The rise of microfluidic technology: inspiring multi-disciplinary innovation and collaboration

Global Engage

Contents

The following speakers were interviewed at The Microfluidics Congress:

- **Andrew deMello**, Professor, Department of Chemistry and Applied Biosciences at ETH Zurich. Also Professor of Bioengineering at the MRC Clinical Sciences Centre, Imperial College London.

- **Charles Henry**, Professor in and Chair of the Chemistry Department at Colorado State University.

- **Séverine le Gac**, Ph.D., Associate Professor at the University of Twente and director for the research program Nanomedicine at the MESA+ Institute for Nanotechnology.

- **Daniel Mark,** Head of Division Lab-on-a-Chip, HSG-IMIT, University of Freiburg, Germany.

- **Nicole Pamme**, Professor in Analytical Chemistry, University of Hull.

- **Valerie Taly**, Group Leader of Translational Research and Microfluidics, Paris Descartes University, France.

- **Patrick Tabeling,** Directeur de Recherches CNRS, Professor ESPCI, and director of the Institut Pierre-Gilles de Gennes.

1. Introduction

Microfluidics technology has been applied and adopted across many areas of science and technology over the last 20 years. Microfluidic devices and systems work by channeling liquid flow in a defined small volume (µL, nL, pL, or even fL), either passively or with a series of micro chambers, pumps, valves, and sensors, and have brought about major advances. Processes which are normally carried out in a lab can be miniaturized on a single chip to enhance analysis and diagnostic efficiency and speed by reducing sample and reagent volumes. Sophisticated techniques of continuous flow-, droplet based- and digital microfluidics are now commonplace in many laboratories.

Nowhere has microfluidics had more of an impact on research and development innovation than in biological and, in particular, biomedical sample analysis. At the intersection of engineering, physics, chemistry, nanotechnology, and biotechnology, microfluidics is revolutionising the way patients are diagnosed, monitored and treated.

Innovation within microfluidics technology remains very high in sample analysis and detection. Progress has been boosted by the many new tools and procedures created in parallel to enable this. As a result we are now seeing a steady increase in the number of microfluidic diagnostic and analytic tools that are being released and commercialised for this purpose.

"I specialized in analytical chemistry, and microfluidics for analytical application was a really big area at the time, in the early 2000s. I was fascinated by miniaturizing things and making things faster, bringing this to the patient, and all the potential that microfluidic analysis and bioanalysis could have".

- Nicole Pamme -

"As a young graduate student I was interested in developing instrumentation, but I was frustrated by the traditional limitations of what was out there. Microfluidics was a way to reinvent instrumentation, skipping the boundaries of what was considered normal and thinking about things in creative new ways".

- Charles Henry -

The Microfluidics Congress

The breadth and scale of achievement was highlighted recently at The Microfluidics Congress, held in London.

Attracting experts working in microfluidic development and application, including point-of-care diagnostics, single cell analysis, lab-on-a-chip applications, droplet microfluidics and next generation microfluidics, the conference examined the latest developments in the technologies and techniques being used for progressing medical research in areas such as disease monitoring, diagnostics, organ-on-a-chip and synthetic biology. The challenges and possibilities of microfluidics were also examined.

Microfluidics – inspiring multi-discipline innovation

Microfluidics research and development brings together a diverse range of scientific disciplines. Scientists have been attracted to the field of microfluidics from many different backgrounds and include biologists, physicists, chemists, engineers and spectroscopists, creating success with some truly multi-disciplinary collaborations. Speakers at the congress were interviewed and asked to explain how they became involved in microfluidics, to encapsulate what microfluidics offers the researcher.

2. Applications making a difference in the real world

For environmental and clinical detection using paper-based microfluidic devices, to droplet digital microfluidics for detection of cancer markers, and finally microfluidics for assisted-reproductive technology, here are some of the newest applications using microfluidics.

2.1 Paper-based microfluidic devices for sample analysis and diagnostics

Professor Charles Henry, Chemistry Department, Colorado State University, is leading research into surface chemistry, electrochemistry, and chemical separation in order to develop clinical and environmental diagnostics. Part of Professor Henry's extensive research remit focuses on the development of paper-based analytical devices (PADs). PADs are made from a combination of wax and ordinary filter paper and provide a cheap alternative to traditional assays.

The development of the chemistry around these devices was inspired by the need for low cost diagnostic tools in developing countries. Early work by Charles and his group developed innovative assays for metabolic markers such as glucose, including the first electrochemical PAD or ePAD. The work is now extending into other fields relevant to both developed and developing countries including detection of foodborne pathogens and analysis of heavy metals using nanoparticle-modified electrodes to assess occupational exposure.

"We are really excited about some of the work that has been going on in the labs around bacterial detection from food samples, as well as from some clinical samples. We have been working for a number of years on trying to improve detection, sensitivity and selectivity. In the last few months, we've developed a method that is key to this using an innovative electrode manufacturing process. We have been able to use that new technology to profile enzymes being released by bacteria such as E. coli and Salmonella which are huge health concerns around the world".

Professor Henry's group conducted pilot studies last summer with preliminary test devices in India and China for detection in household environments, and the results that came back were "fantastic". "The correlation with current gold standard devices was almost perfect, yet our devices are a fifth of the weight and one-tenth of the price of the other devices that were used". This research opens up access to microfluidics technology which will impact people's lives on a large scale and in a very positive way.

2.2 Paper microfluidics for detecting nucleic acids - Microfluidic diagnostics for Ebola virus

Patrick Tabeling is directeur de Recherches CNRS, Professor ESPCI, and director of the Institut Pierre-Gilles de Gennes. An early pioneer of microfluidics, Professor Tabeling is leader of the group MMN (Microfluidics MEMS and Nanostructures). With the Pasteur Institute in France, the MMN is developing a new RNA-based diagnostic for the Ebola virus. Tests conducted in New Guinea last year were 'very encouraging'. The test uses a microfluidic paper device which is key to providing an inexpensive system that permits affordable diagnosis of infectious diseases in developing countries.

"The initial motivation to start working on an Ebola diagnostic at the Pasteur in France was to come up with a technique that could save lives. For an effective Ebola diagnostic we know that it is important to make an early diagnosis, soon after the fever starts, but there was no technique to do that.

The method behind our Ebola diagnostic was to detect the RNA of the virus, the genomic signature of Ebola. This method of detection has been known for a number of years, but the key difference for us has been to develop it on paper so that can be used widely in developing countries to enable that vital early detection. Coupling the low cost paper technology with the genetic detection has been the key development.
We have demonstrated sensitivity that is comparable with the most sensitive technique of detection currently, so it is very good news.

There is still work needed to bridge the gap between what the assay can detect and what it needs to detect. Efficacy in detecting from blood and plasma still has to be demonstrated fully and there are also a number of issues that have to be addressed for this to be made available in other labs, hospitals and to the public.
In 5 years we hope to have simple systems in place to detect Ebola, dengue, HIV, malaria each with only with a single device. With these available in the field, villagers can have a paper-based test to detect early development of a disease and act quickly to stop the spread of the disease which would contribute significantly to global health".

2.3 Droplet digital microfluidics for cancer diagnostics

Dr Valerie Taly, Group Leader of Translational Research and Microfluidics, Paris Descartes University, France is developing clinical validation of droplet-based microfluidics for the non-invasive detection of cancer biomarkers, identifying new cancer biomarkers and the development of original tools and procedures for their detection. Multiplex digital PCR enables noninvasive and sensitive detection of, for example, circulating tumor DNA in liquid biopsies, with performance unachievable by current molecular-detection approaches (Taly et al. (2013) Clinical chemistry, 59(12), 1722-1731).

Droplet based microfluidics has been central to the development of highly powerful digital PCR platforms. The ability to perform individual assays on thousands / millions of single cells or single nucleic acid molecules is a valuable tool to detect and quantify rare cancer-related events including genetic and epigenetic variations. Recent droplet based digital PCR developments are now being applied in patient follow-up and treatment management for various human cancers.

2.4 Microfluidic devices for advanced cell biology

Séverine le Gac, Ph.D., is Associate Professor at the University of Twente and director for the research program Nanomedicine at the MESA+ Institute for Nanotechnology. Her group is developing microfluidics for mammalian embryo culture Assisted Reproductive Technologies (ART), specifically the culture and characterization of preimplantation mammalian embryo in microfluidic devices.

The field of ART is relatively young but it is growing rapidly (5-10%/year) as a result of the increasing number of sub-fertile couples (~10% worldwide). At the same time, the ART success rate remains low (<30% clinical pregnancies), which can be partly attributed to the lack of maturity of the in vitro techniques employed. Those techniques are entirely manual and have known little change since their introduction.

By providing feedback in real-time on the embryo development, the new microfluidics system is of great interest for optimization of the ART protocol. Such a tool can be applied in clinical settings (IVF clinics and centres). The device includes a culture microchamber (500-2000 µm diam. or 30 to 480 nL volume), and embryos are introduced with the help of reservoirs and microfluidic channels.

"We are working on the development of microfluidics devices for medical applications and especially for the field of assisted reproductive technologies (in vitro fertilization / IVF). In my team we have developed a device to culture embryos after fertilization but before the transfer to the uterus of the mother, to maintain the embryos in a very controlled and confined environment. Firstly we validated this with an animal model (mouse embryos) and secondly we worked with human embryos."We are not aiming only to culture embryos. We would also like to integrate analytical tools to monitor the growth of the embryos during the pre-implantation development and we are working to get to the point where these devices are used in the clinics".

3. New microfluidic technologies bring both challenges and advances

Nicole Pamme and her group are studying lab-on-a-chip devices for bioanalysis, chemical processing and medical diagnostics. They are exploring magnetic forces inside microfluidic channels as a tool for precise handling of magnetic particles, cells and droplets with simple magnet setups for applications in DNA analysis, clinical diagnostics recognition and the specific isolation of magnetic objects from complex sample mixtures (Pamme, N. (2012). On-chip bioanalysis with magnetic particles. *Current opinion in Chemical Biology,* 16(3), 436-443).

"We are interested in working with magnetic devices as it allows us to take processes that normally take a long time and take up a lot of space and fit them into a microfluidic device, to do them in a very elegant and simple and fast way." Magnetism is used in a number of devices already in the market as they are so convenient, they permit use of a big surface area to capture the molecule of interest from your sample. This could be a urine sample, blood sample, saliva sample or even an environmental or food sample. By moving the magnet we can capture the molecules of interest onto magnetic particles and then move the particles into zones within our microfluidic device for the next steps, leaving behind any waste such as the matrix."There are challenges with air bubbles when working with microfluidics devices, if you get an air bubble in the system it can be very difficult to flush it out. We also have very high surface-to-volume ratios in microfluidic devices, so if our surfaces are negatively charged and our particles or magnetic cells are positively charged, they stick to the surface and it is very difficult to get them off. Also, when working with droplets the droplets have to be stable enough. If they are not stabilized then they merge to each other or break open leaving a big mess in the chip. We have been through a very big learning curve".

In his presentation, Daniel Mark, Head of Division Lab-on-a-Chip, HSG-IMIT, University of Freiburg, Germany highlighted the point that commercialization of microfluidic based products often fails due to the focus on the technology rather than the suitability for the application and compatibility for scale-able production.

Scalability and translation from lab to product is a common challenge in developing microfluidic assays and diagnostics. In order to address this Daniel Mark and his group have focussed on providing manufacturing strategies solutions which specifically allow easy transition from research prototypes to cost-efficient mass fabrication, with a series of modules for microstructuring, functionalization, reagent storage and sealing in an attempt to reduce the time and cost issues commonly experienced when bringing a prototype assay or device.

"We noticed that a lot of projects stop at the stage of having a working prototype, where it is most interesting. It can be very frustrating if you develop something, it works and then a manufacturer tells you they can't make it because it's too complex and expensive. Our idea was to use a consistent approach to the development, prototyping and manufacturing process right from the start to avoid this.We also had the inspiration of using technology similar to blister packs for our microfluidics products. It keeps things safe and stable, allows you to ship it easily and it is very inexpensive".

4. What does the future hold for microfluidics?

We asked this question of a number of speakers at the congress, and their responses were overwhelmingly positive:

Charles Henry, Professor in and Chair of the Chemistry Department at Colorado State University.

"We are deploying some of our technology with grade school children, getting them to probe the environment and to understand things that they are being exposed to as well. In one particular study we are looking at the correlation between environmental exposure and asthma attacks; this will be a chance for the first time for scientists, epidemiologists and clinicians to be able to understand that correlation and hopefully help those children who are prone to acute asthma attacks to head off those exposure scenarios prevent attacks occurring. I think microfluidics will give us the ability to help them implement those safeguards at the individual level".

Nicole Pamme, Professor in Analytical Chemistry at the University of Hull. Research focused on bioanalysis in microfluidic devices, in particular applications of magnetism.

"Microfluidics has been around for 20 years now and is maturing as a technology, but it has taken a long time for products to be successful on the market. We are now seeing more and more engineers working together with scientists and clinicians to ensure a device is made that is functional, robust and useful for the end-user, the clinician, thanks to the input from the engineer. We are seeing a lot more devices entering the marketplace now and I think microfluidics is here to stay and grow".

Daniel Mark, Head of Division Lab-on-a-Chip, HSG-IMIT, University of Freiburg, Germany

"The market, according to many market studies, is expected to grow quite significantly. I think we are now at a time where the technology matures and where more and more products are at the level of functionality and price that is right for the end-user, which are clinics. The end-user can be in developing countries, where there is no sophisticated laboratory infrastructure, or for laboratories that want to optimize their workflow. I'm hoping that in 5 years' time we'll highly increase the number of microfluidics products in diagnostics and analytics in developing countries thanks to the research that participants of this congress are now doing".

Dr. Adrien Plecis, CSO and co-founder of Elveflow, a company which specialises in high performance scientific instruments for microfluidics.

"We are at the very beginning of the exponential expansion of microfluidics. Microfluidics still resides a lot in the lab as new technologies are being developed by scientists, but transfer from the lab to the markets will increase drastically in the next few years".

5. Conclusion

Conferences such as The Microfluidics Congress held by Global Engage are vital as a platform for the diverse microfluidics community to keep coming together to build on the collective of ideas and expertise which underpin current and future successes. Feedback on the meeting:

"There was a good audience, and I'm very impressed with the exhibitions".

"I'm looking forward to being here for the rest of the meeting and engaging with the other scientists and engineers who are here".

"There are great speakers and the exhibition here is wonderful with a mix of scientific posters that are really interesting and the industrial exhibit. Yes, it's a brilliant event".

"I think the participants of this conference are of very high quality. I was really impressed by the quality of the talks that I heard today. I also had some interesting discussions in the exhibition. Overall, I think it's a very well organized and excellent congress with great participants".

The mood of enterprise and collaboration described above across science and engineering has generated a large body of impressive research and development using microfluidics and has resulted in a big leap in our understanding of the technology and how to apply it. The focus for the next 5 – 10 years is clearly now on turning the knowledge gained into robust, practical and affordable tools and solutions to meet the need for diagnostics and analytical tools to address a growing and more in-depth range of human healthcare issues.