative transfer and release concept that enables the high-speed assembly of micro-components with unprecedented accuracy levels."

This technology is perfectly suited for the mass-production of LED and micro-LED displays, where precision and high throughputs are key. Moreover, this technology has great potential for other domains as well, such as the manufacturing of optical sensors.

Semiconductor and photonic chip packaging

Together with research partner CITC, we are exploring new domains for TNO at Holst Centre technologies that could revolutionise semiconductor and photonics packaging. The laser-printing technology used for the fine printing of interconnects from the previous case, could also be applied to create interconnects within chip packages.

Another promising packaging technique could be TNO at Holst Centre's highly acclaimed thin-film technology. Originally used for patterning and the fabrication of flexible displays and imagers, it offers great possibilities for chip packaging as well. Additionally, with current resolutions and throughputs, TNO at Holst Centre's 3D printing could also be perfect for packaging applications. When used for RF chip packaging, 3D printing offers more design freedom compared to conventional PCBs, plus the possibility to integrate more functionalities.

Francesca Chiappini, research scientist from TNO at Holst Centre and Program Manager at CITC, concludes: "The knowledge, lab infrastructure and potential are there; together with our partners we can find promising new applications that can radically change chip packaging."

Want to learn more on CITC?

Energy Storage & Conversion

Innovating green hydrogen production to accelerate the energy transition

With a track record and successful spin-off in innovative energy storage solutions, TNO at Holst Centre is expanding this extensive expertise into a new domain. By developing groundbreaking electrolyser components we can upscale the production of green hydrogen and accelerate the global energy transition.

With its innovative spatial Atomic Layer Deposition (sALD) technology, TNO at Holst Centre pushed the envelope in the development of 3D solid-state lithium-ion batteries. This technology uses the same precise control and uniformity of film composition and thickness as traditional atomic layer deposition (ALD), but at much higher deposition rates. Furthermore, sALD is an atmospheric pressure process that does not require costly vacuum equipment. This technology enables the fast and low-cost production of applications that generate, store and convert energy. To further develop and commercialise 3D solid-state batteries, sALD technology and other battery-specific innovations, we have successfully spun off LionVolt.

Increase production, reduce costs

An important clean energy-carrier that will help us meet the Paris Agreement goals against climate change, is green hydrogen. TNO at Holst Centre is working on various ways to optimise the production of green hydrogen and to reduce costs. Electrolysis, splitting water into oxygen and hydrogen, using electricity from wind and sun is the main option. It's a proven technology, but there are still several challenges to deployment on a large scale. In order to supply our country with CO2-free hydrogen, we have to go to electrolysers at gigawatt level, but current capacity is limited to around 10 megawatts. That means scaling up by a factor of a thousand. The cost of producing green hydrogen is also two to three times higher than grey hydrogen produced from natural gas. TNO at Holst Centre uses its in-depth knowledge of electrochemistry from battery technology, as well as its thin-film manufacturing technology expertise, to develop new integrated electrolyser components. These components feature alternative materials and innovative, optimized integrated designs to significantly reduce costs and extend lifespan, enabling the large-scale production of sustainable hydrogen.

UWB

IR-UWB chip demonstrates ultra-wideband's greater potential

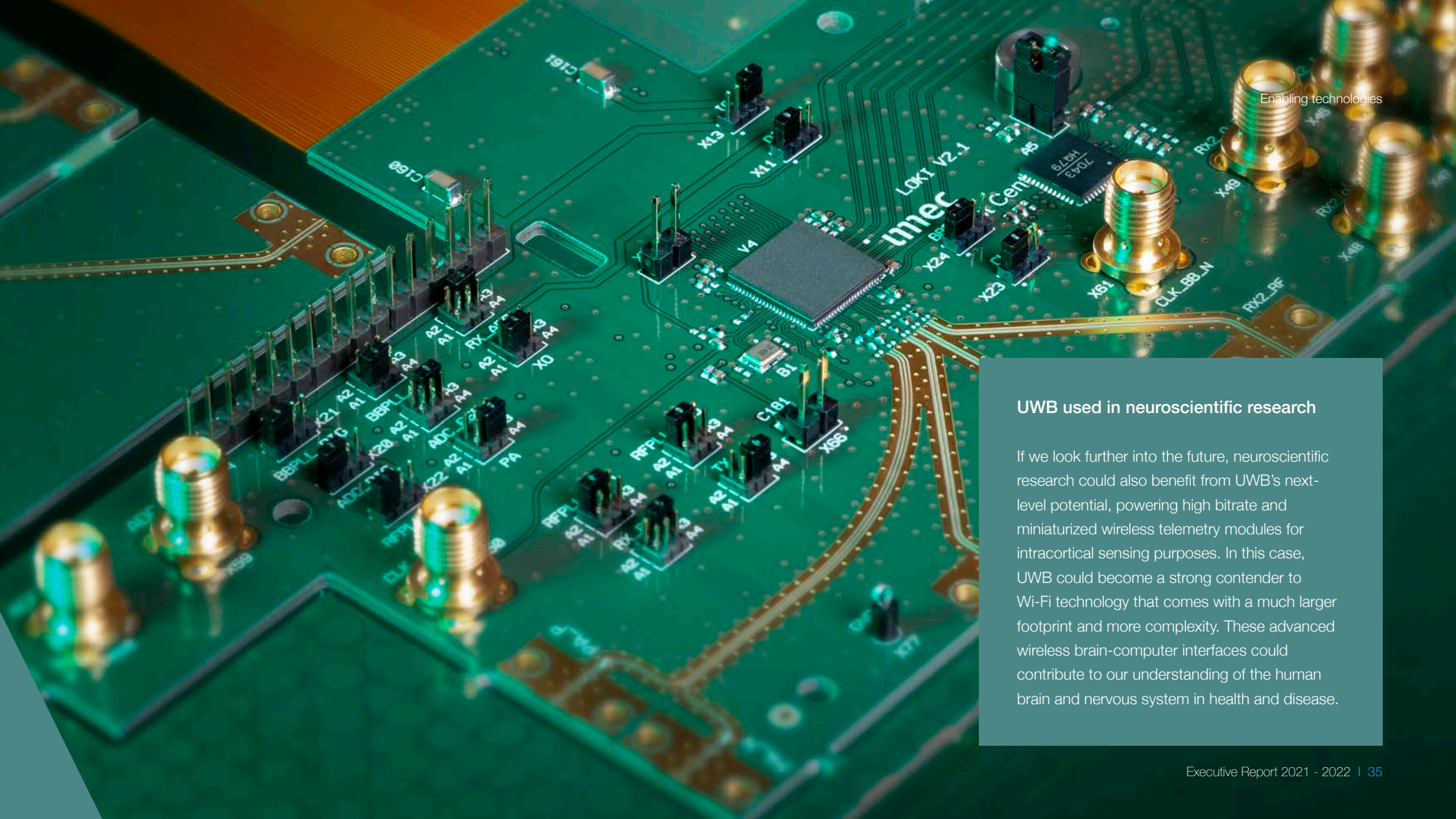
At Holst Centre we continue to push innovation of ultra-wideband technology (UWB) in both hardware and software, and with new applications. Our latest impulse-radio ultra-wideband (IR-UWB) transmitter chip has the potential to drastically change the future of UWB technology.

Ultra-wideband is already commonly used to support applications such as secure keyless entry for automotive and hospitality, indoor localization, and asset tracking. But this wireless ranging/positioning and communication technology is expected to gain even more momentum when large industry ecosystems such as FIRa Consortium will set global application-level standards for UWB in the coming years.

At Holst Centre, currently leading the way with high-speed, high-accuracy and low-power UWB chips, we believe this technology can have an even bigger impact on our society. Christian Bachmann, Program Director UWB at Holst Centre: "By using UWB not only to measure the distance but also the angle between devices, you can have 3D localisation. Furthermore, our chips can enable novel UWB radar applications, for instance presence and vital sign detection. These enhanced abilities have the potential to make our homes, health care and car environments safer and more intelligent; for instance by using presence detection to detect babies in unattended vehicles, or by monitoring hospital bed occupancy."

IR-UWB chip

Our firm belief in UWB's possibilities has led Holst Centre to further investigate the technology's full potential for future low-power, higher bitrate applications. This resulted in the development of a brand-new ultra-wideband high-data-rate transmitter chip. The IR-UWB chip accommodates data transfer rates up to 1.66Gb/s for in-body and short-range applications, which is more than 50 times faster than the current standard. Despite this incredible performance, the transmitter comes with a power consumption of less than 10 milliwatt (mW). These results prove that UWB is indeed capable of supporting a wide range of new applications that combine the need for high data-transfer rates at short distances with very low energy consumption, and a small form factor. Just one of the matching use cases for this new transmitter chip is the next generation of smart glasses to enable immersive AR/VR experiences.



UWB used in neuroscientific research

If we look further into the future, neuroscientific research could also benefit from UWB's next-level potential, powering high bitrate and miniaturized wireless telemetry modules for intracortical sensing purposes. In this case, UWB could become a strong contender to Wi-Fi technology that comes with a much larger footprint and more complexity. These advanced wireless brain-computer interfaces could contribute to our understanding of the human brain and nervous system in health and disease.

Large-Area Sensing Surfaces

Smart sensor mat revolutionises unobtrusive, non-contact vital-sign measuring

Over five years of research on large-area sensing surfaces has culminated into a convincing proof of concept. TNO at Holst Centre's prize-winning multi-modal sensor mat successfully integrates hundreds of individual sensors and non-contact vital sign measuring for a wide variety of applications.

From long-term monitoring of patients with sleep apnoea, to comfortable vital signs monitoring of babies; TNO at Holst Centre creates adaptable, multi-sensory surfaces for non-contact sensing that can easily be integrated into everyday objects and electronic applications. All this knowledge is combined in TNO at Holst Centre's smart sensor mat.

Senior scientist Margreet de Kok: "Because direct body-contact is not required, we can easily hide the sensing mat under a sheet in bed, or under the upholstery of a chair for unobtrusive measuring of heart and breathing rate, as well as posture."

By combining multiple sensors and by using a large-area matrix of piezo-electric and piezo-resistive force sensors, the state of the patient's health can be determined with greater certainty. Peter Zalar, Program Manager for Large-Area Sensors: "Because these sensors are printed on a thin elastomer, they are very sensitive, quickly picking up a signal again even if the patient has moved. This maximizes data quality, enabling patient monitoring to be performed completely remotely and reliably."

Successful system integration

In 2021 the team from TNO at Holst Centre managed to integrate all the individual components, such as sensors and software, into one system that significantly increases the amount of data, giving new insights. At the same time significant steps were made in terms of resolution, reliability and conformability of the sensor mat.

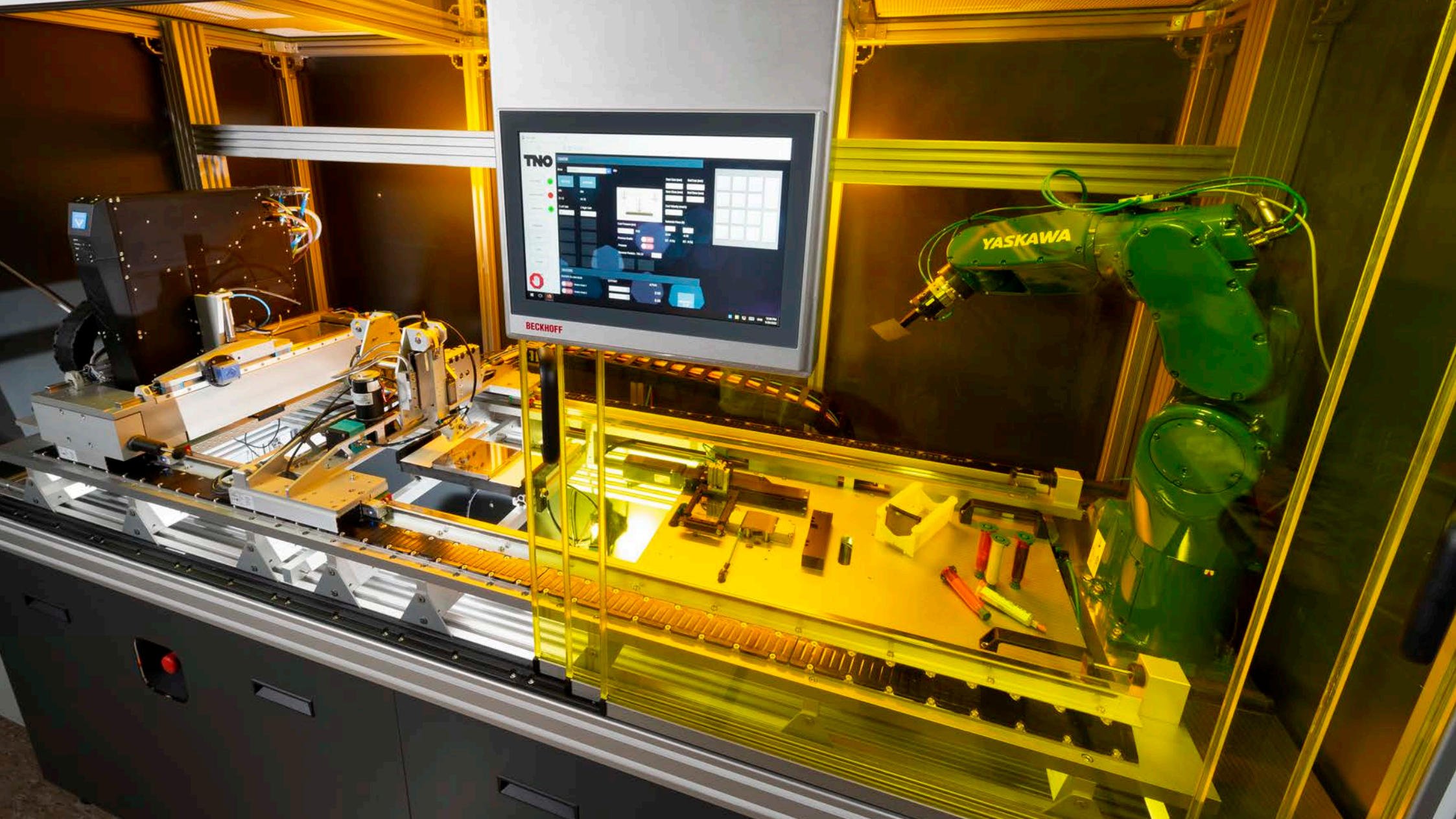
The smart sensor mat contributes to home care and preventive care, which ultimately helps to reduce healthcare costs and improve people's lives.

Furthermore, the sensor-mat technology can also easily be integrated into an office chair, increasing workplace vitality, or into a car seat, contributing to driver alertness and safety. This is achieved using cost-effective, high-resolution printed electronics embedded in a thin elastomeric mat.

BabyBed: prize-winning proof of concept

To prove their solution for comfortable, contact-free and accurate vital-sign determination without disturbing sleep, experts at Holst Centre created the BabyBed. This thin, flexible mat contains multi-modal sensors for detecting the baby's heart rate and respiration rate to indicate a baby's health, while pressure sensors detect the baby's position and activity. Together, this smart sensor system is capable of uncovering breathing difficulties or apnoea, allowing parents and specialists to monitor sleeping habits and health developments. The BabyBed received the Best Freestyle Demonstrator Award and the Public Choice Award at LOPEC 2022.

Watch the video of our BabyBed


TNO
BECKHOFF
YASKAWA

3D Printed Electronics

Enabling the low-cost production of tomorrow's miniaturised, complex electronic devices

With 3D-additive lithography, TNO at Holst Centre combines structural and electronic manufacturing in a revolutionary process with an extremely high resolution and production speed. This technology will boost the performance of miniaturised, next-generation electronic devices like sensors and medical instruments where volumetric constraints apply.

As electronic devices are getting smaller and at the same time more complex, new system-in-package (SiP) technologies are needed for 3D-heterogenous integration of functional performance and faster time-to-market. 3D heterogeneous integration is crucial in multiple fields, offering ultimate freedom of design, combined with advanced circuitry. Researchers of TNO at Holst Centre have been pioneering with 3D-printed electronics since 2017, and revolutionised the process by using 3D-additive lithography. This method offers all the advantages of 3D-rinted electronics, without the drawbacks, allowing for a cost-effective and fast manufacturing process with less waste to produce highly complex, miniaturised devices on a large scale.

Patented manufacturing process

Rob Hendriks, Program Lead of TNO at Holst Centre: "With our 3D-additive lithography process we are aiming for feature sizes of 20 micrometer and less, with a throughput of 30 seconds per functional layer. Recently we have made significant progress in building our manufacturing prototype, resulting in new patents and innovative technologies, like our groove cleaning and filling process, and the use of microfluidic channels to cool the electronic device. The next step is to fully automate the entire manufacturing process, going from a 3D CAD design to creating multi-functional devices in the order of minutes."

Multi-functional freeform products

By combining structural and electronic manufacturing in a single step, there is no longer a need for separate circuit boards or electronics layers, offering the possibility to integrate electronics with waveguides, microfluidics and antennas in one multi-functional freeform product. The design advantages are beneficial in multiple fields, like the medical industry, for the production of sensor-equipped surgical instruments, and the automotive industry, where complex forms, advanced user-interfaces and multi-functionality are key.

Funded projects

5E is a Coordination and Support Action aimed at federating three European Electronics Ecosystems. A joint vision and meta-roadmap were created that lead to adoption by the commission of the term ‘Functional Electronics’ that combines expertise in nano-electronics, flexible and wearable electronics, and Electronic Smart Systems. It aims at providing European industry with a competitive edge in the global arena.

IoN (Internet of Neurons) targets a breakthrough in the ability to transfer data from intracortical recording devices by developing a transcranial telemetry system that enables the efficient transfer at high data rate from such high channel count systems. Most importantly, it will also fulfil the form factor required for minimally-invasive surgery, needed to minimize the surgical risk and the complications after insertion. It will also significantly scale up brain-wide recordings with a new telemetry network.

ANDANTE’s goal is to leverage innovative hardware platforms to build strong hardware / software platforms for artificial neural networks (ANN) and spiking neural networks (SNN) as a basis for future products in the Edge IoT domain, combining extreme power efficiency with robust neuromorphic computing capabilities and demonstrate them in key application areas.

Within the **AMPERE** project is developing a new generation of software programming environments is developed for low-energy and highly parallel and heterogeneous computing architectures, capable of implementing correct-by-construction advanced Cyber Physical Systems (CPS). The key innovation of the AMPERE software architecture will be its capability of transforming the system model description of the CPS based on specific model-driven languages to the parallel programming models supported by the underlying parallel architecture, and so providing the level of performance required to implement the most advanced functionalities.

Moore4Medical accelerates innovation in electronic medical devices. The project addresses emerging medical applications and technologies that offer significant new opportunities for patients as well as for industry including bioelectronic medicines, organ-on-chip, drug adherence monitoring, smart ultrasound, radiation-free interventions and continuous monitoring. The new technologies will help fight the increasing cost of healthcare by reducing the need for hospitalisation, helping to develop personalized therapies, and realising intelligent point-of-care diagnostic tools.

A-Patch aims to research, develop and validate a novel non-invasive wearable sensing patch for detection of infectious disease at point-of-care, such as Tuberculosis (TB), from the skin, with an ability to serve as a monitoring and epidemic control tool. The device will be a wearable autonomous sensing patch incorporating newly printed sensors and thin-film oxide-based flexible electronics, self-repairing components, self-powered components, and a communication layer for wireless transfer of sensor readout. The patches will be produced in a pilot-line setting for validation trials, and at the same time aligned for subsequent volume manufacturing. A supply-chain and roadmap for large-scale production, regulatory approvals, and go-to-market strategy will be prepared to enable full post-project commercialization and exploitation of the A-Patch platform.

Funded projects

5E
A-patch
Amanda
AMPERE
Andante
Applause
Charm
Comp4Drones
CosMos
Critical
Critical Chains
Dynamore
EICHO - echOpen
EsAirQ
Gaitkeeper
HyPerStripes
Inno4Health
Internet of Water
Intranet of Neurons
LEE BED
MADRAS
Mem-Scales
Moore4Medical
NextPerception
Partners voor Water
PEROXIS
Plantar
Secredas
SMARTEES2
StormBots
SUBLIME
Sunrise
Tempo
The Vitality Living Lab
TREASURE

Partnerships

ahrend

Atlas Copco

AIXTRON

BAYER

Aledia

BEYOND EYES

AMOREPACIFIC

BioTelemetry inc

AMSYSTEMS

CEVA

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GlobalFoundries

LionVolt

nexperia

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DENSO

Heliatek
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Lohmann
The Bonding Engineers

NXP

SALDtech

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DUPONT

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High Tech Solutions for Global Challenges

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SEKISUI

WATER
FUTURE
when every drop counts.

Empo Health

ILLUMIX
SURGICAL

Maxscend

OSRAM

ShinEtsu

water-link

EPFL

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