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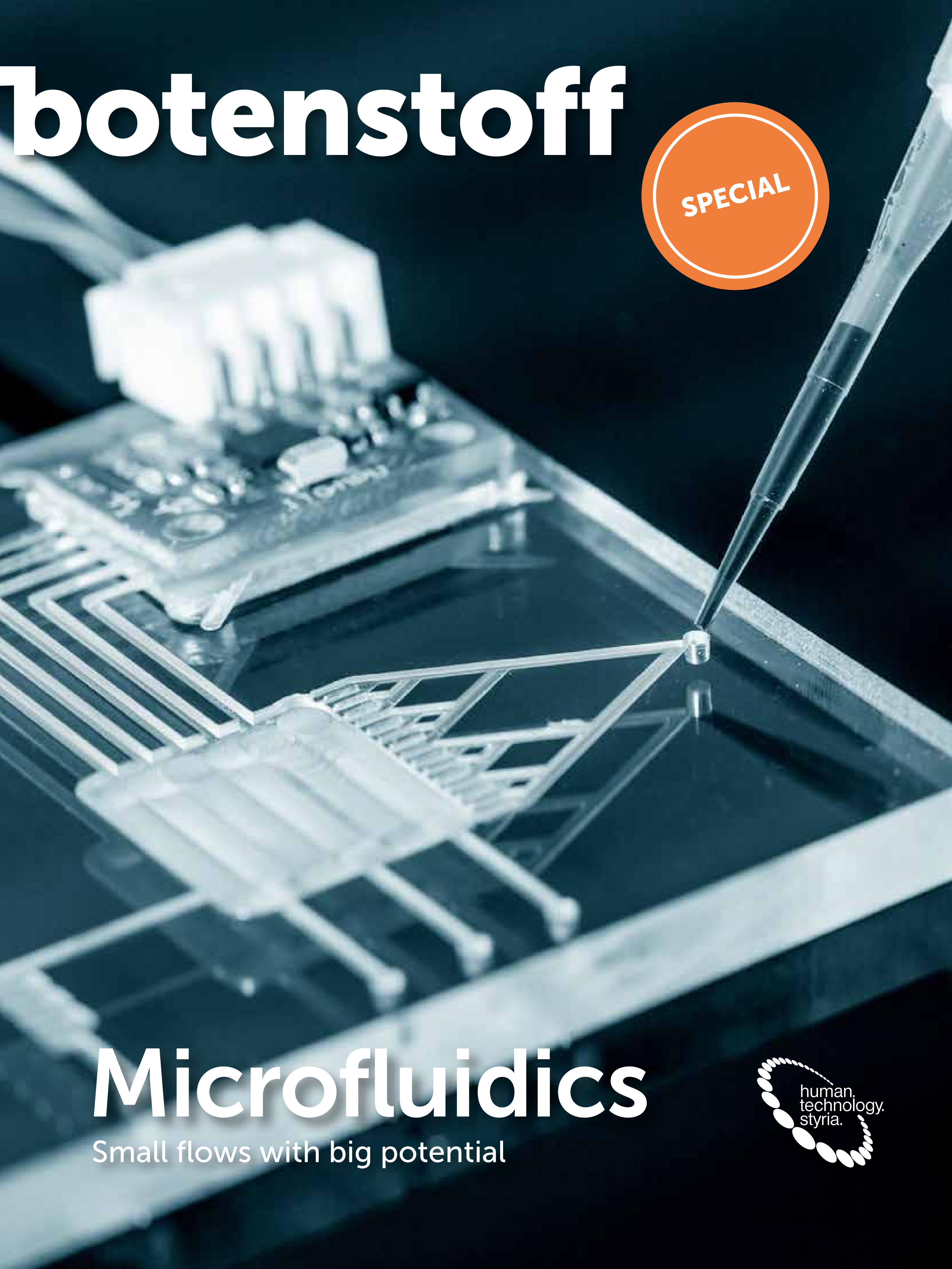

Microfluidics

Small flows with big potential

human. technology. styria.

Contents

Foreword

„... Microflu... what?"

That's how most non-researchers react when they hear the term microfluidics. However, this technology has the potential to be a true game changer in many healthcare applications. At the same time, in Styria, we have a wealth of people and networks, research institutions, startups, and companies that are researching this topic, advancing the technology, and developing new applications. Just to name a few, we have Joanneum Research, Graz University of Technology, Meon, Exias, Roche, BRAVE analytics, Kilobaser, Payer, Norganoid, BioNanoNet, and last but not least, the Microfluidics Innovation Hub.

Reason enough for us, as the Human Technology Cluster, to take a closer look at this and shed light on the topic of microfluidics, as well as to showcase the leading microfluidics experts in Styria.

There is another reason why we find microfluidics so interesting as a cluster, and that reason lies in its strong interdisciplinarity. Experts from various fields such as materials, sensors, microelectronics, and biomarker research are working together on this technology. The cooperation and collaboration among users, technology providers, research, and industry from different areas are essential for the advancement of microfluidic applications - and, of course, a central part of our work as a cluster.

So, one can already be very excited about what will emerge in the future!

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Foto: Oliver Wolf

Small flows with big potential

Where microfluidics came from and what it can do

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From tentative beginnings more than 20 years ago, microfluidics has emerged as a significant and independent field of technology today. An event mentioned as a starting point of the modern field was the development of a technique for creating microscopic-scale channels and devices published in Science in 1991 by George M. Whitesides, a Harvard chemistry professor. The term 'microfluidic channels' is often credited to Andreas Manz in a 1992 paper on chemical analysis in small channels. Manz was working at Ciba-Geigy, the Swiss company that later became part of the pharmaceuticals multinational Novartis. However it took some more years for 'microfluidics' to emerge as a recognized field. Crucial to this development was a process of combining techniques and materials borrowed from other areas of research.

According to Whitesides, four main fields contributed to the development of microfluidics: molecular biology, molecular analysis, national security, and microelectronics. The oldest of these is molecular analysis, which involves methods such as gas-phase chromatography (GPC) or capillary electrophoresis (CE). These techniques were developed in the 1950s and 60s and involve the separation of chemical compounds or biomolecules by flowing small samples through narrow tubes or capillaries, allowing for high sensitivity and resolution.

When microfluidics diverged from microelectronics

The most well-known parent of microfluidics is probably microelectronics. At the beginning, researchers attempted to apply fabrication methods and materials from microelectronics directly to microfluidics. They chose this approach because glass and silicon were available and because micromachining techniques for shaping them at small scale were already advanced. However, microfluidic devices made in this way turned out to be costly to manufacture and prone to breakage, as well as lacking self-sealing capabilities.

To overcome these limitations, efforts shifted towards new flexible materials that could deform, bend, and stretch under mechanical stresses. Current generations of microfluidic devices use a variety of materials such as thermosets, thermoplastics, elastomers and thermoplastic elastomers. So in this sense microfluidics has diverged from microelectronics and semiconductor technology, and now has its own materials and microfabrication methods.

What does microfluidics do?

But what exactly is microfluidics? It is the technology and field of science dealing with the behaviour, precise control, and manipulation of small amounts of fluids, typically on the micrometre scale. A microfluidic system is a device or chip that contains numerous channels on a scale from nanometres to microns and are usually made up of miniature components that manipulate fluid and flow, such as microchannels, microvalves, micropumps, micromixers, and microseparators.

Wide range of applications

But what is microfluidics useful for? One of the most common applications of what we could now call microfluidics – though the technology predates the field of this name – is your inkjet printing. There are two styles of inkjet printheads. One contains a piezoelectric component that forces droplets out a nozzle. The second type is thermal, where air bubbles are heated and expand inside the nozzle ejecting droplets. Another successful use of microfluidics is in energy storage, where the technology enabled the creation of new battery designs with better energy efficiency.

Many applications of microfluidics are analytical, for measuring and testing properties of fluid samples. Microfluidics is relevant wherever there is an advantage in taking as small a sample as possible (e.g. many medical samples) or if the material of interest only exists in tiny quantities (e.g. circulating tumour cells in blood). Also, microfluidic devices can be integrated into a variety of systems, enabling an automated sample-to-answer analysis with less need for a skilled

„The integration of microfluidics and AI has the potential to revolutionize the fields of medicine, biotechnology, and environmental monitoring."

Pablo Zardoya-Laguardia

human analyst. And finally, microfluidic systems are often portable, and can be deployed in remote locations or in point-of-care situations. Being small and portable makes microfluidics sensors attractive for environmental monitoring.

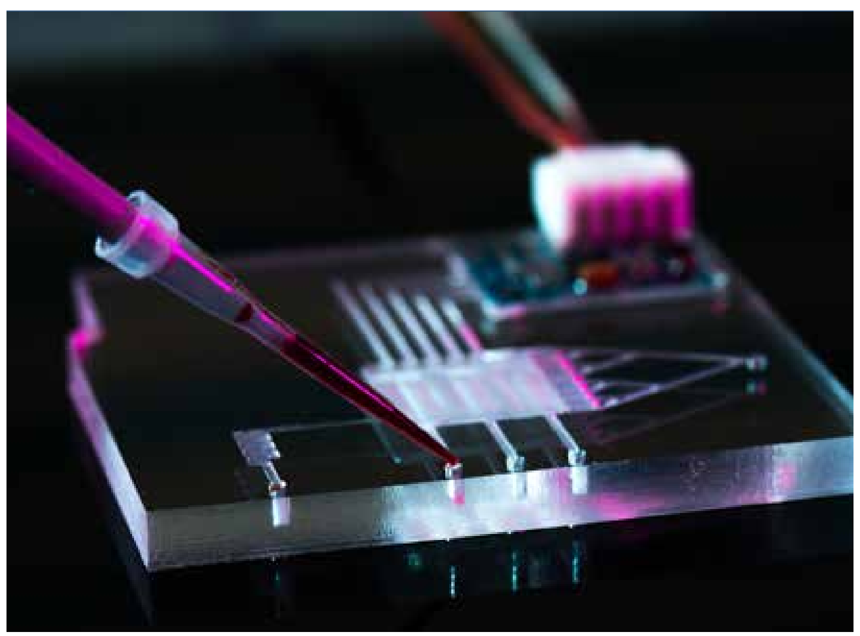
Working with the smallest possible amounts of material is also desirable in industrial settings, where there is a need to improve efficiency and reduce waste. In the cosmetics industry, microfluidics technology is used for formulation and testing of different product qualities (viscosity or stability), in the food and beverage industry it is especially useful in quality control and creation of films, particles and fibres, with potential applications in packing and manufacturing new products (emulsions or encapsulated active compounds), and in the chemicals sector, portable devices can be used to perform chemical reactions in small volumes efficiently (reducing reagents and waste), with high precision.

Microfluidics in the life sciences

In life science and biotech, microfluidics has many applications in both basic research and clinical practice:

» 1. Bacterial microfluidics → Traditional cell culture experiments have limitations as the growth phases of bacteria depend on various factors. Microfluidic systems provide a solution by allowing long-term growth of cells with continuous exchange of nutrients and waste removal. It makes cell culture an excellent application of microfluidics.

» 2. Model organisms → These are organisms used in basic research due to the feasibility of working with them to answer research questions (often related to small size, fast life cycle, developmental biology, genome sequencing, and the ability to genetically manipulate them).
 – a. Insects → A new microfluidic device was created to disrupt the natural segmentation development patterns of embryos from Drosophila melanogaster, commonly known as fruit flies. One half was subjected to cold and the other to heat. This thermal gradient would be hard to achieve without microfluidics. Studies on fly embryos include trapping them in a chamber with a valve or making embryo sorters with microfluidic valves. Although flies are not typically studied with microfluidics, the usefulness of these methods remains to be seen.
 – b. Plants → Microfluidics is helpful in studying root growth by modulating environments with the use of microfluidic 'RootChips', enabling physical and chemical control of the root environment while at the same time monitoring the roots by microscopic imaging. This method allows for continuous tracking of roots, unlike traditional hydroponics, which is not compatible with microscopy. Additionally, microfluidic valves can be utilized to modulate the environment of the roots, something that is not easily achievable with standard culture methods.



» 3. Immunology and chemotaxis → Microfluidics has been used to investigate chemotaxis (cells migrating towards or away from substances), for example of immune cells.

» 4. Tissues and organs on chip → Scientists are interested in creating microfluidic systems to simulate organs or tissues, as a way to conduct experiments, for example in toxicology or pharmacology, without using humans or animals. Tiny assemblies of cells in microfluidic devices can be used in this way, as 'organs on a chip'.

» 5. Biochemistry → Biochemical assays amenable to microfluidics include quantification of concentrations, separation, purification, enzyme kinetics, ligand dynamics, toxicology, and drug screening.

» 6. Diagnostics → Microfluidics has the potential to improve global health in developing countries by providing easy-to-use, lightweight, and affordable diagnostic devices that can identify a range of diseases such as respiratory diseases, HIV, malaria, tuberculosis, and more.

Challenges and Problems

While microfluidics is a very powerful tool, it is important to consider its potential drawbacks and limitations:

» 1. Manufacturing techniques, supply, and demand → Microfluidic industrialization faces limitations in manufacturing techniques, supply, and demand.
» 2. Leakage → Microfluidic systems often suffer from leakage, which can disrupt device performance and create safety concerns.
» 3. The need for standard test methods combined with the lack of harmonization in vocabulary → One of the biggest challenges in developing and using microfluidic products at present is the lack of a common vocabulary to communicate and understand terms.
» 4. Ability to form strong bonded interfaces → The material properties of microfluidic components play a critical role in the reliability of the device and the strength of bonded interfaces.

As Albert Einstein said: once we accept our limits, we go beyond them. Since the industry has identified these problems, standardised and innovative solutions are now being developed to help with these issues so that we can fully exploit the potential of this technology. Firstly, despite the problems with the manufacturing techniques, supply, and demand, the market for microfluidics and nanotechnologies continues to grow, and we can soon expect to enter a transition period where microfluidics gains more traction as a disruptive technology.

Secondly, an emphasis is being put on leakage tests during the prototype and development stages that can help identify design flaws and ensure compliance with regulations during the development of microfluidic products. Continual testing during production ensures that the end product functions as intended and meets safety standards. Corrective action can be taken if leaks are detected to improve the production process and meet specifications. However, according to a survey by the Microfluidics Association, a lack of standardised test methods means that developers have been using their own protocols for microfluidic leakage testing. Progress toward agreed testing standards is needed; fortunately, with an increasing number of microfluidics-based medical device submissions to regulatory agencies like the FDA, there are already signs that the regulatory institutions are beginning to take the initiative in this area. Finally, advanced materials and new, improved manufacturing techniques are being developed and tested, in order to achieve the material quality after bonding that is needed to ensure safety and device performance.

Future perspectives

A hot topic in microfluidics development at present is 3D printing, as it offers a flexible and rapid manufacturing process, allowing for the creation of complex and customized microfluidic devices. However, 3D printing for microfluidic applications is still limited by technical constraints and high costs. Researchers are working on new printing techniques and materials to overcome these limitations.

A trend has emerged where traditional fields are being combined with artificial intelligence to create new fields with significant research and application value. Microfluidics is not an exception and has been being powered by artificial intelligence (AI) to create new tools for medical diagnostics and drug discovery. AI algorithms can be used to analyse and interpret large amounts of data generated from microfluidic experiments, allowing for the discovery of new patterns and relationships. In addition, microfluidic devices can be used as platforms to develop AI-powered diagnostic tools, such as biosensors and lab-on-a-chip systems. The combination of these two technologies has led to significant research breakthroughs in various fields due to their excellent synergy. The integration of microfluidics and AI has the potential to revolutionize the fields of medicine, biotechnology, and environmental monitoring.

One further trend in microfluidics is the integration of multiple functions into a single device, which has the potential to revolutionize fields such as healthcare and environmental monitoring. Advances in microfluidic technology are enabling the development of more sensitive and accurate diagnostic tools, particularly in point-of-care testing.

In addition, there is a growing interest in using microfluidics for applications beyond the biomedical field, such as in energy, agriculture, and chemical synthesis. For example, microfluidic devices can be used to improve the efficiency of fuel cells, to optimize crop yields, and to synthesize complex chemical compounds.

By understanding the basics of microfluidics and the variety of applications, one can get a bigger picture of how microfluidics is influencing science and therefore, our society. Microfluidics is here to stay and is at the forefront of interdisciplinary research in many fields.

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„What exactly is microfluidics? It is the technology or field of science dealing with the behaviour, precise control, and manipulation of small amounts of fluids, typically in the micrometre scale."

Pablo Zardoya-Laguardia

Drone flight with organs on chips

A conversation with Peter Ertl, Professor at TU Wien and expert in microfluidics, about the current state and future of this technology, which has applications in so many sectors.

botenstoff: A lot has happened in microfluidics in recent years. What are the most important milestones and developments, as you see them?

Peter Ertl: There are two major advances. The first is the meeting of microfluidics with biology, what we call 'organ on a chip', and other microphysiological systems. That is on the application side. And the other big thing is since the end of last year, the FDA now accepts microfluidic systems as a substitute for animal experiments. This is a transformative process which will percolate through the whole pharmaceutical industry as animal testing is replaced, step by step, by 'organ on a chip' systems. So now the regulatory direction of travel is set, and experience tells us the European EMEA will probably follow soon. In Europe, standardization and harmonization are also very important questions.

In terms of technology, 3-D printing for microfluidics has come on by leaps and bounds – especially thanks to new, transparent high-performance materials. Along with this, roll to roll manufacturing processes have become established. This is an area where we are leading the world here in Austria. The main applications of this technology are in the clinical and medical fields.

From your experience, how would you say the fields of microelectronics and microfluidics have "grown together"?

In completely contrary ways. Microfluidics worked with plastic materials, in order to manipulate fluids in tiny channels, and microelectronics creates actuators and sensors using complex semiconductors made of silicon and other materials. It is only now that we are seeing signs of the two disciplines coming together in the "silicon meets microfluidics" approach – where we have microelectronic components being integrated into microfluidics systems. In this context the digital transformation is interesting, because for example in mobile diagnostics we need to be able to save, transmit and authenticate the data that we collect. The whole analytical instrument is on the chip – the power supply, the actuators and sensors and the readout. These data need to get to the person's doctor; these are the future things that have to be solved. Microfluidic systems are going to be especially interesting for home care and telemedicine applications.

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„Microfluidic systems are going to be especially interesting for home care and telemedicine applications."
Peter Ertl

What is the role of artificial intelligence in all of this?

In mobile diagnostics, AI is not that relevant yet. In these applications the main needs are fast yes/no answers and high data security. The intelligent detection of patterns and analyses are more of a general healthcare topic. Probably artificial intelligence will have more of a role in "chemical computing".

Another field where microfluidics is being used increasingly is environmental diagnostics …

That's right – for example, you can monitor soil very precisely for pollutants and other substances, for fertilizers, pests, etc. Microfluidics is also very good for testing "micro environments". Right now, oceanography is an area where this technology is gaining ground as an analytical tool.

What future projects are you working on yourself at the moment?

We have a wide range of projects – we are using microfluidics for thermochemical energy storage, for mobile diagnostics and as drone-mounted sensors. Drones with "organs on a chip" fly to particular locations and test how these cells react to pollutants or similar substances that are present there. Replacing animal experiments is another important topic for us, and so is precision medicine.

How do you see Austria in an international comparison – are we among the leaders, the chasers or somewhere in the middle of the field?

Up to a few years ago we were up with the leaders, now we're definitely in the chasing group. In the European context we are at the forefront. We have a large number of microfluidics research groups in Austria and we have the advantage of a strong industry manufacturing microfluidics products.

How do you view the role of the "AMI Advanced Microfluidic Initiative"?

The realization has set in that we need to bring the players in the field together, from researchers to industry. It's important to use such groups to talk about topics in industry and not just to think about basic research. Worldwide, microfluidics has existed now for more than 20 years – we are in the third generation of researchers who have worked on cellular analytics on a chip – and the activities of AMI also reach beyond just Austria.

Where do you see problems?

Microfluidics is a technology that touches many other fields. The questions will be how we can get digitalization to work on these chips, how we can combine the semiconductor components with the microfluidics, and what applications all of this will lead to. In the Covid crisis, we saw that with the flow assays, the powers that be chose cheap, qualitatively not so good systems. That shouldn't happen again in future crises. But for this we have to work with strong partners to make this technology known at the European level.

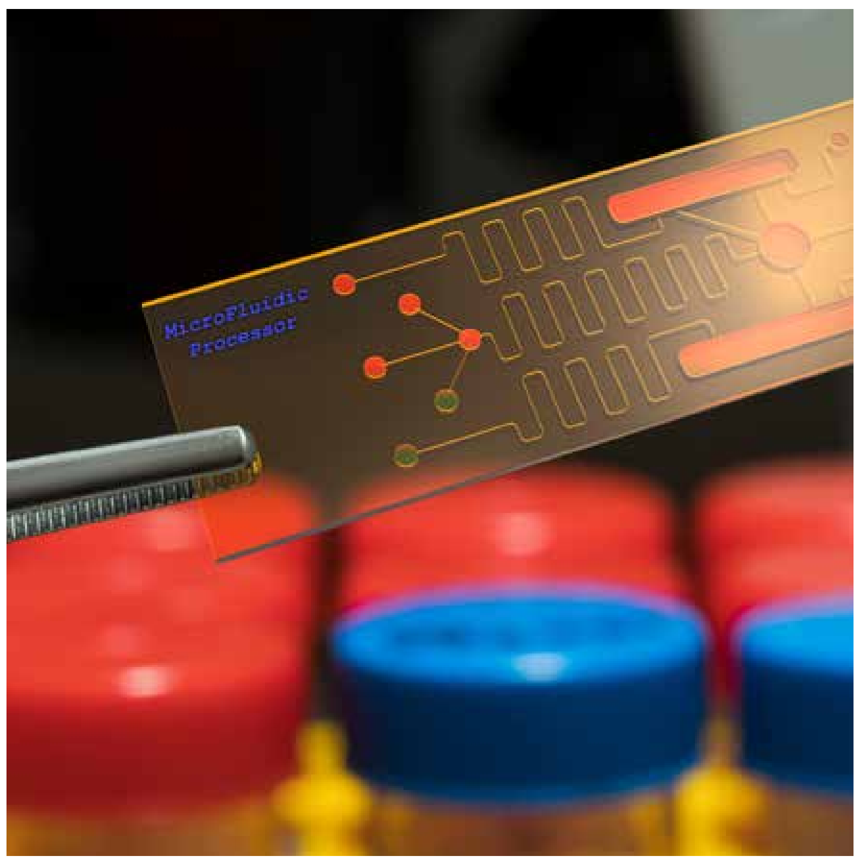
Right now the sector is working on cutting down the time it takes from prototyping to scaleup and fabrication; this is still too slow and too costly. There are also a lot of microfluidics startups around that don't have the necessary financial resources to set up a large-scale production. But there, too, there are some promising initiatives. We are not running out of challenges.

Thank you for the conversation!

Microfluidics: history – milestones – future promises

Microfluidics is a multidisciplinary field that deals with the manipulation and control of small volumes of fluids, typically on the microliter or nanoliter scale, within microscale devices. It has found applications in various fields, including biology, chemistry, medicine, and engineering.

Early research in microfluidics has started in the 1980s, however over the past decade, there have been several significant breakthroughs in microfluidics, revolutionizing the capabilities and applications of this technology.



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Droplet microfluidics: Droplet-based microfluidics involves the manipulation of small discrete droplets within microchannels. It offers advantages such as high throughput, compartmentalization, and precise control over reaction conditions. Droplet microfluidics has been utilized for applications like high-throughput screening, single-cell encapsulation, and emulsion-based synthesis.

Organ on a chip: One major breakthrough in microfluidics has been the development of „organ on a chip" systems. These devices aim to replicate the structure and function of human organs in a miniaturized format, providing a platform for drug testing, disease modelling, and personalized medicine. Organ-on-a-chip devices incorporate microfluidic channels and living cells to mimic organ-level physiology.

Single-cell analysis: Microfluidics has greatly contributed to the advancement of single-cell analysis techniques. By leveraging microscale devices, researchers can isolate, manipulate, and analyze individual cells with high throughput and precision. This has led to breakthroughs in understanding cellular heterogeneity, genomics, and proteomics.

Among the many potential areas of impact, microfluidics may play a large role in enabling truly personalized medicine. Personalized medicine aims to tailor medical treatments to individual patients based on their specific characteristics, including genetic makeup, lifestyle, and environmental factors. Microfluidics offers several key advantages that make it well suited for advancing personalized medicine.

High-throughput analysis: Microfluidic platforms enable high-throughput analysis of biological samples at the single-cell level. This allows for comprehensive profiling of individual patients, providing a more accurate understanding of disease mechanisms and treatment responses.

Point-of-Care Diagnostics: Microfluidics can be combined with portable and user-friendly devices to create point-of-care diagnostic systems. These devices enable rapid and sensitive analysis of biological samples, enabling early disease detection and monitoring. Such systems can be deployed in resource-limited settings, bringing healthcare closer to patients.

Biomarker Detection: Microfluidics offers precise control over fluid manipulation and reaction conditions, making it ideal for biomarker detection. By integrating microfluidic platforms with various sensing techniques, such as optical, electrochemical, or biological assays, it becomes possible to detect and measure specific biomarkers indicative of diseases or treatment responses.

Related technologies

Microfluidics is a multidisciplinary field that is closely related to several other technology fields, often overlaps with them to advance research and applications. Some of the closely related fields include:

Nanotechnology: Microfluidics and nanotechnology often go hand in hand. Nanotechnology deals with the manipulation and control of materials at the nanoscale (typically less than 100 nanometers). Microfluidic devices can incorporate nanomaterials, such as nanoparticles or nanofibers, to enhance functionalities, improve sensing capabilities, or enable precise fluid control at smaller scales.

Biosensors: Microfluidics is often integrated with biosensor technologies to enable rapid and sensitive detection of biological analytes. Biosensors utilize various sensing techniques, such as optical, electrochemical, or biological methods, to detect and quantify specific analytes in biological samples. Microfluidic platforms can be designed to deliver samples to the biosensor, enhance signal-to-noise ratios, and improve detection limits.

Analytical chemistry: Microfluidics has a strong connection with analytical chemistry, as it provides innovative tools for sample preparation, separation, and analysis. Microfluidic devices can be used for on-chip chromatography, electrophoresis, mass spectrometry, and other analytical techniques, enabling faster and more efficient chemical analysis.

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The Microfluidics Innovation Hub

Ronald Tingl
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Consortium members of the European project "NextGenMicrofluidics" have established the Microfluidics Innovation Hub as a non-profit association designed to act as a single-entry point to the combined competencies and the wide range of microfluidic technologies collectively offered by the partners.

So rather than figuring out yourself which is the best scale-up technology, how to transfer your assay, how to improve your analysers you contact the MIH which will do the math-making between your problem and the services of 21 partners and eventually present you with a solution and further on manage the realization of your solution.

The MIH brings together technologies along the entire value chain in the creation and advancement of customized microfluidic lab-on-a-foil systems, from assay development to manufacturing and quality control. So rather than figuring out yourself which is the best scale-up technology, how to transfer your assay, or how to improve your analysers, you contact the which will put you in touch with relevant partners from among the 21 members, or even suggest a solution.

And of course you may find partners in the network for further realization steps, as well.

The most innovative projects may also have a chance to win funding of up to € 200k for the services needed to realized their solution. For more details please visit www.microfluidicshub.eu.

Role of the MIH

In the course of the NextGenMicrofluidics project, the MIH is already cooperating with Austrian universities (Graz University of Technology) and RTOs (Joanneum Research Forschungsgesellschaft mbH). A closer cooperation with AMI is under discussion. THE MIH vision is to become a microfluidics Open Innovation Platform that enables and manages the implementation of microfluidic solutions for both experts and non-expert clients.

The insight into tissues

The open flow microperfusion (OFM) invented by Joanneum Research Health allows an analytical view into the skin, fatty tissue and brain.

Organ-on-chip systems are among the top 10 emerging technologies and consist of small microfluidic platforms that integrate living organ substructures into a controlled micro- environment, imitating one or more aspects of the organ's in-vivo dynamics, functionality, and (patho)physiology. This enables complex human biological processes to be physiologically simulated outside of the human body. Organ-on-chip systems combine the characteristics of classical cell assays (human cells and genes) and animal models (complex 3D tissue and blood circulation). With these in-vitro test systems, a wide variety of medical, biological, pharmacological, and toxicological questions can be answered without having to resort to animal testing.

Like all novel technologies, organ-on-chip systems have to be evaluated by comparing them to existing state-of-the-art and conventional biological systems such as animal tests and clinical studies. JOANNEUM RESEARCH HEALTH has a patented technology - open flow microperfusion (OFM) – which has been shown to be particularly useful for such comparisons. OFM uses thin probes that are implanted into living or artificial tissue and then continuously perfused with a physiological fluid. Each probe has an exchange area with macroscopic holes that provide access to the tissue. Because OFM probes serve a similar purpose as microfluidic channels in an organ-on-chip system, OFM probes are thus the ideal reference system to verify the clinical relevance of new organ-on-chip tests. OFM is currently used in skin, brain, muscle, mucosa, and adipose tissue and new application fields are being investigated. Dermal OFM applications are CE-certified medical products and have been further developed with the US regulatory agency FDA to provide an established method for clinical bioequivalence studies for the approval of generic topical drugs.

Besides these regulated clinical applications, OFM is also used in basic research, e.g. to investigate processes that lead to the development of atopic dermatitis, a widespread disease that causes chronic itching and inflammation of the skin. The cause is unknown but believed to involve genetics, immune system dysfunction, environmental exposures, and impairment of the permeability of the skin. Within the European IMI project ImmUniverse, OFM is used to investigate the complex interaction between tissue, skin barrier, and the immune system that leads to the development of atopic dermatitis and holds the key to developing improved therapies.

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We get microfluidics rolling

Roll-to-roll UV nanoimprint lithography enables high-throughput production of microfluidic lab-on-a-chip systems.

The potential of microfluidic lab-on-a-chip (LoC) systems is enormous: in medicine, pharmaceuticals, production and analytics. For instance, microfluidic LoC platforms enable convenient and rapid multiplexed testing of pathogens, e.g. for severe hospital infections. An advantage of these systems is that complex analyses can be automated with relatively little technical equipment and without specially trained personnel or large laboratory infrastructure. The devices consist of microfluidic structures, reaction chambers, and detection regions for signal readouts. However, there is a need for cost-effective large-scale production technologies for these biochips, because most IVD bio- chips currently employ injection moulding.

At the JOANNEUM RESEARCH Institute MATERIALS, we are working intensively on the introduction of roll-to-roll technologies for the high-throughput production of microfluidic lab-on-a-foil systems. In the production of chip structures e.g. for the clinical detection of the antibiotic-resistant pathogen MRSA, we achieved a production speed of 4500 chips per hour with our roll-to-roll (R2R) UV nanoimprint lithography (UV-NIL) pilot line. In comparison, the most commonly used injection-moulding technology allows the production of about 600 chips per hour. Our pilot line provides large-scale structure imprinting for cost-effective polymer biochips and consists of the following process steps:

We can perform the imprinting process with custom-developed resins on polymer foils with resin thicknesses up to 150 µm. These structures can be microfluidic channels or other microfluidic elements like valves. To enhance the efficiency of light capture and thus improve the system's detection sensitivity, we can also integrate optical structures into the design.

In order for liquids to enter the Lab-on-a-Chip and for air to exit the space inside, we laser-cut inlets and outlets into the chip.

Then, we can functionalise foil-based chips with fluidic channels in our roll-to-roll micro-array spotter following the imprinting. For the first time, we have been able to implement a straightforward process of sequential imprinting and multiplexed DNA functionalization on a single foil. Another possible functionalization is printing of electrodes. Not all applications will require this step.

In the next step we then close the channels with our patented lamination technology.

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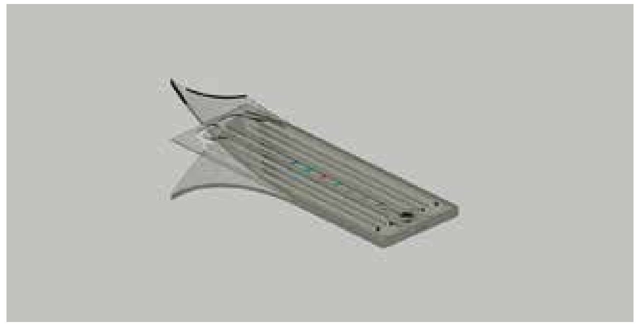

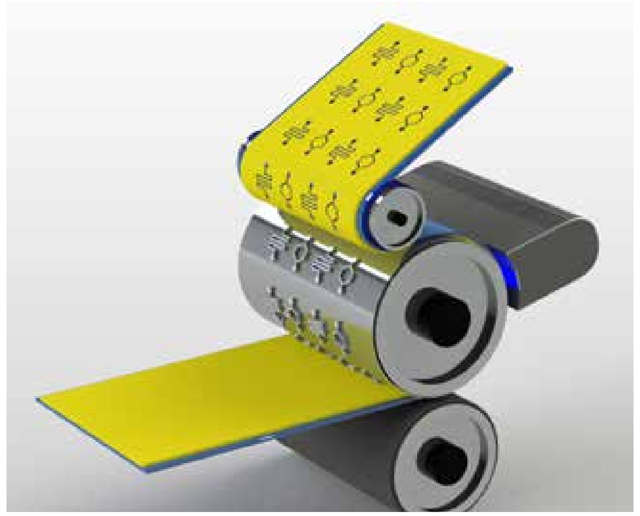

In-Air Microfluidics for Advanced Fibre Production

In contrast to classical microfluidics, which relies on specially designed microchannels to connect and manipulate fluids, in-air microfluidics uses capillary effects to assemble jets and/or droplet streams on the fly [1]. This approach offers several advantages. The absence of a microfluidic chip obviously eliminates the risk of clogging. It also eliminates the need for an immiscible carrying phase and significantly reduces possible contamination between different experiments and successive droplets produced in the same experiment. Also, the viscous stresses associated with airflow are negligible compared to those developing in microchannels. This allows for much higher flow rates and thus greater throughputs, as well as significant energy savings.

One practical application of in-air microfluidics is the production of bio-compatible advanced fibres [2]. A regular droplet stream, containing active substances or elements of interest such as living cells, collides in the air with a first continuous liquid jet made, for example, of alginic acid, to obtain a specific liquid structure called drops-in-jet. The drops-in-jet can be described as a continuous liquid jet in which monodisperse droplets of another liquid are regularly embedded. If we then add a second jet, cross-linking agents such as calcium cations can be gently brought into contact with the drops-in-jet structure, which is quasi-instantaneously turned into a fibre made of alginate, a bio-compatible hydrogel (Fig. 1a). The mechanical properties of the fibre enable its immediate collection on a spinning plate placed below (Fig. 1b). The resulting fibre's geometry is unique (Fig. 1c). It has a constant and adjustable diameter, which is determined by the diameter of the first jet, typically ranging between 50 and 1000 µm. More importantly, it contains controlled inclusions whose size, spacing, and composition can be adjusted by tuning the size, spacing, and composition of the embedded droplets. The resulting fibre can be made continuously at a rate of approximately 5 m/s.

The characteristics of this technique suggest promising biomedical applications, especially for the production of fibres loaded with cells, which could then be assembled for tissue engineering purposes, or used to screen cells at high throughput.

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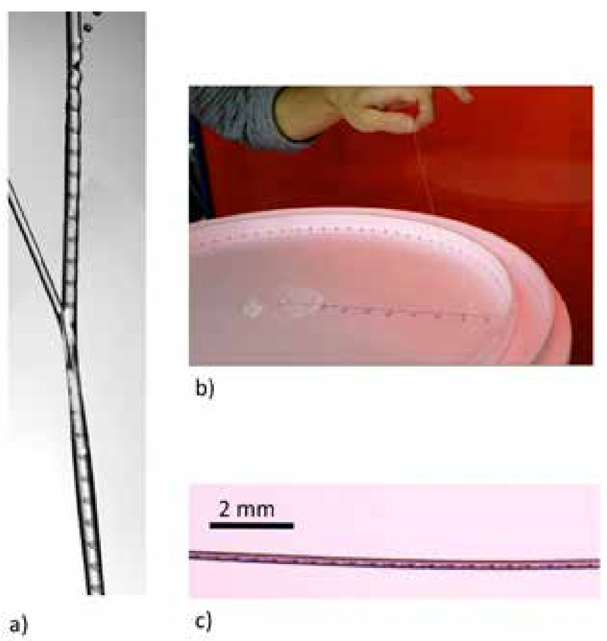


Figure 1: a) In-air microfluidics arrangement showing a central alginate jet and coloured aqueous droplets (right) forming a drops-in-jet structure, which is hardened on the fly by a cross-linking jet (left). b) Fiber collected from the spinning disk right after production. c) Close view on the resulting fiber with inclusions

Refs.
[1] Planchette et al., 2018, Phys. Rev. Fluids 3, 093603
[2] Marangon et al.,2023, Phys. Rev. Applied 19, 054006

Every breath you take – I'll be watching you!

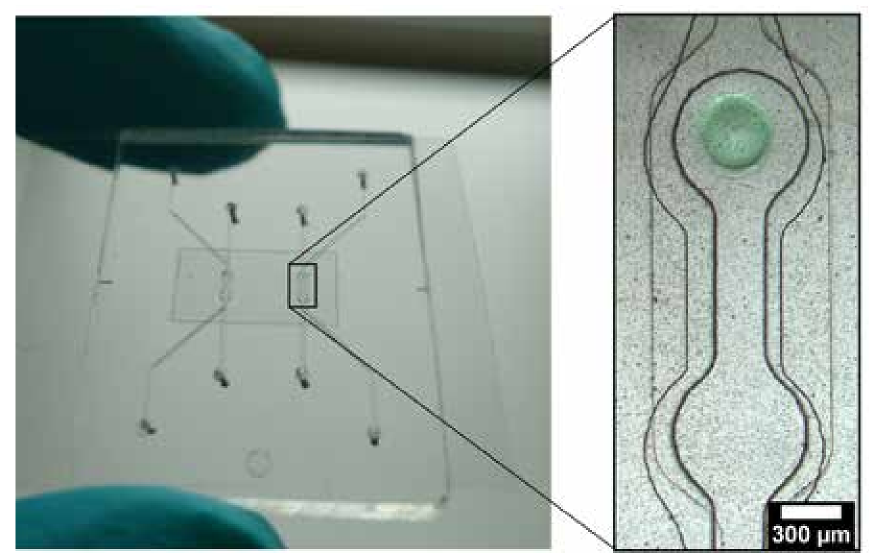
Monitoring of cell metabolism in organs-on-chips with integrated sensors

Organs-on-chips are microfluidic cell culture systems designed to mimic the structure and function of human organs, and have attracted a lot of attention in recent years. These 3D cell models offer an alternative to conventional testing methods by recreating the complex interactions and physiological conditions found within the human body. These models can accurately replicate the behaviour and responses of specific organs, such as the lungs, liver, heart, or kidneys. Researchers can use them to study disease mechanisms, test drug efficacy and toxicity, and to explore personalized medicine approaches, all in a highly controlled and reproducible environment. Organs-on-chips have immense potential for advancing biomedical research, drug discovery, and the development of safer and more effective treatments.

For all these types of studies in organ-on-chip devices, the assessment of the cell metabolism is of highest interest. Torsten Mayr and his team from the Institute of Analytical Chemistry at the TU Graz work on developing miniaturized sensors to continuously measure the key metabolic parameters oxygen, pH, glucose and lactate within microfluidic devices. Sensor elements on the scale of 300 to 800 µm are made from a fluorescent polymer formulation applied as a film inside the microfluidic chambers using ink-jet printing. The tiny sensor elements are read out using a contactless optical effect, with an optical fibre connected to an opto-electronic instrument. The sensors are non-invasive and measure cell viability for several days without using label substances.

The potential applications of this type of cell metabolism monitoring are numerous. Torsten Mayr and coworkers demonstrated the analysis of glycolysis and mitochondrial respiration of human induced pluripotent stem cells (hiPSCs) in a microfluidic chip. They integrated sensors into a heart-on-chip to measure the oxygen consumption of cardiac cells during beating motion with electrical stimulation. They also investigated the toxicity of nanomaterials on cells from the intestine and blood vessels by measuring the cell viability with integrated oxygen and pH sensors.

Torsten Mayr
Institute for Analytical Chemistry and Food Chemistry
Graz University of Technology
www.tugraz.at/institute/acfc



Heart-on-Chip with integrated optical oxygen sensors (green dots). Collaboration with MicroOrganoLab at University Tübingen.
https://doi.org/10.1016/j.mtbio.2022.100280

Disrupting the drug development process

At NORGANOID, we are on a mission to disrupt the way we conduct research and development in the life sciences and biopharma industry. Our vision is to create a world where preclinical experiments are highly automated, scalable, and closely resemble the clinical reality of diseases, all while keeping the cost of failure at a minimum. We believe in making drug development flywheels and precision medicine a tangible reality.

In the vast field of life sciences, precise liquid handling in small volumes is not just desired, but often essential. However, the challenge lies in handling small quantities accurately, which often leads to unnecessary growth and amplification of materials, resulting in increased resource consumption and waste generation. The good news is that we have the solution. Our micro fluidic technology enables us to overcome these challenges and streamline the research and development processes.

Take, for example, the critical testing phase before a drug hits the market. Traditional methods involve using cell, tissue, and animal models. While necessary, these methods can be costly, time-consuming, and may cause animal suffering. This is where our automated cell culture models come in. By leveraging microfluidics, we can significantly reduce the need for animal experiments, lower costs, and minimize the ethical concerns associated with traditional testing methods.

We are constantly pushing the boundaries of what microfluidics can achieve. By integrating this technology with imaging, machine learning, nanotechnology, and electronic sensors, we unlock a world of possibilities.

At NORGANOID, we specialize in developing our NanoLab SYSTEM (see picture), a scalable, automated, and high-throughput microfluidic organ-on-a-chip platform. By embracing scientific excellence, human-centricity, ethics, and reproducibility, we are disrupting the drug development process. We understand that reducing the cost of failure is paramount in this industry, and our innovative approach is driving us toward that goal.

Microfluidics has already made significant strides in various applications, from DNA sequencing to diagnostics and high-throughput screenings. However, we believe there is still untapped potential in this field. We envision a true "lab-on-a-chip" future, where standardization, education, and overcoming technical obstacles will unlock even greater possibilities.

We invite you to join us on this journey. As the European life science and medical industries continue to thrive, capturing the growth potential of microfluidics is strategically crucial. Together, we can shape the future of preclinical experiments, drive innovation, and make a lasting impact on the world of healthcare. Contact us today and be a part of the microfluidics revolution.

Charlotte Ohonin
CEO & Founder Norganoid
www.norganoid.com

Harnessing the power of microfluidics for in-flow particle analysis

Christian Hill and Gerhard Prossliner
Co-founders of BRAVE Analytics
www.braveanalytics.eu

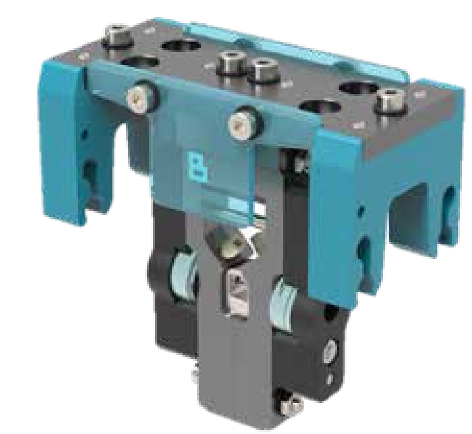
We so often discuss microfluidics in connection with exciting lab-on-a-chip applications that it's easy to forget it has potential applications in quite different fields. For example: the Graz-based company BRAVE Analytics is leveraging one important strength of microfluidics in its measuring instruments. Which strength? In the BRAVE devices, microfluidics is essential for establishing laminar flow as the basis for accurate particle measurements. Designed for the continuous analysis of particle size in liquid samples and currently focused on biotech applications such as anaesthetics, intravenous nutritional supplements, vaccines and cell cultures, the BRAVE sensors pump microliters of sample through a measuring cell and measure the particle sizes using a novel measuring principle.

As the name suggests, the OptoFluidic Force Induction principle, OF2i for short, combines optics and (micro) fluidics. To determine the particle size and particle concentration of a sample, OF2i uses a laser to set the particles and nanoparticles in motion in one direction through the measuring cell. The speed of each accelerated (nano)particle correlates with its size; larger particles move faster than smaller particles. A camera-chip films the particles as they move through the cell and the software tracks the speed of each particle and calculates the size and concentration values from each particle's path. For the measuring device to accurately monitor and evaluate the speed of each particle, it is essential to know the position of the particles at all times, from taking the sample out of the production line until its actual measurement. Losing track of particles within the measuring setup would lead to inaccurate results; and this means the system has to ensure highly stable laminar flow conditions. This means controlling dwell times, dead volumes, unswept volumes and other fluid behaviours. To achieve this control it is crucial to understand microfluidic principles, how to use them in pumping and the correct implementation of microfluidic components within the fluid-handling setup and the measuring cell itself.

Christian Hill, CEO and CTO of BRAVE Analytics, explains the importance of microfluidics for the company. "At BRAVE Analytics we greatly benefit from progress in the field of microfluidics. Components are improving in leaps and bounds and we are currently seeing a boom in expertise in this area. Besides implementing microfluidic parts and principles in our measuring cells and tubing, we also use a lab-on-a-chip within the automatic sample preparation system for our PAT sensor."

Knowledge of the particle size and concentration is essential, e.g. for

- Vaccines and medicines: depending on their "target" in the human body, the particles must have the right size to, e.g., pass through cell walls, dissolve only under certain pH conditions or interact with specific proteins.
- Sunscreens and skin creams: EU regulations stipulate a minimum permitted size of nanoparticles.
- Anaesthetics and nutritional emulsions: the distribution of particle sizes in these formulations influences safety and stability in storage.



Measuring cell of the BRAVE nanoparticle analyzer and PAT sensor

Microfluidic | PAYER Group

The PAYER Group with its headquarters and its Technology & Innovation Center in Styria specializes in products for medical technology in the fields of surgery, respiration and diagnostics. We manufacture precision plastic and metal parts and assemble them into specialized medical devices or consumables devices.

Microfluidic parts and products have been of special interest to us for many years. This extends our history in manufacturing technology, for example in injection molding: with conventional methods and tooling we can produce structures of 50 µm in a stable reproducible manner.

Many of our products are for single use in order to guarantee a safe and reliable process during use and to facilitate the disposal of contaminated samples after use. The entire process from the requirements of the respective microfluidic product, to the safe transport of the sample to the sensor surface for evaluation, to safe disposal is considered in the course of the development and manufacturing process.

VALIPRO 2009–2012

We already started research on a microfluidic product in 2009, in the field of sepsis diagnosis. The aim of the VALIPRO project was to replace the longstanding routine methods in diagnosis of sepsis diseases by making a compact point-of-care device that could be used close to the patient and which would enable rapid and reliable detection and early treatment of sepsis. We developed and produced the disposable sensor module, which consists of an optical chip and a fluidic chip. The transparent optic chip is injection molded from a special polymer. A microarray is located on the substrate. The spots of the microarray contain capture molecules for the detection of sepsis-related proteins.

In the fluidic chip, whole blood is separated into serum and plasma by negative pressure. The plasma is then passed over the microarray through the incorporated channels and microfluidic structures. After that, another solution of antibodies coupled with a fluorescent dye flows through the chip. These antibodies bind to the proteins and are visualized by fluorescence. The sophisticated chip design takes account of the analysis requirements as well as the flow behaviour of the (sample) fluids. Filling simulations enabled the chip design to be optimized in terms of production technology. Among other things, the chip had to be made of a material whose intrinsic fluorescence would not falsify the analysis result. The fluidic chip, capped with the optical chip, forms device is easy and safe to use: its closed system minimizes the risk of infection. The production process means that the chip can be produced cost-effectively in large numbers.

Advantages of the flexible point-of-care system for the diagnosis of sepsis:

» Fast and close-to-patient diagnostics
» Parallel analysis of multiple inflammation markers
» Results within 20 minutes
» Small sample volume
» Easy and hygienic handling
» Minimal risk of infection
» Determination available at any time
» Cost-effective and compact

Microfluidic Chip

Several years ago, PAYER started to develop microfluidic chips for tissue staining in close collaboration with a Swiss start-up business. The aim was to shorten the tissue staining process and to enhance the outcome by minimizing undefined results. After a successful joint development, we made tools using our rapid tooling process in order to reduce the time-to-market as well as to achieve a significant cost reduction for the customer. The challenge was the injection molding of the microfluidic structured chip in combination with the small through holes (200 µm), which allow the fluid to move between layers in the mounted chip.

The keys to success were the tooling, the injection molding and the assembly process. We designed and built the tools, which set new standards. The assembly process included a special bonding step and a newly developed testing method ensured the expected quality. After positive evaluation of clinical pilot studies, the series production became possible just eight months from the beginning of the project, including the validation. The tools from the rapid tooling process were upgraded to serial production tools, which enabled an efficient scale-up for market entry.

Several tens of thousands of these microfluidic chips are produced per year.

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Miniaturizing DNA synthesizer

DNA synthesizers are laboratory devices for life sciences that produce artificial DNA pieces with arbitrary sequences from the four basic DNA building blocks and some other chemicals. At Kilobaser, we use microfluidic technology to miniaturize our novel DNA synthesizer, as well as make it far more efficient and user-friendly than previous devices on the market.

Classical synthesizers use individual chemical bottles connected to a network of tubing and solenoid valves within the device to control the flow of chemicals through the reaction chamber (also called a "column") where the DNA strands are created. We have developed an injection moulded microfluidic chip (size 75mm x 25mm x 2mm) containing ultra-fine fluid pathways (about 100µm), tiny membrane valves (diameter 2mm) and a micro-column (ø 0.8 mm, h 0.6mm). This replaces the network of tubing, solenoid valves and large columns – giving us a 50-100 fold reduction in chemical consumption and doubling the speed of synthesis.

Since the chemical bottles now also require correspondingly less volume, we were able to develop a single small cartridge (approx. 10 x 5 x 5cm) containing all 12 necessary chemicals, thus greatly improving user friendliness.

The biggest challenges on the way to a working chip were the material selection of the chip substrate and matching the synthesis chemistry to it, the development of the complex membrane valves and channel arrangement, and the development of the synthesis column.

Alexander Murer
CEO Kilobaser
www.kilobaser.com

Technology Platform: Advanced Microfluidics Initiative

Q&A with Clemens Wolf

Technology platforms can help solve relevant socio-economic challenges by bringing together and preferably uniting industry, academia, and government. Strategic research agendas need to be defined, competitiveness strengthened and research and innovation promoted. The Advanced Microfluidics Initiative (AMI-AT) links the Austrian academic and industrial research landscape with business players in the field of microfluidics. It thus forms the elementary platform for microfluidics-based innovations and their technical implementation from the laboratory to the market. We sat down with AMI-AT Coordinator Clemens Wolf from BioNanoNet Forschungsgesellschaft to learn more about the Initiative.

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Clemens Wolf
Coordinator of the Advanced Microfluidics Initiative (AMI-AT)
www.microfluidics-initiative.com

Hi Clemens! Tell us a little bit about the AMI-AT platform and its structure:

Hi! Advanced Microfluidics Initiative was launched in 2017 and has been active both nationally and internationally over the past 6 years. AMI-AT is an open group to which any organization can join, provided it has the necessary expertise and agrees to the organizational requirements. The platform's core group is led by three chairs who contribute their expertise on specific topics to the platform's content and strategic direction. The participatory nature of the initiative is the central element, and the platform thrives on the activity and expertise of our many members. Anyone who is active in the microfluidics field and is interested in joining is welcome!

What is the motivation and the mission behind these activities? What kind of impact can this Platform have?

We want to bring together the expertise of Austria's microfluidics sector to create momentum for collaborative large-scale projects. Another important goal is to support advanced research in microfluidics and facilitate the transfer of knowledge, technology, and personnel to the industry. By working together, we can address societal challenges and overcome related obstacles with the help of existing technical solutions and the use of cutting-edge advanced technologies.

You mentioned solutions for societal challenges. How can the general public benefit from the work conducted by the platform?

Microfluidics enable novel analytical methods that provide rapid, reliable, and reproducible early diagnostics at the point of care, which means I do not need large laboratory or highly trained personnel. This relieves some of the burden on the healthcare system. Microfluidic devices can also ensure food safety by quality control and efficient and cheap process control. Furthermore, these analytics have applications in environmental monitoring and agricultural monitoring for soil health. Automated and evidence-based sensor technology also plays a crucial role in digitalization. As a final example, the so-called "organ-on-chip" technology will improve drug discovery while reducing or even replacing animal testing. Clearly, advanced microfluidics and biosensing offer a wealth of valuable solutions for a wide range of challenges. So, promoting and strengthening this community can have a huge impact.

This sounds really promising! Now, microfluidics is a broad field. Does AMI-AT have a specific focus?

The exact thematic positioning of AMI-AT is done according to the core competencies of the Austrian actors, which are generally but not exclusively focused on the healthcare sector, the chemical sector, life sciences and environmental sciences.

> „We want to support great research, both theoretical and practical, to improve Austria's research and technology infrastructure in a lasting way."
> **Clemens Wolf**

Tell us about some of the activities of the platform.

By promoting transparent and open communication, the organization cultivates a collaborative environment that encourages active participation in community activities. This includes organizing thematic workshops and webinars, hosting an annual conference, assisting in joint funding applications, offering training and education programs, promoting participation in national and international conferences, facilitating technology dialogue forums for society, and encouraging cooperation projects.

If you had a vision for the platform, what would it look like?

That's easy *laughs*, I can quote the vision statement of our platform:
Visibly position microfluidics as a future-proof cross-sectional technology in Austria, promote excellent basic and applied research and thus sustainably strengthen the research and technology infrastructure in Austria.
In other words, the aim is to make microfluidics an important and reliable technology for the future in Austria. We want to support great research, both theoretical and practical, to improve Austria's research and technology infrastructure in a lasting way.

Last question! Where can interested parties get even more information and who can they contact if they want to get involved?

Feel free to browse our website www.microfluidics-initiative.com and if you have any questions at all, reach out to our team at office@microfluidics-austria.at and we will respond as soon as we can.

Thank you for the interesting insight!
Thank you for the invitation!

ADVANCED Microfluidics Initiative

Microfluidics in their PRIME:

Integrated Chips, Active Valves, Smart Sensors, and What Comes Next

Thursday, 14 September 2023
9:30-14:00 incl. lunch
TUtheSky | Getreidemarkt 9 | 1060 Vienna, Austria

Microfluidic devices manipulate tiny amounts of fluid, enabling cost-effective, fast, accurate and high-throughput analytical assays. Progress in microfluidics has huge impact in environmental pollution monitoring, biohazard detection and biomedicine, contributing to the development of new tools for drug screening, biological studies, point-of-care diagnostics and personalized medicine.

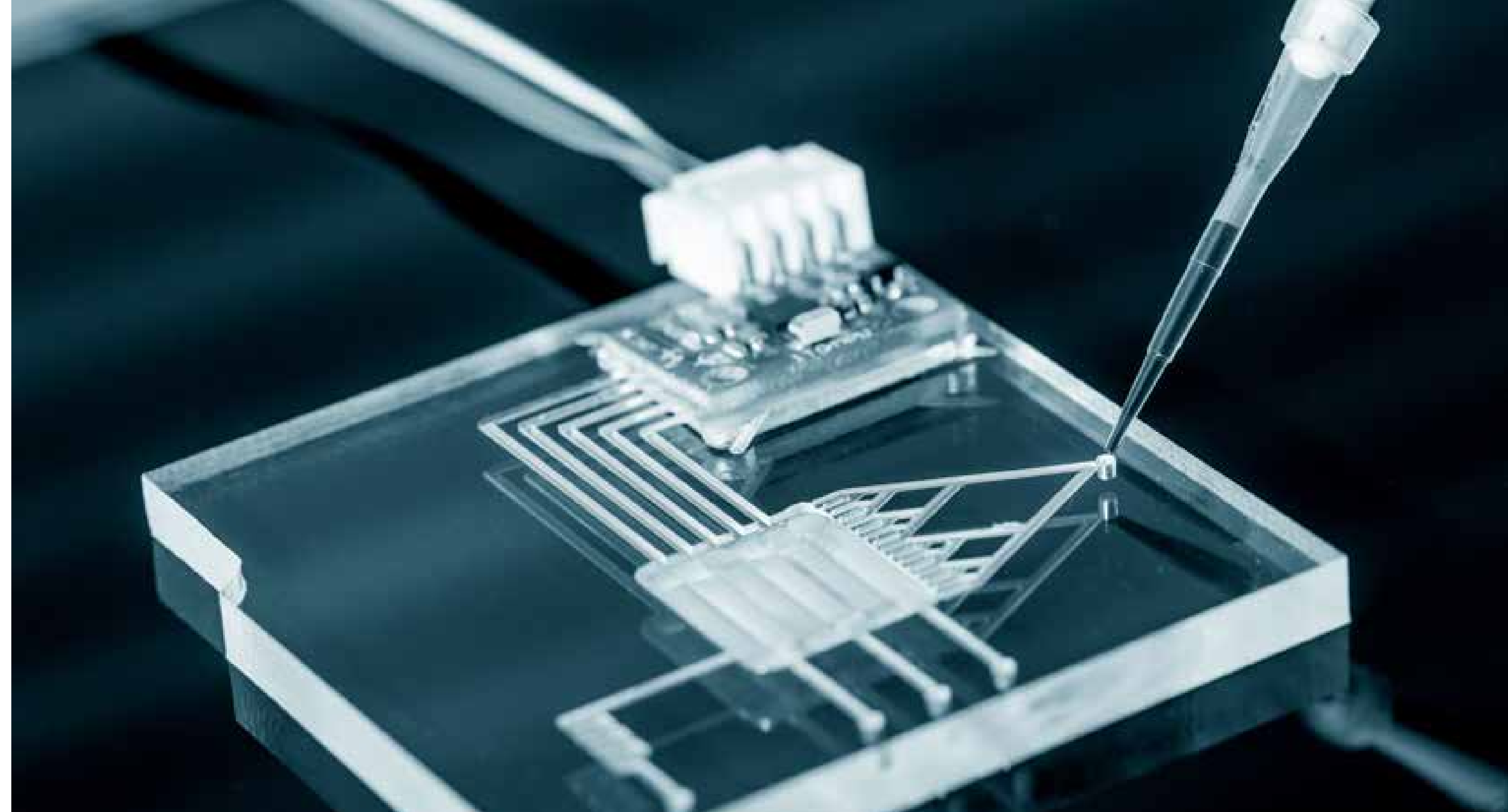
Despite this huge potential, microfluidics market growth is heavily constrained by the complexity and high prices of the required large-scale off-chip equipment and its operational cost.

PRIME, an EU-funded H2020 project, has used additive manufacturing technologies to integrate smart valves in a microfluidic chip. PRIME is also producing new ultra-sensitive and selective sensors embedded in the chip and readable with light. The final device is to be remotely addressed and read using simple photonic elements that can be integrated in compact, portable and cheap operation&read devices.

Save the date to join the PRIME consortium and others from the field of microfluidics to learn more about this technology for their final dissemination event in Vienna, Austria on Thursday, 14 September 2023.

Contact: Caitlin Ahern
Project Communications
BioNanoNet Forschungsgesellschaft mbH
www.bnn.at

More details to follow on the website:
www.project-prime.eu/event/final-event



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