



MfHS 2026

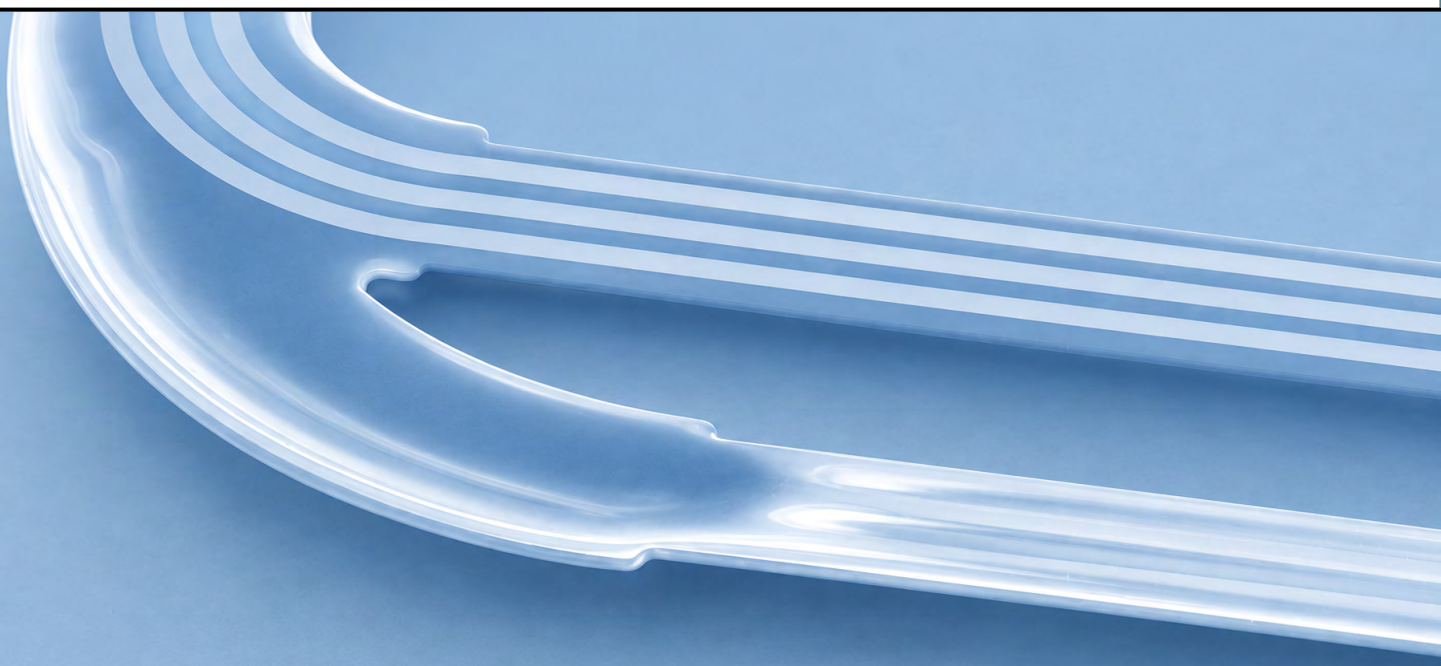
Conference Proceedings

The 6th Conference
on

MicroFluidic Handling Systems

28-30 September 2026

Enschede
The Netherlands





Conference: The 6th Conference on MicroFluidic Handling Systems (MFHS 2026).

Dates: 28-30 September 2026.

Chairs: Joost Lötters and Martin Richter.

Technical program committee: Dennis Alveringh, Klaus Drese, Jankees Hogendoorn, Remco Wiegerink, Bernhard Jakoby, Jaap den Toonder, Bonnie Gray, Paola Fanzio, Holger Becker, Karin Bauer, Regina Luttge, Christing Ruffert.

Sponsors: Bronkhorst High Tech, NWO, Hahn Schickard, Fraunhofer EMFT, MESA+ Institute, Demcon, MDPI Micromachines, Krohne, Chiptech Talent, University of Twente.

Location: De Kleine Willem, Langestraat 45, 7511 HB Enschede, The Netherlands.

Organization: Joost Lötters, Remco Wiegerink, Marthe Kampman, Lars Holm.

Proceedings: Lars Holm.

Welcome to the 6th International Conference on Microfluidic Handling Systems

From 28–30 September 2026, the 6th International Conference on Microfluidic Handling Systems (MFHS 2026) will be held in Enschede, in the picturesque setting of former theatre De Kleine Willem, as a follow-up to the successful previous conferences in Enschede in 2012, 2017 and 2019, and in Freiburg and Munich in 2014 and 2024, respectively.

Worldwide, accurate handling—i.e., analysis, dosage, measurement and control—of small and extremely small mass flow rates of both gases and liquids is becoming more and more important, driven by numerous applications. In 2023, the market for microfluidic devices was \$19 billion, and it is expected to grow to \$22 billion in 2029, according to a market forecast issued by Yole (2024).

Examples of economically and societally relevant applications are, e.g., printing technologies, haptics; monitoring of air, soil and water quality; multi-infusion systems, respiratory systems for patients with lung diseases, diagnostics, personalised medicine; equipment for high-pressure liquid chromatography (HPLC) and mass-spectrometry (MS); flow and pressure control in organ-on-a-chip systems; research on catalysts, energy content measurement in (mixtures of) fuel gases including biogas and hydrogen, oil testing; dosage systems for accurately dosing additives like, e.g., vitamins to food and beverages, production of specialty baby food with high nutritional value, food safety; production of vaccines and pharmaceuticals by means of flow chemistry and fermentation; production of solar cell panels with CVD and ALD processes, electronic cooling now emerging as a particularly promising application.

Whether in analytical instrumentation, flow chemistry, energy, pharma, semiconductor industry, food and beverage or life sciences—microfluidic handling systems are facing several major trends:

1. a need for accurate measurement and calibration facilities;
2. a need for complete functional systems rather than for the individual components;
3. commercialisation of academic research results;
4. standardisation of fabrication technology & materials, modules & connections, and quality assurance & test equipment;
5. cross-overs between technologies, e.g., microfluidics and electronics, and microfluidics and robotics, and last but not least
6. the rise of machine-learning enhanced fluidic systems.

In the future, the impact of this field of research may become even bigger and potentially large target markets may arise, especially when spin-off companies start manufacturing and selling their products, systems or pilot plants.

The focus of the conference is mainly on the technology, components, devices and systems that enable the application in microfluidic systems. At the conference, papers will be presented on systems and devices for accurate handling (e.g., dosing, measurement, analysis and control) of (extremely) small flows of both gases and liquids, and corresponding measurement and control principles, including cross-over technologies with, e.g., electronics and robotics, and machine learning enhanced fluidic systems.

MFHS2026 provides an excellent opportunity to bring together scientists and engineers from academia, research institutes and companies to present and discuss the latest results in the field of microfluidic handling systems. The conference goals are to stimulate interaction and knowledge exchange between the delegates in a friendly atmosphere. The most recent academic and industrial developments in the field of microfluidic sensors, actuators, fluidic systems and applications will be presented in 5 oral sessions and 1 poster session.

We are looking forward to seeing you at the MFHS 2026 conference!

Prof. Joost Lötters
Conference chairs

Dr. Martin Richter

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Chairs



prof. dr. ir. Joost Lötters

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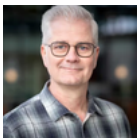
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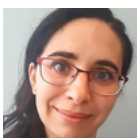
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prof. dr. -ing. Christine Ruffert

Fraunhofer-Institut für Photonische Mikrosysteme IPMS - Institutsteil Integrated Silicon Systems, Cottbus, Germany.

Brandenburgische Technische Universität, Cottbus-Senftenberg, Germany

Program

Monday, 28th of September

Time	Program	Location
17:00–21:00	MESA+ networking event: dinner and drinks	Colosseum Party Colosseum 72, Enschede

Tuesday, 29th of September

Time	Program	Location
8:30–9:15	Registration	Lobby
9:15–9:30	Welcome & announcements	Theater
9:30–10:00	Invited talk 1: “The Adventure of Commercializing Microfluidics”	Theater
10:00–11:00	Session 1: Flow and fluid composition	Theater
11:00–11:30	Coffee break & exhibition	Lobby
11:30–12:00	Invited talk 2: “Magnetic Polymer Microfluidic Actuators for Flexible and Wearable Microfluidic Flow Control”	Theater
12:00–12:40	Session 2: Flow control	Theater
12:40–13:45	Lunch & exhibition	Lobby
13:45–14:15	Invited talk 3: “Next-Generation Organ-on-a-Chip Platforms with Integrated Sensors for Dynamic Cell Measurements”	Theater
14:15–15:15	Session 3: Fluidic Systems	Theater
15:15–15:45	Coffee break & exhibition	Lobby
15:45–17:45	Poster session & exhibition	Lobby
18:00–20:00	Conference dinner	Muziekcentrum Noorderhagen 27, Enschede
20:00–22:00	Evening show	Theater

Wednesday, 30th of September

Time	Program	Location
8:30–9:15	Registration	Lobby
9:15–9:30	Opening & announcements	Theater
9:30–10:00	Invited talk 4: “Precision Fluid Handling in Low-Flow Reactor Systems: Challenges, Lessons Learned, and Future Needs”	Theater
10:00–11:00	Session 4: Applications	Theater
11:00–11:30	Coffee break & exhibition	Lobby
11:30–12:30	Session 5: Late News	Theater
12:30–13:00	Closing session & Awards ceremony	Theater
13:00–14:00	Lunch & exhibition	Lobby
14:30–16:00	Optional lab tour: MESA+ nanolab	University

Invited talk 1



Dr. Peter Koltay

Serial Entrepreneur and Microfluidics Researcher

Tuesday, 29 September 2026 09:30–10:00

Theater

The Adventure of Commercializing Microfluidics

Short bio: Dr. Peter Koltay was assistant to Prof. Roland Zengerle at the University of Freiburg, Germany, from 1999. He is currently heading the department laboratory automation at Hahn-Schickard, a non-profit organization supporting industry through contract research in innovative MEMS technologies. During his career, Dr. Koltay has co-founded three start-ups and served as CEO of several of them. His research focuses on microfluidics, with particular emphasis on miniaturized laboratory automation, in-vitro diagnostics, and cell-handling technologies. He has published more than 280 research papers, reviews, and book chapters, and his commercialization activities have resulted in more than 20 international patents and several spin-off companies.

Abstract: The talk focuses on three categories of microfluidic devices and solutions: micro- and nanoliter dispensing, molecular diagnostics at the point of care using centrifugal microfluidics, and absolute quantification of proteins and protein–protein interactions. It provides an overview of challenges, pitfalls, and success stories in translating academic concepts into successful products through the creation and development of spin-off companies.

Invited talk 2



Dr. Bonnie L. Gray

Professor, Engineering Science, Simon Fraser University

Tuesday, 29 September 2026 11:30–12:00

Theater

Magnetic Polymer Microfluidic Actuators for Flexible and Wearable Microfluidic Flow Control

Short bio: Dr. Bonnie L. Gray is a Professor of Engineering Science at Simon Fraser University in Canada, a Fraser Health affiliated researcher, and a member of the board of the Vancouver Medical Device Development Center. She has more than 140 peer-reviewed journal and conference publications and has given more than 35 invited, keynote, and plenary presentations. Her research covers novel materials and fabrication techniques for biomedical and microfluidic devices and systems, flexible and wearable microfluidics and biosensors, additive manufacturing of microdevices, and chip-based cell research platforms. She serves on the Editorial Boards of *PLOS One* and the *Journal of Micromechanics and Microengineering*, and was general co-chair of IEEE Nano 2025.

Abstract: Magnetic polymer actuators have become an increasingly important class of smart materials for microfluidic flow control. Research has progressed from ferrite-filled elastomers and magnetorheological composites toward hard-magnetic polymer composites capable of large deformation, programmable shape change, wireless actuation, and multifunctional operation. The talk describes permanently magnetized polymer composites developed for microfluidic flow control and biomedical MEMS applications. Beginning with rare-earth magnetic powder embedded in PDMS and SU-8, the work includes characterization of the magnetic and mechanical properties of these materials and the development of design criteria for microfluidic actuators. Applications include artificial cilia, flap valves, membrane actuators, reconfigurable valve arrays, micropumps, mechanobiology platforms, and wearable actuators.

Invited talk 3



Dr. Darwin R. Reyes, Ph.D.

Project Leader, BioMEMS Project, National Institute of Standards and Technology (NIST)

Tuesday, 29 September 2026 13:45–14:15

Theater

Next-Generation Organ-on-a-Chip Platforms with Integrated Sensors for Dynamic Cell Measurements

Short bio: Dr. Darwin R. Reyes is a project leader at the National Institute of Standards and Technology (NIST) and a lecturer in the Division of Biotechnology at Johns Hopkins University. His work at NIST focuses on integrated electronic capabilities for manipulating and measuring cells in organ-on-a-chip devices, enabling real-time heart-on-a-chip and cancer-cell-based testing for drug development and toxicity assays. Dr. Reyes is also a co-founder and chair of the Microfluidics Association and chairs the Standardization Interest Group of the International Microphysiological Systems Society. He has received the American Institute for Medical and Biological Engineering's Emerging Leader Award and the PML/NIST Outstanding Achievement in Measurement Services and Standards Award.

Abstract: Organ-on-a-chip and microphysiological-system platforms provide controlled microenvironments in which human cells can be exposed to drugs and chemicals. However, many platforms still rely on endpoint measurements, which can limit the temporal information available about cellular responses. Integrating sensing capabilities can provide a more complete dynamic picture of cell behaviour. Dr. Reyes and his team have developed a platform that integrates electrodes on both sides of porous polyester membranes to manipulate cells through dielectrophoretic trapping while measuring cellular behaviour, including cell migration and heart cell beating. The platform can simultaneously assess barrier integrity and changes in the frequency and amplitude of heart-cell beating, providing a multiparametric approach for drug efficacy and safety studies in preclinical testing.

Invited talk 4



Dr.-Ing. Matthias Lübbert

Technical Sales Engineer, Integrated Lab Solutions

Wednesday, 30 September 2026 09:30–10:00

Theater

Precision Fluid Handling in Low-Flow Reactor Systems: Challenges, Lessons Learned, and Future Needs

Short bio: Dr.-Ing. Matthias Lübbert is a technical sales engineer at Integrated Lab Solutions (ILS), a Berlin-based provider of automated chemical R&D testing systems and contract research services. He holds a Diploma in Chemical Engineering from Technical University Berlin and a PhD in Chemical Engineering from Hamburg University of Technology, where he studied adsorption equilibria in supercritical fluids. Prior to joining ILS, he held senior process engineering positions at KNAUER Wissenschaftliche Geräte GmbH, where he worked on advanced chromatography systems and scalable lipid nanoparticle production. His expertise includes liquid chromatography, SMB, SFC, adsorption processes, microfluidic mixing, pharmaceutical process engineering, laboratory automation, and project management.

Abstract: Low-flow reactor systems are increasingly important for catalyst development, reaction screening, and process intensification. Reliable and reproducible operation depends critically on accurate measurement, distribution, dosing, and control of fluids over a wide range of operating conditions. This presentation examines fluid handling from a system-level perspective, drawing on experience with high-throughput low-flow reactor platforms at Integrated Lab Solutions and lipid nanoparticle systems at KNAUER. Particular attention is given to low-flow challenges including measurement uncertainty, broad turndown requirements, pressure stability, and flow distribution across parallel reactor networks. The talk also discusses the scale-up of lipid nanoparticle production, including the mRNA-vaccine manufacturing process, and concludes with future opportunities for advanced sensing, pressure and flow control, and integrated measurement and control in automated research platforms.

Session 1: Flow and Fluid Composition

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Chairs: Klaus Drese & Dennis Alveringh

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HEADSPACE VOLUME TRACKING USING FLEXI-FLOW ADVANCED FEATURES FOR FED-BATCH BIOREACTOR APPLICATIONS

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² Westfälische Hochschule, Recklinghausen, Germany

ABSTRACT

In this report, a robust and cost-effective method for tracking the working volume inside a fed-batch or continual bioprocess is investigated. The method relies on the utilisation of a headspace volume measurement by the addition of a gas volume in a temporarily closed bioreactor. The *Bronkhorst Flexi-FLOW digital mass flow and pressure controller* advanced functionality can be used to measure a slight pressure increase in the bioreactor due to an incidental small gas volume addition, allowing volume tracking during the bioprocess.

In a fed-batch yeast process, a calibrated pump was used for continual medium addition with a total volume of approximately 1 litre. The headspace volume measurement system proposed was used to calculate the added volume during the experiment, which yielded 0.999 litres. The system proposed in this work can be used for sterile, accurate, robust and cost-effective volume tracking in bioreactors of any scale.

KEYWORDS

Bioreactor, headspace volume, working volume, fed-batch bioprocess, Flexi-FLOW, VOC-sensor

INTRODUCTION

Advancements in bioreactor technology for bioprocessing applications require better understanding and control of the biological process that happens inside the bioreactor. These advancements should lead to *minimised losses and increased efficiency* of product production through deepened understanding of the biology in the bioreactor. To achieve this, additional sensor equipment is often added to obtain more information about this biological process. One advantage of more sensor equipment is the possibility to run fed-batch and continual processes, which can allow for more efficient product production^[4].

In fed-batch bioprocesses, fresh liquid medium is added 'on demand' to for example achieve ideal nutrient concentrations. To keep this concentration ideal, the bioreactor user needs to track the liquid **working volume** in the bioreactor. Disadvantages of currently used methods that rely on either calibrated pumps or a combination of pumps with scales include:

- Touch-sensitivity (for scales)
- Drift due to tube degradation (in calibrated, peristaltic pumps)

The *Bronkhorst Flexi-FLOW digital mass flow and pressure controller*^[2] is already used in bioreactor systems for the gas feed. It's advanced multiparameter functionality can additionally be used to periodically measure the **headspace volume** inside the bioreactor. When the total

bioreactor volume is known, the working volume can be calculated (Equation 1):

$$V_{\text{working}} = V_{\text{total}} - V_{\text{headspace}} \quad (1)$$

When the Flexi-FLOW mass flow controller (MFC) is combined with a shutoff valve in the bioreactor gas output, it is possible to insert a small volume of gas to realise a slight pressure increase, as is shown in Figure 1.

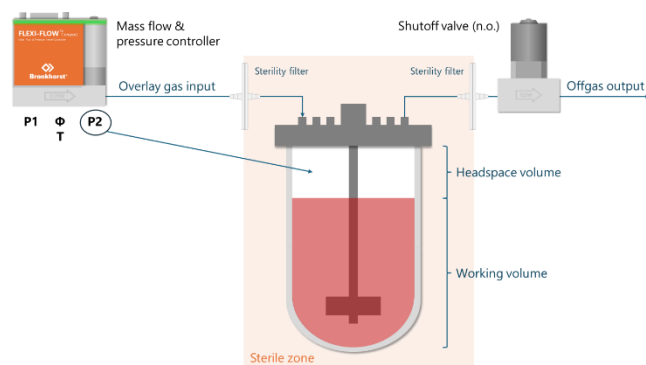


Figure 1: Schematic representation of the headspace volume measurement system using Bronkhorst Flexi-FLOW multiparameter functionality.

The pressure increase can be measured using the downstream pressure sensor (P2 in Figure 1) and can be used to calculate the headspace volume in the bioreactor according to Equation 2:

$$V_{\text{headspace}} = \frac{p_N \cdot \Delta(V_{\text{counted}})_N \cdot \frac{T_{\text{end}}}{T_N}}{p_{\text{rsd}} - p_{\text{srt}} \cdot \frac{T_{\text{end}}}{T_{\text{srt}}}} \quad (2)$$

The Flexi-FLOW is used to add a known gas volume ($\Delta(V_{\text{counted}})_N$) to the bioreactor after the shutoff valve is used to close the gas output. The pressure increase caused by this added volume ($p_{\text{srt}} \rightarrow p_{\text{rsd}}$) in combination with the change in temperature ($T_{\text{srt}} \rightarrow T_{\text{end}}$) can be used to calculate the headspace volume ($V_{\text{headspace}}$). After headspace volume determination, the bioreactor is depressurised by opening the shutoff valve and the Flexi-FLOW MFC can be used for gas feed to the bioprocess.

Flexi-FLOW MFCs are already utilised for bioreactor gas feed. The strategy for volume tracking described herein therefore provides a sterile, robust and cost-effective volume tracking in bioreactors of any scale. For testing the accuracy of this strategy in a real bioprocess, a **fed-batch bioprocess** was conducted using yeast (*Saccharomyces cerevisiae*) in a bioreactor system outfitted with the shutoff valve, Flexi-FLOW and a *FermSYS volatile organic compound (VOC) sensor* (Figure 2).

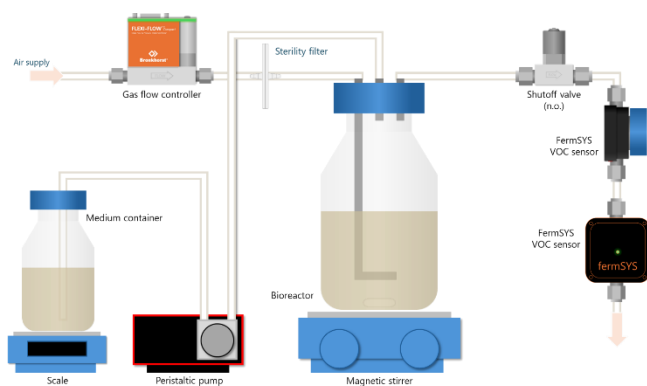


Figure 2: Schematic representation of the fed-batch bioprocess setup used in combination with the FermSYS VOC sensor and the Flexi-FLOW based headspace volume measurement system.

The FermSYS VOC sensor can be used to measure ethanol production by yeast, indicating the biological activity^[3]. In this yeast growth bioprocess, fresh medium with a total volume of 1 L was continually supplied using a peristaltic pump. During this process, both the headspace volume and the ethanol production were periodically measured.

RESULTS

Given a constant liquid flow addition by the peristaltic pump of approximately 1 g/min, it is expected that the total volume of 1 L is completely added to the bioreactor in approximately 16 hours. The expected headspace volume reduction (blue line) and the measured headspace volume (grey dots) are both shown in Figure 3: Expected headspace volume in blue. Measured headspace volume in grey. Two deviations from the expected trend are highlighted in red and green. Figure 3.

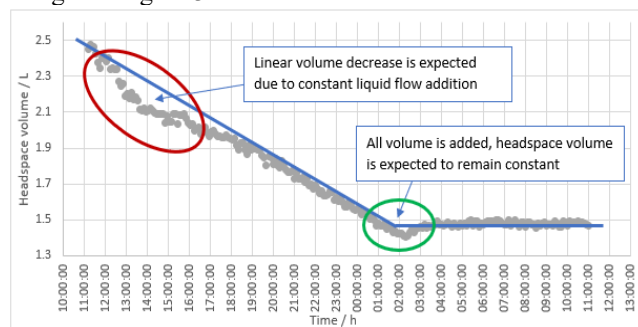


Figure 3: Expected headspace volume in blue. Measured headspace volume in grey. Two deviations from the expected trend are highlighted in red and green.

There are two areas where the measured headspace volume differs from the expected headspace volume. These two deviations are highlighted in red (top-left) and green (middle-bottom) in Figure 3. Both deviations show a measured headspace volume that is lower than expected. The process was started at approximately 11:00h and ended at approximately 11:00h the next day.

The measured headspace volume can be compared to the ethanol production of the yeast as measured by the FermSYS VOC sensor. This sensor signal (in arbitrary

units) correlates with the ethanol concentration in the gas output of the bioreactor and can therefore be used as a measure for the ethanol concentration in the bioreactor. The VOC sensor signal is compared to the measured headspace volume in Figure 4.

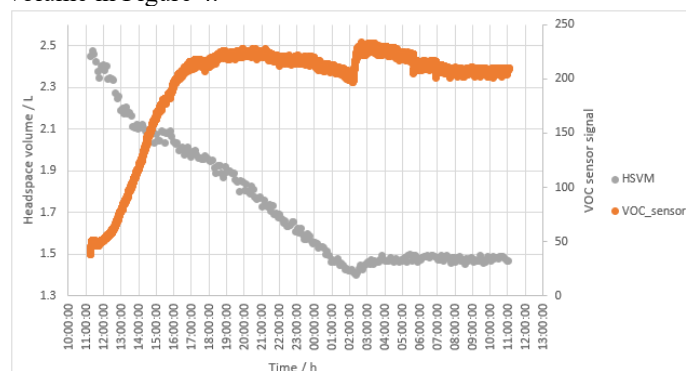


Figure 4: Headspace volume measurement and VOC sensor signal during the experiment.

The VOC-sensor signal correlates directly with the produced volatile organic compounds by the yeast. It can therefore be used as a measure for the biological activity of the yeast. From a biotechnical perspective, the yeast growth process^[3] can be divided into four parts:

1. **Lag phase:** The yeast adapts to the medium provided. There is little growth because the yeast is still adapting the metabolic pathway on the provided nutrients in the medium.
2. **Growth phase:** After adaptation, the yeast growth is high (often exponential growth is observed).
3. **Stationary phase:** In this phase, there is little growth. The yeast is metabolically active.
4. [Optional] – **Diauxic phase:** When nutrients in the medium are all consumed, the yeast must adapt the metabolic pathway again to another substrate available.

In the VOC-sensor signal curve, these four phases can be identified. The first phase, characterised by low VOC production due to little growth and little metabolic activity, can be observed in Figure 4 from approximately 11:00h to approximately 12:00h. The second phase, characterised by much larger growth and subsequently increasing metabolic activity and VOC production, can be observed in Figure 4 from approximately 12:00h to approximately 16:00h. The third phase, characterised by high metabolic activity but no large growth, can be observed in Figure 4 from approximately 16:00h to approximately 02:00h. Here, the VOC production remains relatively stable at a higher value than the starting value, suggesting a higher number of yeast cells with a relatively constant metabolism. A fourth phase can also be observed in Figure 4 from approximately 02:00h to approximately 11:00h (next day). This phase correlates nicely with the headspace volume measurement data. It occurs when the total medium volume of 1 L was completely added (based on the headspace volume measurement data). When medium addition with fresh nutrients stops, it is possible that the yeast has consumed all

nutrients in the medium. At this point, the yeast must change substrate triggering a diauxic phase.

DISCUSSION

Added liquid medium amount

The difference between the expected volume of 1 L and the volume based on headspace measurement (0.999 L) may be caused by temperature changes during the measurement. In a theoretical investigation about the influence of pressure and temperature on the calculated headspace volume, it was observed that both environmental temperature (approximately 0.3% deviation per °C) and temperature difference (approximately 2.1% deviation per °C) between the situation before gas addition and after gas addition may both influence the calculated headspace volume. The MFC can measure the temperature of the gas supplied to the bioreactor. The temperature of this gas was warmer than the temperature inside the bioreactor. To correct for this effect, a temperature difference before and after gas addition of approximately 1 °C was assumed. Since the bioreactor temperature was not measured, there is no way to verify this assumption.

Based on headspace volume measurement data, the complete medium volume was added around 2:18 h, approximately 15 hours after the start of the experiment. Based on the peristaltic pump flow of approximately 1 g/min, it would be expected that the 1 L medium volume was completely added at around 3:00h (16 hours after starting). Tube degradation of the peristaltic pump or miscalculation of the pump flow can both be a cause of this difference.

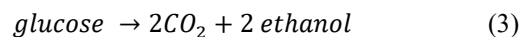
Trend deviations

The deviations encircled in Figure 3 both show a lower than anticipated measured headspace volume compared to what was expected based on the trend of previous measurements. Furthermore, the deviations correlate quite well with the growth phase (red deviation) and the start of the diauxic phase (green deviation) when looking at the VOC-sensor signal data in Figure 4.

For the growth phase, it is known that the metabolic activity is quite high. In this phase, the yeast consume sugar from the medium and produce carbon dioxide (CO₂) and ethanol. The yeast cells may produce a large quantity of gas during the headspace volume measurement. In this case, the added amount of gas to slightly increase the pressure in the bioreactor is caused by both yeast gas production and the gas addition by the MFC. In the calculation of the headspace volume, it is assumed that the pressure increase is caused only by the gas addition of the MFC. When for a certain amount of added gas by the MFC, the pressure rises more than expected, the calculated headspace volume is lower than the actual headspace volume. This yeast gas production could explain the lower than anticipated calculated headspace volume in Figure 3, which overlaps nicely with the VOC-sensor signal data in Figure 4.

At 14:00h, the headspace volume measured is

approximately 2.1 L (Figure 3). Based on the trend of previous (and next) headspace volumes in Figure 3, it was expected to be around 2.25 L. During the headspace volume measurement, 150 mL of gas must have been produced by the yeast to explain the deviation. The headspace volume measurement takes approximately 30 seconds. The yeast must therefore have produced approximately 300 mL / min or approximately 0.013 mol / min of gas. When glucose is the primary substrate:



Glucose consumption is therefore approximately 0.007 mol / min. Using the molar mass of glucose (= 180.16 g / mol), that means a consumption rate of approximately 1.3 g / min. The hypothesis of gas production because of biological activity may also be an explanation for the deviation highlighted in green.

In addition to the deviations from the expected trend due to biological activity, temperature effects caused either by air conditioning equipment in the laboratory or direct sunlight on the setup are also potential explanations for the deviations highlighted in Figure 3. The deviation highlighted in red could also be a start-up effect where temperature equilibrium has not been reached. The same can be true for the deviation highlighted in green; a stop of liquid volume addition may influence the established temperature equilibrium in the bioreactor, causing the calculated headspace to change.

In this experiment, the overlay gas temperature was not measured. It is therefore impossible to correlate temperature effects with deviations in the data. Consequently, temperature influence as an explanation for artefacts in the data remains a hypothesis. A temperature sensor that measures the liquid temperature is quite common in most bioreactor systems. It may be possible to utilise this sensor and compensate for any temperature effects. In the most ideal case, a dedicated temperature sensor is placed in the headspace volume itself. If the headspace temperature can be measured directly, the calculated headspace can be compensated for these effects.

CONCLUSION

The investigated headspace volume measurement is found to have predicted a 0.999 L volume decrease where a 1 L volume decrease was expected. This method can therefore be used to predict headspace volume of a bioreactor with around 0.2% deviation compared to the used volumetric measurement. The accuracy of the headspace volume is influenced by gas production due to biological activity, which likely explains the deviations observed in relation to the measurement data trend. The accuracy also depends on temperature effects, changes in the solubility of gas in the liquid and potential gas leakage from the bioreactor. These factors have not yet been considered in this experiment.

The influence of temperature or any gas leakage on the calculated headspace volume are the most likely

explanation for artefacts and deviations in the data, although this cannot be proven from the data in this experiment alone.

FUTURE PERSPECTIVES

In theory, this proposed headspace volume measurement system using the Bronkhorst Flexi-FLOW MFC in combination with a shutoff valve can be used for any size bioreactor. The bioreactor used in this process had a particular size (2.8 L). For smaller bioreactors, a Flexi-FLOW MFC with a smaller maximum flow can be used in the same method. For larger bioreactors, a Flexi-FLOW MFC with a larger maximum flow can be used. The accuracy of the headspace volume measurement system in these systems depends on the accuracy with which the gas (headspace) pressure, temperature and gas volume flow can be measured. This be investigated in future.

MATERIALS & METHOD

The fed-batch, yeast-growth bioprocess was performed at the Westfälische Hochschule in Recklinghausen, Germany inside a bioreactor with a total volume of approximately 2.8L. A peristaltic pump was used to add medium until the total volume of 1 L was added. At the start of the process, the yeast were placed in the bioreactor containing approximately 400 mL of medium. 2 mL of antifoam was added to prevent excessive foam production. Technical details about the devices used in the setup (Figure 2) can be found in .

Table 1: Technical details of the instruments and materials used in the described bioprocess.

Gas feed MFC (gas input)	Bronkhorst High-Tech B.V. Flexi-FLOW digital mass flow and pressure controller. FF-A2K0 (advanced), $(\Phi_V)_{max} = 2 \text{ l/min}$ (air) SN: 124M00133511IQ
Shutoff valve (gas output)	Bronkhorst High-Tech B.V. Control valve (normally open) F-001AV-LFE-22-K, orifice diameter = 3.0 mm SN: M25220370A
Magnetic stirrer	IKA Magnetic stirrer & heater RCT Classic
Scale	KERN Precision balance PFB 6000-2
Peristaltic pump	Watson & Marlow Peristaltic pump 101 U
Yeast used	<i>Saccharomyces cerevisiae</i> (freeze-dried)
Medium used	Rolinck Brewery Wort complex components
VOC sensor 1	FermSYS fermSYS Flow adapter URL: https://www.fermsys.de/voc-for-laboratory

VOC sensor 2	FermSYS fermSYS CUBE URL: https://www.fermsys.de/feasibility-study
VOC sensor measurement & control software	FermSYS Software FermHUB URL: https://www.fermsys.de/fermhub

The peristaltic pump flow was measured at approximately 1 gram / minute by using a scale. Approximately 10 grams of liquid were added in approximately 10 minutes. This measurement was done immediately after starting the pump.

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TOWARDS ABSOLUTE GAS FLOW IN MICROFLUIDIC HANDLING SYSTEMS EMPLOYING THE FLEXI-FLOW COMPACT

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A framework of more than a dozen absolute active displacement provers (PARs) could be employed to realize an absolute scale from $0.01 \text{ ml}_n \cdot \text{min}^{-1}$ to $50 \text{ l}_n \cdot \text{min}^{-1}$. Above $2 \text{ ml} \cdot \text{min}^{-1}$ these portable provers will reflect the best uncertainty achievable amongst NMIs worldwide to support gas-flow measurements, calibrations and research and development in mass-flow control. First results demonstrate differences in individual realization better than 0.06% [1]. However, in the microfluidic realm of $0.01 \text{ ml}_n \cdot \text{min}^{-1}$ to $1 \text{ ml}_n \cdot \text{min}^{-1}$ gas flow, or even lower, the absence of international comparisons of absolute scale realizations amongst national institutes supports the argument that pursuing traceability below this comparison barrier is futile and one is bound to large uncertainties from extrapolation.

Having the absolute framework of PARs in reach and to support the mass flow range/product-line below $2 \text{ ml}_n \cdot \text{min}^{-1}$, the idea was raised to start a new initiative called Enterprise. That is, to work up a primary scale at Bronkhorst below $2 \text{ ml}_n \cdot \text{min}^{-1}$ with additional alternative traceability routes next to the PAR. The main aim is not to achieve very low uncertainties at first but to create a “peg in the sand” on the uncertainty through comparison of several techniques on one facility. The supportive primary technique is based on small-volume PVTt in combination with a rate-of-rise measurement [2, 3]. Using the strong knowledge base at Bronkhorst on mercury-based pistons (FPPs), the warp core of the facility will be based on three 16 mm internal diameter 1-metre-long piston provers equipped with retroreflectors that have their volumes measured by laser interferometry. The main idea is to submerge the entire facility in 800 liters of water, creating a $\pm 5 \text{ mK}$ stable environment. The latter is obtained by using evaporative cooling from dry nitrogen, bubbling out the main source of uncertainty.

As a pilot experiment an FPP-016 was modified significantly to measure at very low flows. For a start, influence of temperature was significantly reduced through temperature gradient compensation along the tube using conditioned forced air and by placing the entire base under water (Fig. 1). A calibrated Agilent 5519B laser interferometer, acquired also for traceability support on the PARs absolute rod displacement, is brought in from the top through a pentaprism construction to reach the retroreflector inside the prover tube. The interferometer system is equipped with a built-in receiver that can measure absolute displacement and speed of reflective surfaces with an uncertainty well below 10 nm and up to speeds of $1000 \text{ mm} \cdot \text{s}^{-1}$ with uncertainty of $0.13 \text{ mm} \cdot \text{s}^{-1}$. First experiments show that, for this tube, slip-stick effects due to friction and mercury adhesion to the surface-treated tube wall fades away for flows above 0.002

to $0.004 \text{ ml}_n \cdot \text{min}^{-1}$.

In this paper the methodology and proof of weak coupling to environmental conditions will be demonstrated to an equivalent 3 mK stability, which is also foreseen in the Enterprise basin. Having eradicated the influence of the environment, the observed variations in piston displacement can now be attributed to either temperature or pressure variations in the measured gas volume itself and the strategy on how to separate these out will be elaborated in more detail. The paper is concluded by sharing first results on performance measurements in conjunction with a FLEXI-FLOW Compact mass-flow controller in the range of $0.01 \text{ ml}_n \cdot \text{min}^{-1}$ to $5 \text{ ml}_n \cdot \text{min}^{-1}$ (Fig. 2 and 3). For this particular model all flow is passed through its semiconductor-based sensor chip created with surface channel technology [4] hence first contact is made with improved absolute derived SI of flow.

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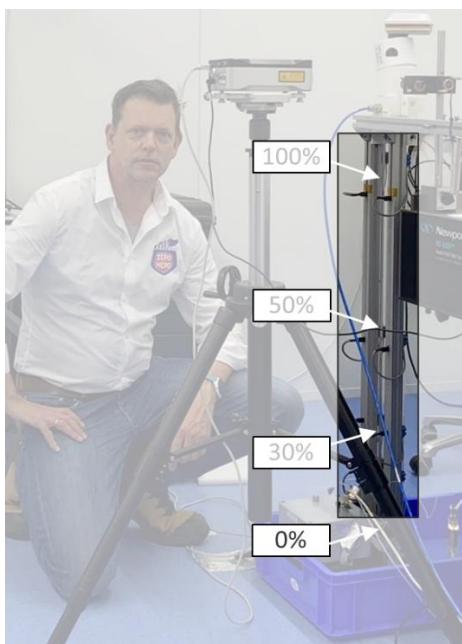


Figure 1: Mercury-sealed piston prover shielded from environment and equipped with laser-interferometer to measure low gas flow rates between 0.01 and $5 \text{ ml}_n \cdot \text{min}^{-1}$.



Figure 2: Body of FLEXI-FLOW Compact is also submersed in water to eliminate environmental effects.

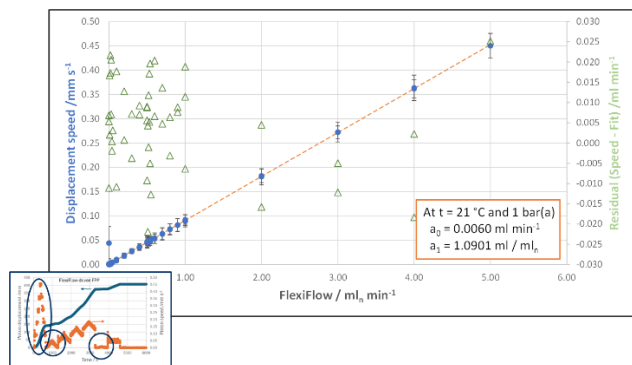


Figure 3: Investigating the measurement capability using a mass flow controller. Inset at the left shows the measurement sequence in time. The average of the last 20 seconds of each one-minute plateau is given the main graph.

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NEW TRACEABILITY BASELINE FOR MICROFLUIDIC GAS-FLOW MEASUREMENTS BASED ON AN ENSEMBLE OF PRIMARY STANDARDS

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A series of at least three models of active displacement provers is under development at Bronkhorst High-Tech B.V. to provide traceability in gas-flow between $0.01 \text{ l}_n \cdot \text{min}^{-1}$ to $50 \text{ l}_n \cdot \text{min}^{-1}$ [1]. By adapting the prototype design and making all individual measurement elements of the prover traceable to SI the prover performance was improved, resulting that the instrument can no longer be calibrated in terms of gas-flow, i.e., compared with a higher standard, but needs to be absolutely realized instead. When maintaining an ensemble of more than a dozen provers and determining their differences in realization for all permutations, a unique cloud of data can be generated that can be used as a baseline for absolute gas-flow measurements.

Capable of measuring most gases including hydrogen, the Bronkhorst Primary Active Rod prover (PAR) measurement principle is based on the displacement of an in roundness-calibrated rod that is moved out of a chamber, maintaining a small, yet controlled, pressure difference of less than 2 Pa over the seal, thus minimizing the leak rate. The measurement principle is very similar to the primary flow meter developed at INRIM [2]. Three models with rod diameters of 10 mm, 38 mm and 145 mm, named PAR-10, PAR-38 and PAR-145 respectively, were developed to have overlapping ranges in mass flow measurement covering the range of $2 \text{ ml}_n \cdot \text{min}^{-1}$ to $50 \text{ l}_n \cdot \text{min}^{-1}$. All PAR provers share the capability of measuring at a nominal flow of $200 \text{ ml}_n \cdot \text{min}^{-1}$, a point that will be used to compare all three models of PAR provers. During a single measurement stroke dedicated microprocessor firmware locks the displacement speed to the given mass flow and after confirmed lock provides sub-second mass flow values to the user. Designed to be transportable, each PAR prover system is tabletop and standalone.

After prototyping, three provers are being evaluated in the field demonstrating successful operation along their design specifications, making the mercury-sealed piston prover (FPP) apparatus legacy when replaced. Direct comparison between identical PAR provers show consistency over days within 0.06% as shown in Fig.1. Absolute intercomparisons were conducted between PARs and FPPs. The latter being traceable only to 0.3 - 0.5%, the associated uncertainty was one order of magnitude larger. More information was obtained though from direct comparison at NMI level. In Fig. 2 the first results of verification are presented from comparison with the primary piston at the Swiss national measurement institute METAS. Using the degree of equivalence of this NMI associated to an international comparison amongst NMIs the results can be presented with

respect to the associated key-comparison reference value. These results agree well within the design specification of the apparatus.

As the fleet of active displacement provers will grow over time, more comparisons will follow including the build-up of an in-house reference value. In this paper this metrological framework design is explained in more detail that will be verified along a harmonized scale of NMI realizations.

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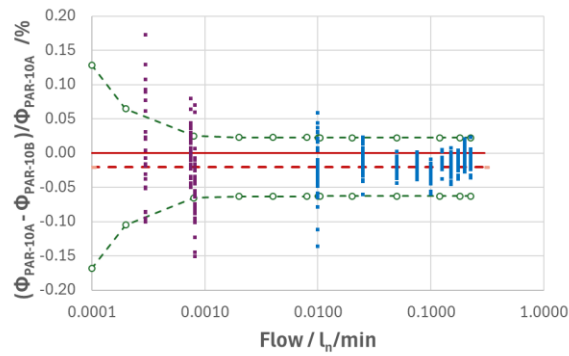


Figure 1: Intercomparison of two PAR-10 models over their entire measurement range over a period of two days. The green lines indicate the expected uncertainty based on calibrated parts. Where the blue dots were obtained from default setting full stroke or maximum of five minutes, the purple dots indicate a measurement obtained from 10 minutes measurement time.

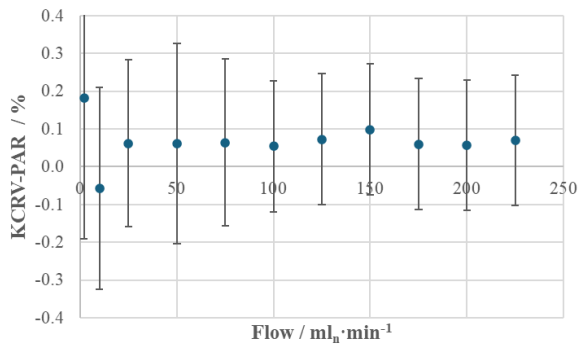


Figure 2. Calibration results of the PAR-10 prototype when (indirectly) compared to a KCRV employing results of latest completed key-comparison amongst NMIs.

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MINIATURIZED PIEZOELECTRIC MICRO PUMP-DRIVEN SYSTEM INTENDED FOR WEARABLE VACUUM-ASSISTED INTERSTITIAL FLUID SAMPLING VIA HOLLOW SILICON MICRONEEDLES

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ABSTRACT

Wearable interstitial fluid (ISF) sampling using hollow microneedles offers a minimally invasive approach for continuous biomarker monitoring. However, passive ISF extraction is limited by tissue resistance and typically requires external vacuum sources or needle removal. This work presents a miniaturized wearable system integrating hollow silicon microneedles with a piezoelectric micro diaphragm pump to provide continuous negative-pressure-assisted ISF extraction. Two prototype concepts were developed and experimentally validated. Peak negative gauge pressures of up to -38 kPa and flow rates of up to 8 mL/min were achieved under zero-backpressure laboratory conditions. In a separate pressure–flow characterization, flow rates of up to 11 mL/min were measured under controlled backpressure. The results demonstrate the feasibility of compact, integrated pressure generation for wearable ISF sampling and provide a basis for further miniaturization toward fully wearable biosensing platforms.

KEYWORDS

Micro pump, ISF extraction, Patch

INTRODUCTION

Blood-based diagnostics require invasive collection and trained personnel, making them unsuitable for continuous or point-of-care monitoring. Interstitial fluid (ISF), the fluid surrounding cells in dermal tissue, contains proteins, metabolites, and biomarkers comparable to blood [1, 2], and can be minimally invasively accessed through the skin. It is therefore a highly attractive matrix for wearable biosensing platforms. Hollow microneedle (MN) arrays allow painless skin penetration without reaching blood vessels, but ISF has limited availability at the puncture site: it is bound within the dermal extracellular matrix and

must be drawn out against the hydraulic resistance of the surrounding tissue. Under passive conditions – diffusion and capillary action alone – extraction yields are therefore severely limited and clinically impractical within relevant sampling timescales [4]. An externally applied negative pressure gradient is required to overcome this tissue resistance and to achieve extraction rates compatible with continuous monitoring. In contrast to previous approaches relying on external vacuum sources [2, 3], the vacuum source is integrated into the wearable device, and suction is applied continuously through the hollow MNs without needle removal.

Piezoelectrically actuated metal-based micro diaphragm pumps (μ Ps) developed at Fraunhofer EMFT offer a promising path to overcome these constraints. Their compact footprint and compression ratio make them well suited for integrated wearable vacuum generation [5]. Consequently, the aim is the integration and experimental validation of an internally μ P-generated negative pressure for hollow-MN-based ISF sampling.

SYSTEM DESIGN

A prototype was designed, experimentally validated, and transferred into a patch variant. The extraction-only prototype for pump characterization and the miniaturized wearable patch both share a core integration concept: a 3×2 hollow silicon MN array (fabricated by the Tyndall National Institute, Cork, Ireland; 500 μ m needle height, 3:2 height-to-base-diameter aspect ratio, 50 nm– 100 nm tip radius, 50 μ m bore diameter, 1750 μ m pitch) that was bonded to a 3D-printed fluid reservoir using two-component epoxy adhesive. In contrast to common ISF sampling procedures, the MNs are intended to remain inserted in the skin while the μ P generates suction transmitted directly through the needle bores (see Figure 2 (bottom)) [3]. The extraction-only variant (Figure 1 and 2 (top)) in-

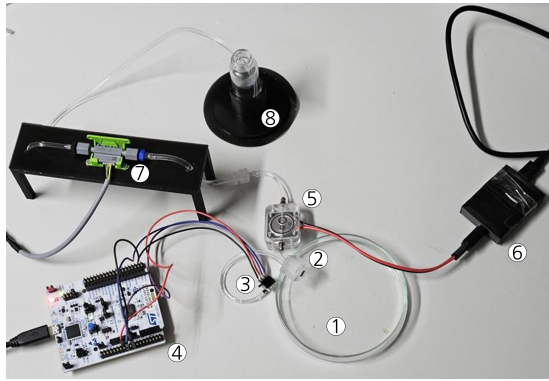


Figure 1: Assembled extraction-only prototype. (1) Inlet reservoir with deionized water, (2) 3D-printed fluid reservoir with MN array, (3) pressure sensor (Honeywell HSCMRN005PD2A3), (4) sensor driver board (STM32 Nucleo G491RE), (5) μ P, (6) pump driver board (MPD015), (7) Sensirion flow sensor SLF3C-1300F, (8) outlet reservoir.

integrates a μ P with the MN reservoir and a differential pressure sensor (Honeywell HSCMRN005PD2A3; $\pm 0.25\%$ accuracy, 0.03% resolution) read out via an STM32-G491RE Nucleo board, providing compact infrastructure for elementary experiments in the lab. The MN reservoir's ventilation side was connected to the pressure sensor, and its outlet side to the μ P's suction. Building on this extraction-only configuration, the two functional subsystems – MN-based extraction and pump-driven suction – were combined and miniaturized into a single wearable patch prototype (Figure 2 (bottom) and Figure 3), which also provides a chamber for chip-sized biosensor insertion at the reservoir outlet. This eliminates the external tubing and bench-top instrumentation of the extraction-only setup, moving the fluidic and electrical infrastructure into a single self-contained device targeting a compact wearable form factor. Figure 3 shows the assembled patch prototype: at $5.7 \times 3.7 \times 1.2$ cm, it integrates the MN array, reservoir, and μ P within a 3D-printed fluidic housing, and was successfully tested for leak tightness and unclogged channels.

EXPERIMENTAL METHODS

Three 20 mm stainless steel μ P samples were characterized: P387, P462, and P499. Each was driven with rectangular signals with sinusoidal flanks (SRS) at 20, 50, 100, and 200 Hz within the extraction prototype. The pumps' pressure build-up on the MN reservoir was sampled at 2 ms intervals. All prototypes were assembled and functionally validated. Leakage and blockage tests confirmed complete seal integrity and clog-free needle bores. The transport of deionized

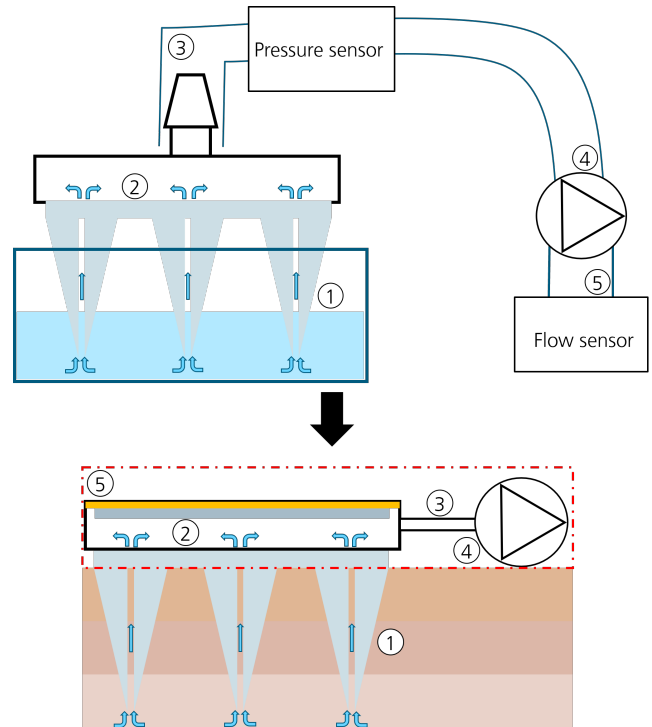


Figure 2: Schematic principle of (top) the extraction-only prototype used for pump characterization: (1) MN array submerged in DI-water reservoir, (2) MN reservoir chamber, (3)+(5) tubing to sensors, and (4) micro pump. Schematic of the patch prototype (bottom) integrating MNs in skin layers (1), reservoir chamber with chip-sized biosensor (2), rigid fluidic channel (3), and a micro pump (4). Dashed line: outer patch dimensions (5).

water was demonstrated to verify system functionality, with volumetric flow measured by a Sensirion SLF3C-1300F flow sensor (5 ms sampling interval).

In a second measurement setup, the MN array and its reservoir are submerged in DI-water inside a pressurized bottle to characterize the hydraulic performance under increasing load. We define p_{load} as the pressure applied to the bottle's headspace surrounding the MNs' fluid source (relative to ambient). Increasing back-pressure ($p_{\text{load}} < 0$) withholds fluid from the pump's suction, analogous to increasing tissue resistance. Pumps P462 and P499 are operated at 20, 50, 100, and 200 Hz for sinusoidal and SRS signals while p_{load} is held at a constant value of 0, -5, -10, -20, -40, -100, -200, and -300 mbar, respectively, using a pressure controller (Mensor CPC4000). For P499, an additional measurement at $p_{\text{load}} = -400$ mbar was performed to identify its stall point. This range was selected to characterize the pressure–flow behavior of the pump–MN assembly and to find the pumps' limits. The volumetric flow produced by the pump is sampled in 5 ms intervals.

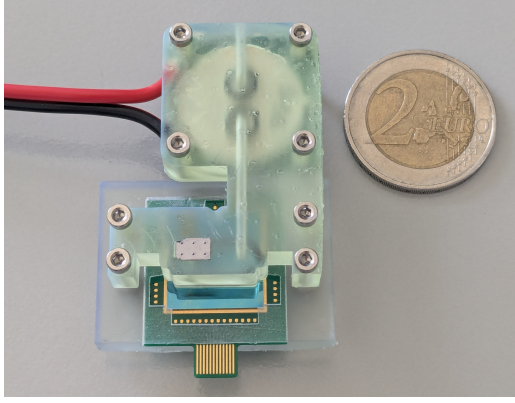


Figure 3: Assembled combined patch prototype ($5.7 \times 3.7 \times 1.2$ cm) integrating the MN array, fluid reservoir, and μ P within a 3D-printed fluidic housing, with a cavity for chip-sized biosensor insertion.

RESULTS

Peak negative pressure up to -38 kPa and hydraulic flow rates up to 8 mL/min under water-based laboratory conditions were achieved with SRS actuation at $p_{\text{load}} = 0$ mbar (see Figure 4). These water-based values represent an upper bound on the achievable hydraulic performance of the pump–microneedle assembly rather than the physiologically relevant ISF extraction rate, which will instead be governed by tissue resistance and ISF replenishment. P499 exhibited the highest vacuum capability and fastest pressure build-up. While the generated vacuum is lower than in some externally driven systems (see Discussion), the suction source is integrated directly into the wearable device and is applied continuously through the hollow MNs (Table 1).

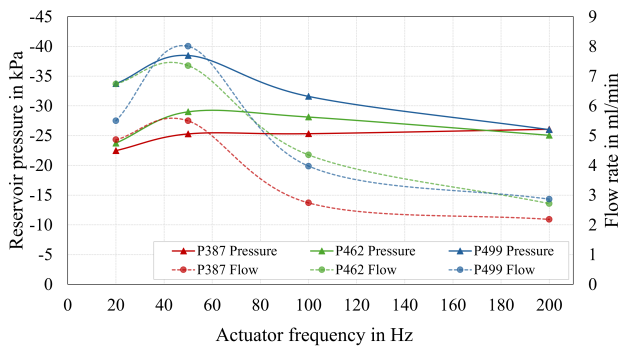


Figure 4: Measured vacuum pressure build-up and flow rate (deionized water) for pump samples P387, P462, and P499 with SRS actuation at 20 Hz, 50 Hz, 100 Hz, and 200 Hz, and $p_{\text{load}} = 0$ mbar (unrestricted fluid source).

Comparing actuation waveforms at the optimal frequency (50 Hz, Figure 5), SRS actuation delivered higher flow than sine actuation across the tested range of p_{load} for both pump samples. At

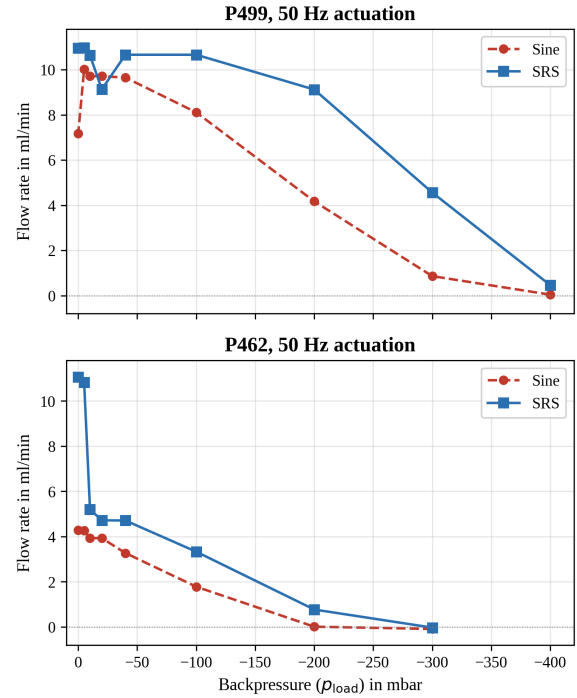


Figure 5: Flow rate vs. source-side load pressure p_{load} at the optimal actuation frequency (50 Hz) for sine and SRS actuation, shown for pump samples P499 and P462.

$p_{\text{load}} = 0$ mbar, SRS flow exceeded sine flow by 53% for P499 (10.95 vs. 7.17 mL/min) and by a factor of 2.6 for P462 (11.07 vs. 4.28 mL/min). For P462, flow under SRS actuation dropped sharply between $p_{\text{load}} = -5$ and -10 mbar (10.83 to 5.20 mL/min); this steep transition was not observed for P499 and warrants further investigation before being interpreted as a general feature of SRS actuation.

Table 1: Comparison of MN-based ISF extraction systems with negative pressure assistance.

System	Vacuum source	Pressure	Suction mode
Jiang et al. [2]	External pump	-44 kPa	After MN removal
Hung et al. [4]	External vacuum	-64 kPa	After MN removal
Xie et al. [3]	External vacuum	≤ -20 kPa	Through hollow MNs; damage observed
This work	Integrated piezoelectric micro pump	-38 kPa	Continuous suction through hollow MNs

DISCUSSION

While SRS actuation achieved higher time-averaged flow than sine actuation across the tested

range of p_{load} (Figure 5), the hydraulic advantage arises from steep signal components (rectangular parts) in the SRS signal. This actuation therefore offers greater hydraulic performance, but a future biosensor may impose its own requirements on temporal flow stability; waveform selection must ultimately consider both pumping efficiency and downstream sensor requirements, once a specific sensing chemistry has been selected.

This carries a broader design implication: the pump's demonstrated capacity, up to -38 kPa and 11 mL/min, is expected to substantially exceed the ISF supply from tissue, which will instead be governed by capillary filtration and interstitial resistance – consistent with Xie et al., who report extraction rates of only ~ 0.037 μ L/min per needle, orders of magnitude below the flow shown here. The lower peak pressure relative to Jiang et al. and Hung et al. (Table 1) should therefore not be read as a shortfall: both rely on a single, short-duration extraction after MN removal and require aggressive vacuum for that reason, whereas continuous MN-in-place operation is not time-constrained. Higher pressures also carry documented risk – Xie et al. observed tissue/gel damage within their tested 0–20 kPa range, well below the capacity demonstrated here. If tissue transport is the rate-limiting step, the pump's primary role in the final patch may be to establish and maintain sufficient negative pressure at very low, tissue-limited flow rather than sustain high volumetric flow – shifting design priorities toward achievable pressure level, near-zero-flow holding capability, low leakage, low power consumption, and low device height, with this headroom serving as operational margin rather than a target; the eventual operating point is expected to be tuned considerably lower.

A key limitation of the present study is that the integrated system has so far only been validated using deionized water and controlled hydraulic p_{load} . No in-vivo or ex-vivo ISF extraction experiments were performed. Consequently, the demonstrated pressure and flow values cannot be directly translated into an ISF extraction rate. Future experiments will evaluate the system in tissue and investigate the relationship between applied negative pneumatic pressure, tissue resistance, ISF replenishment, and extracted sample volume. In parallel, the integration of a suitable biosensor will be required to assess the complete sampling-and-sensing chain.

The patch prototype's height of 1.2 cm is currently

dominated by the micro pump and its driver electronics and is the primary target for further miniaturization toward a low-profile wearable form factor.

CONCLUSION

This work demonstrated a miniaturized vacuum-assisted ISF sampling concept based on hollow silicon microneedles and an integrated piezoelectric micro diaphragm pump. The pump generated negative gauge pressures of up to -38 kPa and hydraulic flow rates of up to 11 mL/min under controlled load conditions, with SRS actuation providing higher time-averaged flow than sinusoidal excitation. The demonstrated pressure–flow characteristics indicate that the micropump provides substantial hydraulic capacity compared with the expected ISF supply from tissue, suggesting that future extraction rates will primarily be governed by tissue transport rather than pump capacity. The results demonstrate the feasibility of integrating continuous negative-pressure generation directly into a microneedle-based wearable platform. Future work will focus on reducing the patch height and validating ISF extraction in ex-vivo and in-vivo tissue, followed by integration of a suitable biosensor.

ACKNOWLEDGEMENTS

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MICROFLUIDIC INTEROPERABILITY STANDARDS FOR RAPID COLLABORATION: TOWARDS AN ISO 22916 COMMUNITY

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The increasing complexity and diversity of microfluidic technologies have amplified the need for standards that support interoperability across devices and laboratories [1]. ISO 22916 provides guidance for dimensions, connections, and initial device classification to facilitate the interconnection of modular microfluidic components [2]. Adoption of such standards may reduce development effort, improve accessibility, and accelerate innovation through interoperable system architectures.

Organ-on-chip (OoC) technologies provide a compelling test case for implementing and evaluating microfluidic standards. These systems integrate diverse components, including tissue models, fluid actuation modules, reservoirs, and sensing elements [3]. This complexity necessitates robust interfacing strategies and integrated device ecosystems. To address these challenges, the Translational Organ-on-chip Platform (TOP) leverages ISO 22916 to establish an open, interoperable ecosystem for OoC research.

As a practical implementation of these principles, we presented STARTER, a stand-alone, modular platform that demonstrates how TOP-enabled standardization can support flexible OoC experimentation (Fig. 1) [4]. Built around ISO 22916-compliant footprints and interfaces, STARTER integrates pumps, reservoirs, sensors, and diverse OoC models within a compact and reconfigurable architecture (Fig. 1a). Our testing shows that ISO 22916 allows enables material-agnostic interfacing. Furthermore, STARTER system architecture allows custom fluidic circuit configurations without significant redesign, supporting both established and emerging technologies without requiring application-specific redesign. Through successful integration of multiple OoC models and in-line sensing capabilities (Fig. 1b-e), STARTER demonstrates how standardized, interoperable components can lower technical barriers, enhance reproducibility, and facilitate rapid design iteration for microfluidic systems.

To demonstrate the capability of our ISO 22916-based approach to support advanced OoC applications, we developed a TOP hypoxia platform for the controlled induction, distribution, and quantification of oxygen tensions within MPS systems (Fig. 2). The platform integrates gas routing, liquid handling, and optical sensing within a TOP-compatible architecture (Fig. 2a). By decoupling gas exchange, sensing, and culture components into modular units, the system enables flexible hypoxia workflows without specialized atmospheric control equipment. Validation using in-line optical oxygen sensing and ratiometric imaging demonstrated predictable oxygen dynamics and reproducible control over physiologically relevant dissolved oxygen concentrations (Fig. 2b,c).

To support dissemination and implementation of standardized microfluidic approaches, we embrace an open-source philosophy through the development and sharing of design resources, software tools, and implementation guidelines. In addition to accessible hardware designs, we co-developed computational tools for modular microfluidic design, including automated routing block generation for STARTER-compatible configurations (Fig. 3) [5]. These tools reduce the time and expertise required to develop customized fluidic architectures while ensuring compliance with ISO 22916. By making these resources publicly available, researchers can adopt, adapt, and extend existing solutions, enhancing reproducibility, accelerating innovation, and fostering collaboration within the OoC community.

We envision community building not merely as a complementary activity, but as an essential component for realizing the translational potential of modular and interoperable microphysiological systems. The success of standardized and open-source approaches depends on active participation from stakeholders who collectively contribute to, refine, and adopt shared technologies and practices. Beyond developing tools and platforms, TOP aims to cultivate a collaborative ecosystem for exchanging designs, knowledge, and expertise within the ISO 22916 design paradigm.

To facilitate this ecosystem, we are developing an online platform for disseminating and discovering open-source designs compatible with ISO 22916 and TOP principles. Accompanying documentation, datasets, protocols, and publications will support reproducible implementation and further development. Together with discussion forums, workshops, and educational activities, these efforts aim to establish a sustainable community that accelerates innovation and broadens access to OoC technologies.

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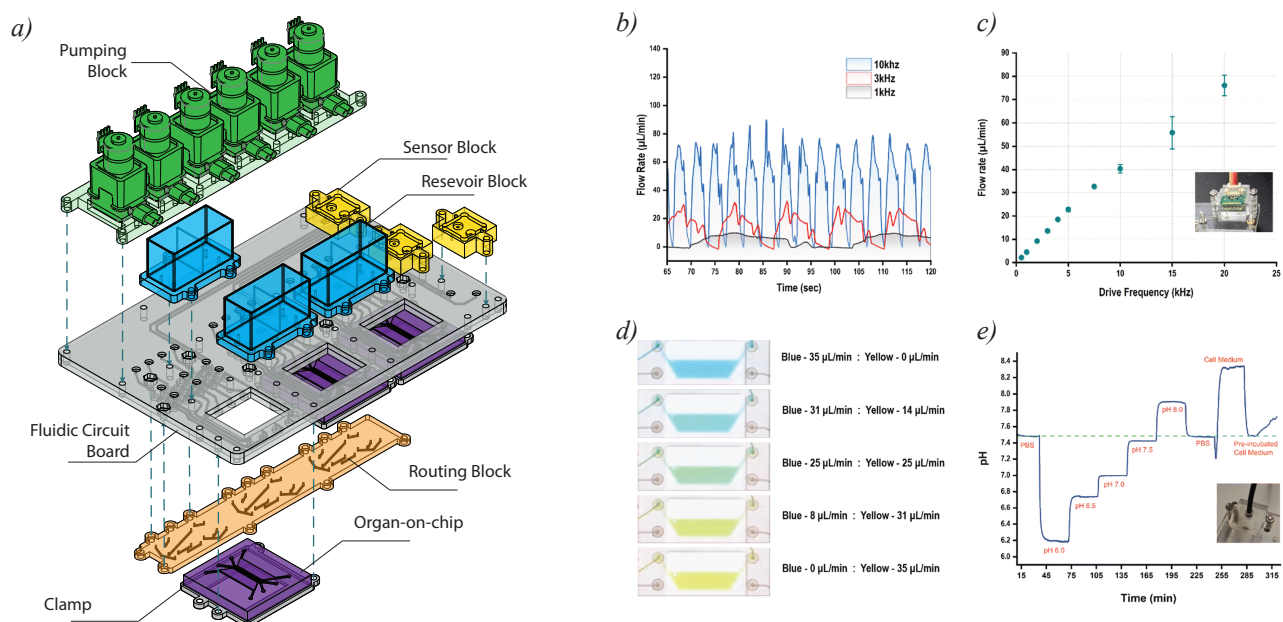


Figure 1. TOP STARTER kit. (a) Exploded view of TOP STARTER Kit indicated where a pumping block, reservoirs, sensors, organ-on-chips, and routing blocks interface with a fluidic circuit board (FCB) to form a complete microfluidic system. Examples of system readouts: (b, c) peristaltic flow rates reported using a commercial flow sensor (d) controlled fluid mixing and (e) In-line fiber-optic pH measurements

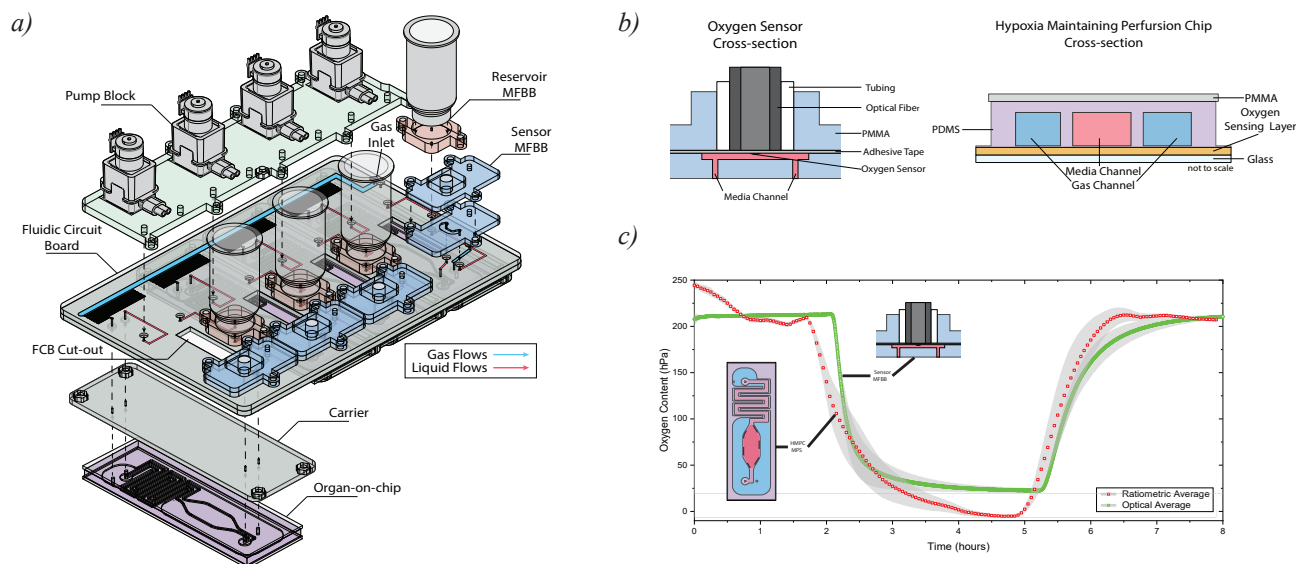


Figure 2. TOP-based hypoxia platform. (a) Exploded view of a hypoxia platform FCB and module. (b) Cross-sectional images of the fiber optic and ratiometric oxygen method integrations. (c) Oxygen measurement data from simultaneous averaged ratiometric (red, $n = 4$) and optical measurements (green, $n = 3$)

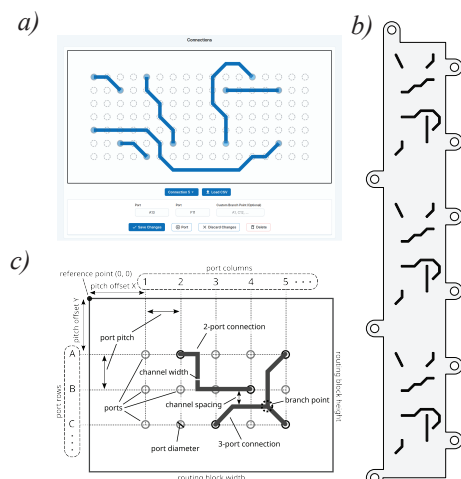


Figure 3. Open-source tool for STARTER routing block design. (a) Example of the user interface for point-to-point connections (b) a routing block for STARTER Kit (c) online tool uses user-defined inputs

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A COMPACT, AUTOMATED DUAL-MODE CHROMATOGRAPHY PLATFORM FOR RAPID EXTRACELLULAR VESICLE ENRICHMENT

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ABSTRACT

The purification of extracellular vesicles (EVs) remains a bottleneck in analytical and preparative workflows. The purification of extracellular vesicles (EVs) remains a bottleneck in analytical and preparative workflows. Dual-mode chromatography (DMC) is used to deplete the lipoproteins and soluble proteins that overlap EVs in size and are therefore not resolved by size-exclusion chromatography alone. For this purpose, a size-exclusion bed is layered over a cation-exchange bed in a single column; however, this requires an additional packing step, the outcome of which depends on the individual operator when performed manually. We present two instruments that automate packing and processing. We present two instruments that automate both. **ColumnPack** packs six 12 mL columns in parallel against fill-level sensors in 45 minutes. **ColumnPro** processes up to ten columns simultaneously in approximately 10 minutes per run, with dispensed volumes varying by 1.3% across the instrument. Protease activity in EV-enriched plasma fractions varied by less than 10% between five columns processed simultaneously, and this reproducibility was sustained over three consecutive runs of the same regenerated columns.

KEYWORDS

Extracellular vesicles (EV), dual-mode chromatography, laboratory automation, parallel column processing, automated column packing

1 INTRODUCTION

Extracellular vesicles (EVs) are lipid bilayer-delimited particles released by essentially all cell types. Lacking a functional nucleus and unable to replicate, they act as carriers of complex molecular cargo such as proteins, lipids and nucleic acids in intercellular communication [1]. Their diagnostic and therapeutic potential in oncology, neurodegenerative disease and immunotherapy is now well established [2].

However, the purification and separation of EVs remain a critical, time-consuming bottleneck in both analytical and preparative workflows. Our work combines size-exclusion chromatography (SEC) and charge separation (cation exchange) within a single column to remove impurities and enrich EVs from

plasma.

While alternative techniques such as affinity chromatography offer high specificity for targeted EV subpopulations, they frequently require disruptive elution conditions that can compromise vesicle integrity and bioactivity.[3]

Instrumentation for column-based EV enrichment falls into two groups. Preparative FPLC systems such as the ÄKTA family (Cytiva) provide commanded flow and inline detection, but they are costly, require trained operators, and address one or two columns at a time, so throughput scales only through further capital purchase. The field's default is gravity-driven column chromatography, where flow is passive: the rate follows from bed permeability and hydrostatic head rather than from a set point, it drifts as the bed compacts, and a bubble entering the bed can stop the run entirely. Between these sit automated fraction collectors, which handle equilibration, collection, washing and regeneration around a pre-packed, gravity-fed column. The Automatic Fraction Collector (Izon Science, Christchurch, New Zealand) serves a single column per unit, so parallel operation means one instrument per sample [4]; the Ascent (Everest Biolabs) runs up to eight columns and the plate-based Summit up to 48 samples [5]. The plate format has also been described in the literature [6]. Pre-packed dual-mode columns are commercially available, the Apex MM (Everest Biolabs) combining a multi-mode resin beneath the SEC bed to deplete lipoproteins. What no instrument does is pack the resin bed or actively meter the flow through it. For a single-resin bed this matters little. For two resins of differing permeability in series, where residence time in the cation-exchange layer governs lipoprotein capture, both are prerequisites. However, manually packing stacked beds is highly time-consuming and results in inconsistent bed heights and compression, which severely compromises separation resolution and batch-to-batch reproducibility.

Developed with clinical partners, the system provides reproducible, automated methods for packing and processing these dual-mode columns. Two distinct devices were engineered and evaluated: **ColumnPack** (Fig. 1), dedicated to automatically packing the DMC

columns, and **ColumnPro** (Fig. 2), designed to execute the EV purification.

2 MATERIALS & METHODS

2.1 Dual-mode Column

Each column combines two resins in a single housing: 2 mL of Fractogel EMD SO_3^- cation exchanger (particle size 40-90 μm) at the bottom and 10 mL of Sepharose CL-4B (particle size: 60-200 μm) layered above it, both at relaxed-state volumes, yielding a 12 mL bed. Following Van Deun et al. [7], the upper size-exclusion layer retains soluble proteins and HDL, while the lower cation-exchange layer captures the positively charged, ApoB100-bearing LDL and VLDL that overlap EVs in size and therefore pass the SEC layer unresolved. Negatively charged EVs elute unretained, and both mechanisms act on a single sample loading. Resolution consequently depends on a sharp, flat and reproducible boundary between the two layers, the step that manual layering leaves operator-dependent and that **ColumnPack** automates.

2.2 Column Preparation (ColumnPack)

Automating column packing increases both throughput and the repeatability of the subsequent purification. Because separation resolution depends on a tightly and uniformly packed bed, delivering the resin at a defined pumped flow rate rather than letting it settle under gravity produces a denser and more consistent bed than manual layering. **ColumnPack** packs six columns in parallel. Resin is pumped from the Sepharose or Fractogel reservoir through a distribution valve, divided by a passive splitter into six branches, and delivered to each column by its own peristaltic pump, so the fill rate is set independently for every column. Optical fill-level sensors monitor the resin boundaries during bed formation. The Fractogel lower bed is dispensed first until the lower fill sensor is triggered. To prevent cross-contamination between resin phases, the shared valve and splitter manifold are automatically flushed with storage buffer (20 % ethanol) before Sepharose introduction. Sepharose CL-4B is then loaded until it reaches the upper-level sensor. A batch of six dual-layer columns is packed in 45 minutes without user intervention.

2.3 Column Processing (ColumnPro)

Automatic column processing is performed with the **ColumnPro** instrument, which supports up to 10 simultaneous column channels. The fluidic architecture is deliberately minimal:

- **Pumping:** Low-pulsation peristaltic pumps (Boxer GmbH, Ottobereun, Germany; flow rate up to 300 $\mu\text{L/s}$) per channel.

- **Path switching:** A distribution valve combined with solenoid valves selects between different layouts: buffer to column, sample to column, buffer/sample to waste, and buffer to sample. Because each channel keeps its own dedicated sample flow path through the manifold, there is no shared sample volume between channels and therefore no route for cross-contamination.
- **Sensing:** The system uses in-line air sensors (capacity and optical methods available) to check for bubbles, originating from sample connection, valve switching or simply from the buffer reservoirs. Loading stops before air enters the column, preventing irreversible damage to the packed resin beds.
- **Metering:** Flow delivery is governed by individual volume-per-revolution calibration factors per pump rather than timed intervals, ensuring accurate volumetric dosing.
- **Flow-path matching:** Silicone tubing with different inner diameters is selected to meet different requirements, such as fast buffer feeding, cost-efficient replaceability (consumable), and pinch valve compatibility.
- **Fraction collection:** A tray on a linear axis collects up to four fractions per run. Four is sufficient because the EV-containing eluate of a DMC column occupies a narrow, predictable window, so fraction boundaries can be set volumetrically rather than by inline detection.
- **Architecture scalability:** The engineering design of the instrument (control electronics, cable connections) allows flexible scaling of the number of columns for an intended purpose and cost-effectiveness.

Both instruments are enclosed in wipe-down housings suitable for diagnostic laboratory use.

2.4 Control, Visualization and Traceability

Automation runs on custom embedded software driving all actuators and sensors. A graphical user interface (GUI) was developed to enable user-friendly operation of the device and to configure various processing parameters. Every run logs pump and valve states, pumped volumes, and potential errors, giving each processed column an individual record.

2.5 Functional Validation of Column Processing and Column Reuse

Evaluations were performed on a **ColumnPro** instrument featuring a total of 10 columns.

First, to determine volumetric accuracy, we programmed the device to **dispense** 2 mL of PBS and weighed the collected eluate three times at each of five positions.

Activity of ADAM17, neprilysin and renin was

measured in the EV-enriched fractions using a fluorescent FRET peptide cleavage assay. Five columns were processed simultaneously; after each run they were washed and regenerated using the automated protocol, and reused twice, giving three runs per column. The linear slope of increasing fluorescence measured over 60 minutes was used as a proxy for protease activity.

3 RESULTS

3.1 Instrumentation

Working prototypes of both **ColumnPack** and **ColumnPro** were successfully developed and validated.

The **ColumnPack** packs six columns in parallel, each served by a dedicated resin line and a double fill-level sensor, completely automating the packing process. The instrument is illustrated in Fig. 1.



Figure 1: *ColumnPack* instrument: automated packing of DMC columns

Two different versions of the **ColumnPro** were designed, assembled, and tested. The fluidic and biological performance is detailed for a 10-column version (Fig. 2, right), having an industrial prototype design, focusing on throughput. Furthermore, a three-column version (Fig. 2, left) was also designed, offering sophisticated design language and features, and cost-effectiveness through fewer columns.



Figure 2: *ColumnPro* instrument - automated platform for Dual-Mode Chromatography (DMC), Left: three-column variant; Right: ten-channel variant

The variants differ in how the tray couples to the linear axis: on the three-column version the coupling is magnetic, so the complete tray, rather than an insert, lifts off without tools and leaves a flat instrument

surface with no tray fixtures to clean around, consistent with the diagnostic-use requirement. Actively pumped processing yields a run time of approximately 10 minutes for a 12 mL column, excluding the washing procedure.

The operational workflow is shown in Fig. 3.

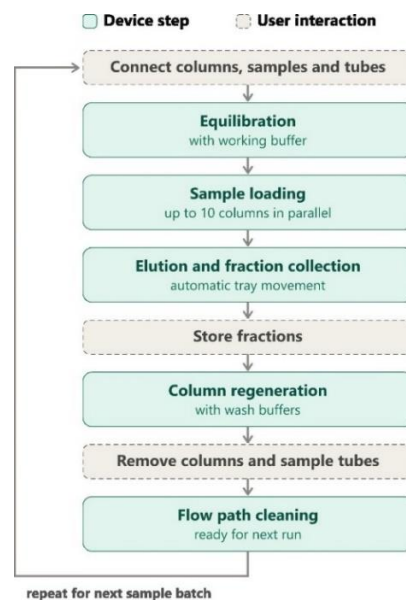


Figure 3: *ColumnPro* instrument workflow visualization

Operator involvement is limited to three points: connecting columns, sample tubes and tubing at the start, retrieving the fraction tray, and disconnecting at the end. Equilibration, sample loading, elution and fraction collection, column regeneration and flow-path cleaning proceed unattended. Because these three interaction points are independent of the number of channels in use, hands-on time per sample falls as the batch size increases, which is where parallel processing differs from running the same protocol on several single-column instruments.

The GUI (Fig. 4) presents a real-time synoptic view of the fluidic system: active column paths, buffer feed, valve positions and pump status, are displayed simultaneously for all ten channels, so an operator can trace the protocol/processing steps at a glance.

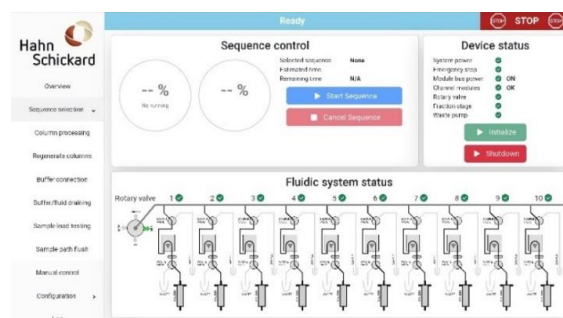


Figure 4: *Graphical user interface of the ColumnPro* device, highlighting real-time display of the column status

3.2 Fluidic Performance

The system demonstrates a measured repeatability (within-pump precision) of 0.9% and a pump-to-pump variation of 1%. The average dispensed volume was 2.013 mL with a global CV of 1.3%.

3.3 Protease Activity of Enriched EVs

Protease activity in the EV-enriched fractions was highly reproducible across the five columns processed simultaneously, with coefficients of variation below 10% for all three enzymes. The same column-to-column consistency was observed in the second and third runs of the same columns after automated washing and regeneration (Fig. 5), indicating that the packed beds tolerate the regeneration protocol and can be reused without loss of reproducibility. Absolute activity levels varied between runs within the range expected from the observed column-to-column spread.

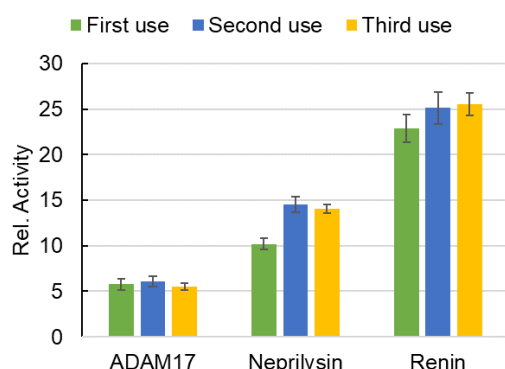


Figure 5: Relative activity of ADAM17, Neprilysin and Renin in EV-enriched fractions from five DMC columns processed simultaneously on the ColumnPro, across three consecutive runs with automated washing and regeneration between runs. Activity is shown in arbitrary units.

4 CONCLUSION

Automating both halves of the dual-mode chromatography workflow, packing as well as processing, is what makes the resulting biological data interpretable: when columns are packed to sensor-defined bed heights at a controlled flow rate, giving reproducibly dense beds, and then processed simultaneously through matched, individually metered flow paths, differences between samples can be attributed to the samples rather than to the columns or to the order in which they were run. The fluidic layer supports this directly, with dispensed volumes varying by 1.3% across the instrument.

In a functional test, the activities of ADAM17, Neprilysin, and Renin in EV-enriched plasma fractions varied by less than 10% across five columns processed simultaneously, and this column-to-column consistency was maintained across three consecutive runs on the same regenerated columns.

Channel count is limited by manifold size rather than by the control architecture, so scaling beyond the present ten-column capacity is feasible. Ongoing work aims to broaden the biological readout beyond enzymatic activity, to add particle- and marker-level characterization of the enriched fractions, and to demonstrate purification performance with other column types.

ACKNOWLEDGEMENTS

Backgrounds in Figs. 1 and 2 were removed by automated masking; no other image content was altered. This work was supported by the BMFTR project KI-VesD-2 (Grant No. 03LW0339) and BMWE project EVEX (Grant No. 01IF23431N).

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ACOUSTOFLUIDIC FOCUSING AND CONFINEMENT OF A FULLY ACTIVE NEMATODE

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ABSTRACT

We demonstrate the acoustofluidic focusing and confinement of an untreated, fully active nematode in a standing pressure wave using the acoustic radiation force. The nematode used is the microworm *Panagrellus redivivus*, an established free-living comparative taxon to *Caenorhabditis elegans* with similar anatomy and physiology. In contrast to conventional thickness-mode actuation, the design exploits a low-order lateral Lamb-wave mode of the piezoelectric plate transducer, enabling strong acoustic effects at sub-megahertz frequencies on the millimeter scale. The device is numerically optimized, and experiments demonstrate rapid focusing and stable confinement. The nematode remained fully active and continued normal swimming behavior after several repetitions.

KEYWORDS

Acoustofluidics, lateral mode, Lamb wave, nematode, acoustic focusing, confinement, sub-megahertz.

INTRODUCTION

The growing demand for alternatives to vertebrate animal testing is reflected in the increasing number of publications on alternative biological model systems. Figure 1 shows this trend for searches on organoids, nematodes, and zebrafish embryos and larvae.

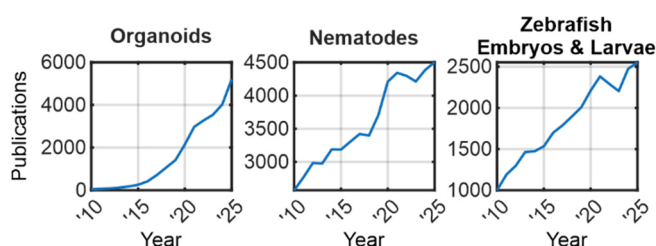


Figure 1: Number of publications per year for searches on organoids, nematodes, and zebrafish embryos or larvae in Scopus (Elsevier). Accessed on April 23, 2026.

Acoustofluidic methods can provide contact-free alternatives to conventional, typically contact-based microfluidic techniques for handling small animals such as *Caenorhabditis elegans* (*C. elegans*) in microfluidic devices [1,2]. However, acoustic

manipulation of actively moving specimens is challenging because they can escape the acoustic field. Consequently, many acoustofluidic methods require sedation or paralysis of the animals, and acoustofluidic manipulation of untreated organisms has been reported in only a limited number of studies [3-6].

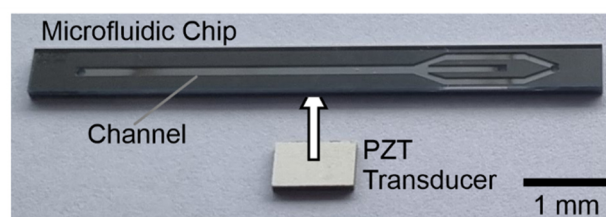


Figure 2: Core device concept comprising a microfluidic chip acoustically actuated from below by a PZT plate transducer.

In this work, we exploit a low-order lateral Lamb-wave mode of a piezoelectric plate transducer to focus and confine an active, swimming nematode in a 1.3 mm wide microfluidic channel using the acoustic radiation force [7]. In contrast to conventional thickness-mode operation, which requires thicker plates to reach the required sub-megahertz frequencies, resulting in bulkier devices, the lateral mode naturally operates at lower frequencies, keeping the device footprint small.

Using the same lateral transducer mode, we previously demonstrated high-performance focusing and separation of microparticles and cells in a similar device [8], as well as trapping of microparticles and cells [9] and trapping and reorientation of nematodes [10] using a different microfluidic design.

MATERIALS AND METHODS

The core elements of the device are a microfluidic chip and a piezoelectric plate transducer (6 mm × 9 mm × 1 mm, PZ26, Meggitt A/S, now CTS Denmark) attached to the underside for acoustic actuation (Fig. 2). The geometry of the microfluidic chip is numerically optimized for acoustic focusing, i.e., generating a high-amplitude horizontal standing pressure half wave inside the channel.

The microfluidic chip, fabricated at Silicon Austria Labs, is 6 mm wide and 65 mm long, and consists of a dry-etched 725 μm silicon bottom layer containing the 200 μm deep fluidic structures and an

anodically bonded 700 μm glass cover layer. In the experiment, the components are mounted into a custom-made chip holder, using a thin layer of glycerol for acoustic coupling between the transducer and the microfluidic chip. The chip holder allows the chip to be mounted directly after dicing, with fluidic connections established by contact pressure. Details on the fabrication, mounting, and design concept are provided in [8,9].

As the desired acoustic channel mode is antisymmetric, we employ the antisymmetric second-order lateral extensional width mode of the piezoelectric plate. To excite this mode, a three-electrode configuration with a split bottom electrode is used. Differential electrical signals, i.e., two complementary sinusoidal signals of equal frequency and amplitude with a 180° phase shift, are applied to the two bottom electrodes while the top electrode facing the microfluidic chip is left electrically floating. The signals are generated by a function generator, amplified using modified evaluation boards (ADA4870ARR-EBZ, Analog Devices), and monitored with an oscilloscope. The maximum output voltage of each amplifier is approximately $40 V_{pp}$, resulting in a maximum differential voltage of approximately $75 V_{pp}$ between the two bottom electrodes. All actuation voltages given in the following refer to the differential voltage between the two bottom electrodes.

Panagrellus redivivus (*P. redivivus*) is a free-living comparative taxon to *C. elegans* and has been used as a model system in many diverse fields of biology [11]. *P. redivivus* is commercially used as live feed in aquaculture and commonly referred to as the microworm.

RESULTS AND DISCUSSION

Numerical Optimization

The cross section of the device was optimized using numerical simulations for particle focusing in the microfluidic channel, following the approach used for earlier devices with a shallower, 100 μm deep channel [12]. Because of the larger specimen in the current work, we chose a 200 μm deep channel, which resulted in a 1.310 mm wide channel. The resulting operating frequency of approximately 530 kHz is essentially determined by the frequency of the lateral transducer mode, which in turn is a function of the transducer width. As observed for the prior device with the shallower channel, we can identify the second-order lateral mode of the transducer, which is approximately a standing S_0 Lamb wave, together with a flexural mode of the chip, a flexural channel-roof mode, and inside the channel a standing pressure half wave (Fig. 3).

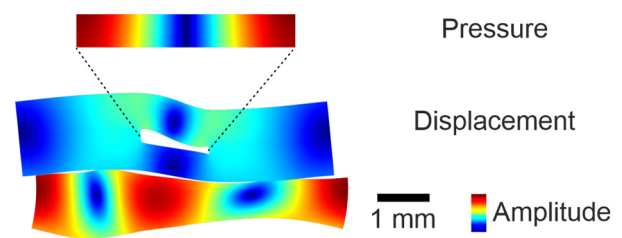


Figure 3: Resulting geometry and vibration pattern of the optimized device cross section. Top: pressure amplitude inside the channel; below: displacement in the solids. Blue color indicates pressure and vibration nodes, i.e., regions with low amplitude; antinodes appear red.

Confinement of *P. redivivus*

Figure 4 shows repeated focusing and confinement of an untreated, fully active, and approximately 430 μm long nematode.

When the acoustic field is off, the nematode is allowed to move around in all directions, whereas with the acoustic field active, the movement is restricted to the channel centerline where the nodal pressure plane of the standing acoustic wave is located. Although the nematode attempts to escape, it remains confined to the channel center.

During the experiment, the nematode was focused six times, with the longest continuous confinement duration lasting approximately 25 seconds. Altogether, the acoustic field was inactive for approximately 60 seconds and active for 40 seconds. The combination of all periods in Figure 5 clearly shows the difference between the unconfined and confined states.

In the experiment, the actuation frequency was 542–543 kHz and therefore approximately two percent higher than predicted by the simulation. The differential actuation voltage was $37.5 V_{pp}$. External flow was applied to the channel occasionally to keep the nematode within the field of view. The overlay images contain every tenth frame (intervals ≈ 200 ms). The final frame in the first sequence of Fig. 4, with the nematode already nearly focused, provides an impression of the specimen's appearance.

Concerning biocompatibility, no noticeable changes in the nematode's behavior were observed in the experiment presented here. The undulation frequency remained unchanged, and swimming behavior during the separate unconfined periods appeared similar. In additional experiments from the same series, larger nematodes of up to approximately 2 mm in length also tolerated actuation at $37.5 V_{pp}$. While small specimens generally tolerated elevated voltages of up to approximately $75 V_{pp}$, larger

specimens showed reduced activity after repeated ultrasonic exposure. A single confinement period, however, was usually tolerated. As the behavioral response seemed to occur upon transducer activation, we think that the change in activity was primarily caused by the acoustic field. Heat generation was low at 37.5 V_{pp} but became significant at elevated voltages.

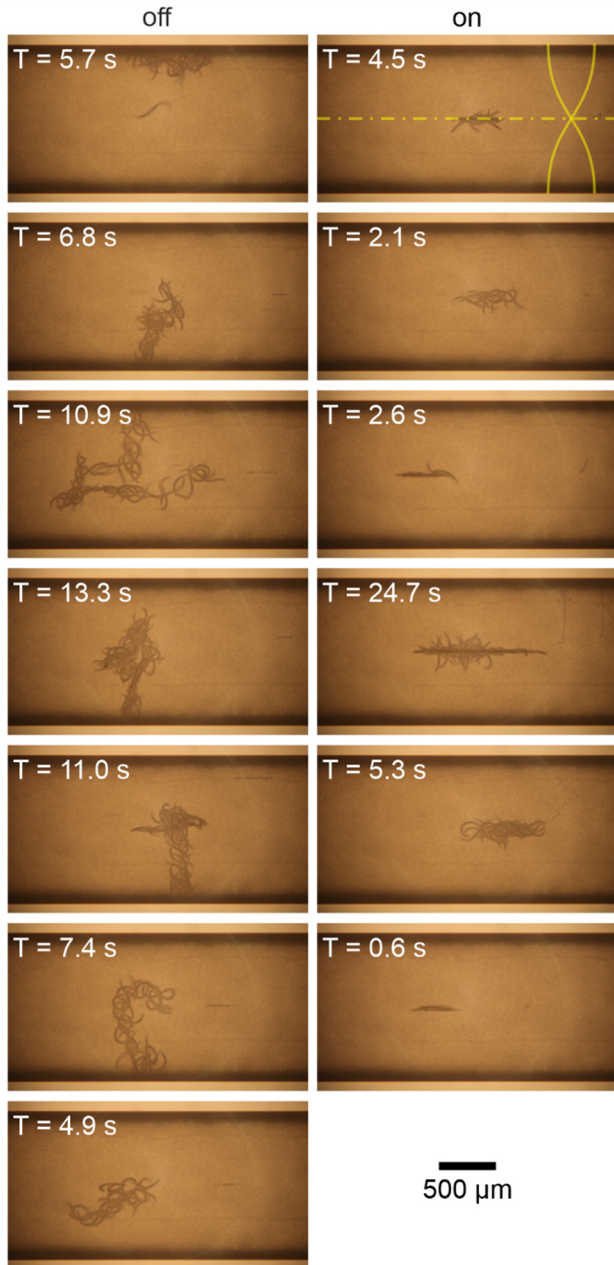


Figure 4: Repeated focusing and subsequent confinement of an untreated, fully active nematode at the center of a microfluidic channel using a standing acoustic wave across the channel; the yellow overlay indicates the nodal plane and the pressure-amplitude envelope across the channel width. Left column: ultrasound off, unconfined; right column: ultrasound on, acoustically confined.

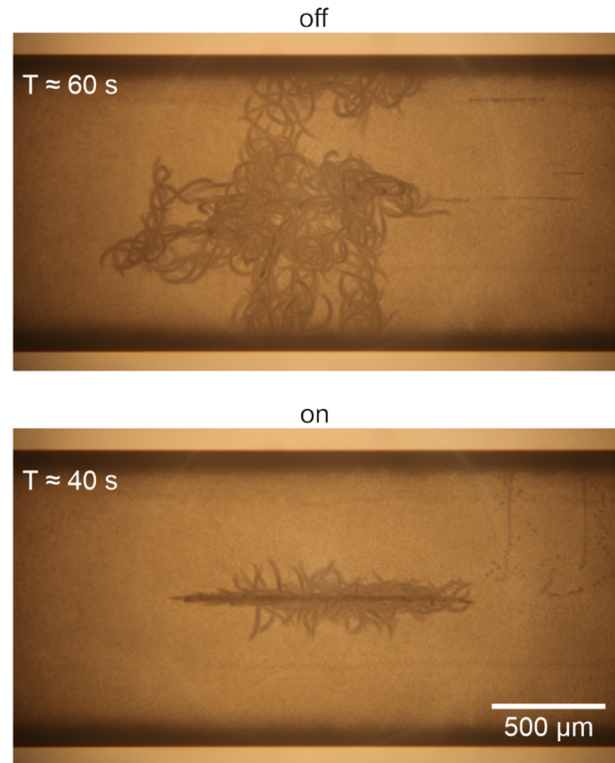


Figure 5: The combined periods for ultrasound off and on from Fig. 4 show a clear difference between the unconfined and confined states.

CONCLUSION

We demonstrated acoustofluidic focusing and confinement of an untreated, fully active nematode using a low-order lateral Lamb-wave mode of a piezoelectric plate transducer. As the specimen is not able to escape the acoustic pressure node, the experiment shows that this approach enables strong acoustic manipulation at sub-megahertz frequencies on the millimeter scale while maintaining compact device dimensions. No noticeable behavioral changes were observed at the actuation conditions used in the presented experiment, whereas, in experiments not shown here, repeated exposure at substantially higher voltages reduced the activity of larger specimens. These results support the suitability of lateral-mode acoustofluidics for contact-free manipulation of small active organisms.

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A POROUS PERFUSABLE POLYSACCHARIDE HYDROGEL TO STUDY TUMOR DEVELOPMENT IN A VASCULARIZED ENVIRONMENT

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Vascularized tumor microenvironments (TME) are central to cancer progression but remain challenging to reproduce in vitro with sufficient structural and functional fidelity [1]. PDMS-based microfluidic systems are easy to perfuse but provide limited biological complexity and rely on stiff materials and tedious processes. In contrast, advanced 3D models can better reproduce tissue organization but are difficult to perfuse, handle, and scale.

Here, we present a three-dimensional pullulan–dextran (PuD) hydrogel platform that integrates the spatial organization of tumor and endothelial cells within a soft and porous hydrogel (Fig. 1). The system combines microwells that promote tumor cell aggregation (A673, see Fig. 2) in a controlled manner [2], with a hollow channel supporting endothelial cell (HUVEC) growth and vessel-like structure development (Fig. 3) [3]. Sequential seeding allows the formation of distinct yet interacting cellular compartments. Endothelial cells organize into lumen-like structures within the channel and pores, while tumor cells form multicellular assemblies within microwells. Together, these features recreate key aspects of the TME in a simple and scalable format (Table 1).

To combine these cell types, HUVEC were grown in hydrogels for 3 days before A673 cells were added, and the coculture was continued for up to 11 days. In coculture, both cell types reorganized by forming multilayered arrangements and heterotypic cell–cell contacts within confined geometries. Indeed, in microwells, HUVEC orient toward the apical part of the microwells, while tumor cells form aggregates underneath, in contact with the hydrogel previously coated with collagen I. This comes with the formation of tumor clusters, insertion of isolated tumor cells inside the HUVEC layer, as well as perturbation of VE-cadherin-positive junctions at the edges of HUVEC sheets (Fig. 4). We also witnessed directional endothelial sprouting starting from the channel toward the microwells, which was not observed in HUVEC monoculture. This is reminiscent of early angiogenic processes [4].

Indeed, multiplex protein analysis revealed that coculture modulates angiogenic signaling and ECM remodeling pathways, with condition-dependent secretion of key mediators from both cell populations. This includes regulation of pro- and anti-angiogenic factors as well as matrix-associated enzymes, reflecting active biochemical crosstalk within the system (Fig. 5). The secretion of matrix metalloproteases in coculture underlines the high remodeling capacity of the system, a prerequisite for tumor

angiogenesis. This vascularized tumor model provides a controllable 3D platform to study tumor–endothelial interactions, ECM dynamics, and paracrine signaling in a microenvironment relevant to tumor progression.

We believe that flow must be integrated into vascularized tumor models, as many cellular processes are highly dynamic and depend on it [5]. Therefore, a custom-made hydrogel chamber was used to clamp the hydrogels and facilitate dynamic cell culture. Perfusion was used to seed cells directly into the channel and to monitor the shear stress experienced by HUVECs during their development.

These findings provide new insights into vascular–tumor crosstalk and demonstrate how biomaterial architecture can guide multicellular organization in engineered tissues. Overall, this platform bridges the gap between 3D models and microfluidic chips by combining biological relevance, mechanical robustness, and compatibility with long-term culture and perfusion. It offers a minimal yet functional vascularized TME suitable for studying tumor progression and angiogenesis under controlled conditions.

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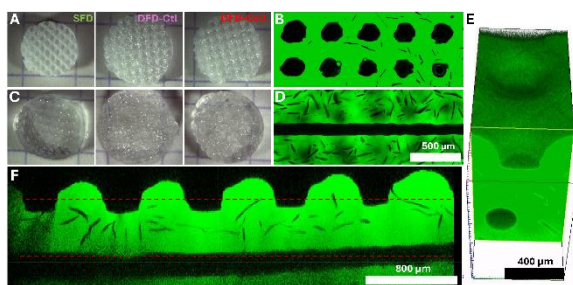


Figure 1. (A) Dry hydrogels after one or two freeze-drying steps, and collagen coating. (B) Top view of microwells. (C) Hydrated hydrogels become transparent. (D) View of the channel and pores. (E) 3D view of the channel and microwells. (F) Side view depicting 5 microwells.

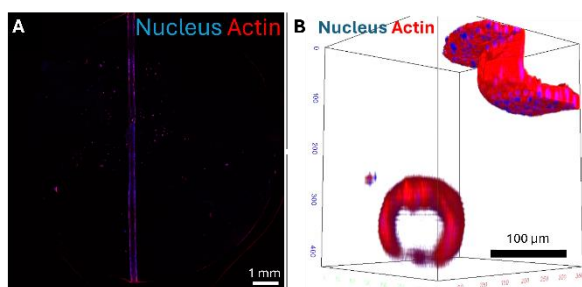


Figure 2. (A) A 10-mm-long channel coated with collagen and lined with HUVEC after 7 days of culture. (B) 3D rendering of one microwell and the underneath channel, both covered by HUVEC, after 7 days of culture. The lumen can be appreciated.

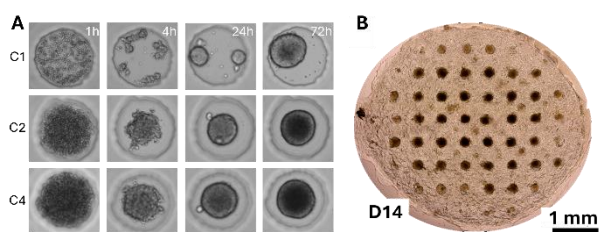


Figure 3. (A) The size of A673 spheroids after 3 days of culture can be controlled by the initial density used. The good contrast of agarose-formed microwells was used to automate image analysis and monitor spheroids evolution. (B) Spheroids could be formed in PuD hydrogels in 3 days with good throughput and spatial segregation. These spheroids can be kept for up to 2 weeks in culture.

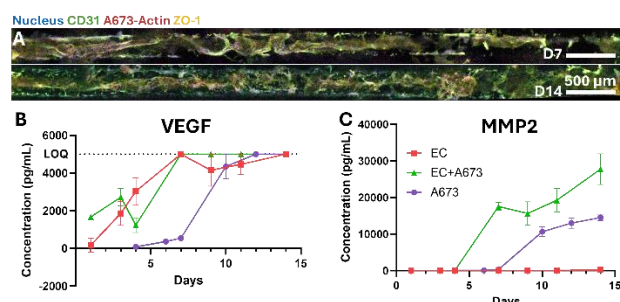


Figure 4. (A) View of an endothelialized channel in coculture. (B) VEGF levels in the supernatant show a pro-angiogenic environment in coculture. (C) Early MMP2 secretions in coculture underlines active remodeling.

Table 1. Main dimensions of the hydrogel platform ($n > 20$).

Well upper diam.	Well upper height	Well lower diam.	Well lower height	Channel -well distance	Channel diam.
$518 \pm 57 \mu\text{m}$	$108 \pm 17 \mu\text{m}$	$282 \pm 34 \mu\text{m}$	$180 \pm 26 \mu\text{m}$	$349 \pm 174 \mu\text{m}$	$149 \pm 8 \mu\text{m}$

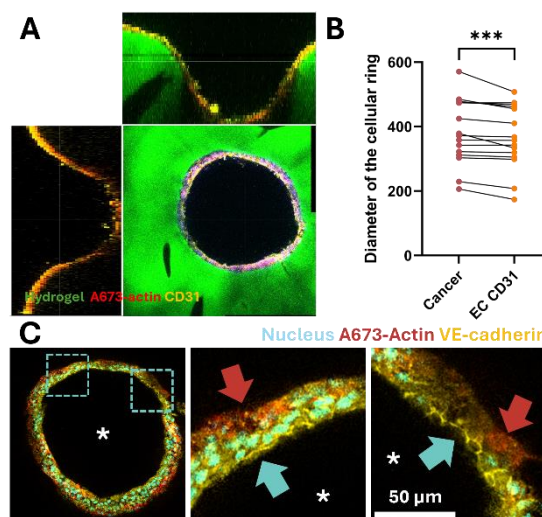


Figure 5. (A) Microwells are covered with A673 (in red) and HUVEC (in yellow) after 4 days of coculture. (B) EC tend to be at the inner core of microwells while A673 stand inbetween the hydrogel and EC. (C) High magnification show A673 (red arrows) and EC (blue arrows) lining in close contact. EC are forming VE-cadherin junctions together, but not with cancer cells. "*" shows well's apical side.

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A VERSATILE MICROPLATE TOOL FOR MONITORING BIO-MOLECULAR DYNAMICS: THE CASE OF MONITORING THERMO-RESPONSIVE HYDROGELS

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ABSTRACT

Microplate screening still relies largely on single-modality, label-based and end-point read-outs. We present a reusable microplate platform that combines two independent read-out principles on one flexible substrate: transient plane source (TPS) thermal sensing and electrochemical impedance spectroscopy (EIS). The same thermal elements can also be driven continuously instead of pulsed, turning them into a local heat source so that a sample can be actuated. Six applications realised on this single platform are presented, ranging from liquid identification to cell monitoring and polymer degradation, with the screening of thermo-responsive hydrogels presented as a detailed demonstrator.

KEYWORDS

Multi-parameter sensing, microplate, thermal effusivity, impedance spectroscopy, thermal actuation, thermo-responsive hydrogel

INTRODUCTION

High-throughput screening underpins drug discovery, toxicity testing and biopharmaceutical validation, and the microplate has become its standard format. The instrumentation that reads those plates, however, has evolved far less than the assays themselves. Most commercial plate readers remain optical, end-point in nature, and dependent on detection reagents or fluorescent labels, so each measurement returns a single parameter at a single moment in time and often consumes the sample.

A single sensing principle also mixes several sample properties into one signal. An impedance read-out of a cell culture responds to biomass, to membrane integrity and to the composition of the medium at the same time, and these contributions cannot be separated afterwards. Recovering them requires a second, physically different measurand acquired on the same sample at the same moment.

This work follows that idea through to a general-

purpose instrument. We combine a transient thermal read-out with electrochemical impedance spectroscopy on a single flexible circuit that seals the bottom of a microplate. Both are label-free, non-destructive and continuous. In addition, the thermal elements can be driven as a constant heat source rather than in short pulses, so the platform can also actuate the sample it is measuring. The purpose of this work is to present versatility: we describe the principles, present thermo-responsive hydrogel screening as a detailed demonstrator, and summarise five further applications realised on the same platform.

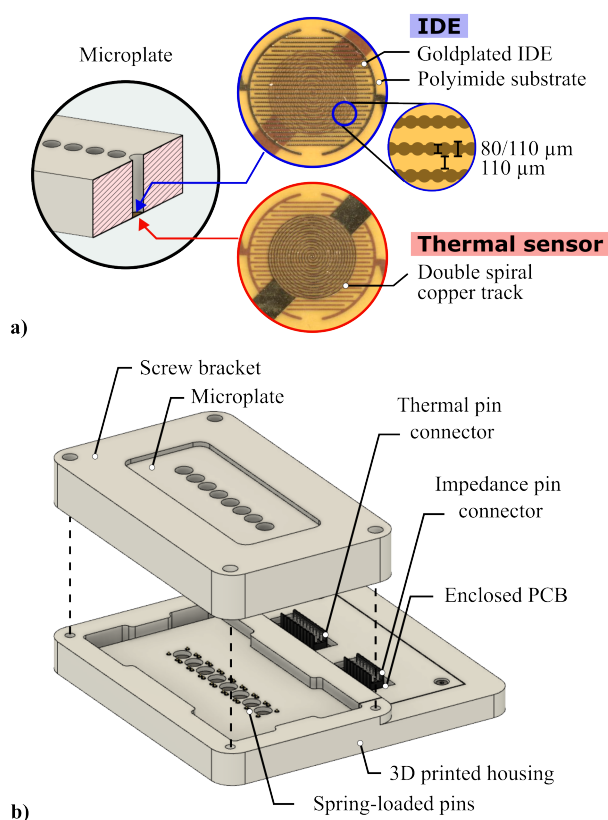


Figure 1: Microplate setup: a) Images of top and bottom of sensing structures. b) The microplate with equipped sensors is attached to an interface station.

SENSING AND ACTUATION PRINCIPLES

Thermal read-out and thermal actuation

A resistive thin-film track on the substrate serves simultaneously as heater and as resistance temperature detector [1, 2]. In sensing mode, a short current pulse raises its temperature and the rate of that rise depends on how quickly heat is carried away by the material above it, so the slope of the transient reflects the thermal effusivity of the sample. This has been used to follow, for example, biomass accumulation, sedimented cells, or the thickness of a polymer film [9, 10, 11].

Driving the same track continuously rather than in pulses changes its function. Instead of probing the sample it now heats it in a controlled way, so a temperature programme can be imposed on a well.

Impedance read-out

Interdigitated electrodes (IDEs) in direct contact with the liquid probe the sample with a small-amplitude AC voltage [3]. High frequencies report bulk solution properties, while low and intermediate frequencies are dominated by double-layer capacitance and interfacial transport. The resulting impedance magnitude forms an electrical fingerprint that has been used to follow, for example, ionic strength, membrane integrity, or changes in local ion mobility [10].

The two read-outs rely on different physical transport mechanisms: heat transport for the thermal channel and charge transport for the electrical one. Because of that independence, properties that are mixed together in one channel can often be separated with the help of the other.

Platform integration

All sensing structures are patterned on a single flexible polyimide strip (Fig. 1). Gold-plated copper IDEs sit on the sample-facing side; on the reverse side, isolated from the liquid, a concentric double-spiral copper track acts as the thermal element. The strip is bonded with a laser-cut acrylic adhesive layer to a CNC-machined, bottomless polyoxymethylene plate, sealing each well from beneath.

A screw-bracket clamps the assembly onto a 3D-printed base station, where spring-loaded pogo pins contact four pads per well without any manual plugging. Impedance sweeps, thermal drive and channel multiplexing are synchronised from custom Python control software.

CASE STUDY: THERMO-RESPONSIVE HYDROGELS

Hydrogels are crosslinked polymer networks with a high water content that are widely used in biomedical applications [4]. Thermo-responsive formulations such as poly(N-isopropylacrylamide) (PNIPAM) are liquid at ambient temperature and collapse into a gel above a lower critical solution temperature, near 32 °C in water [5]. That behaviour is what makes them attractive as injectable carriers, since they can be handled as a liquid and gel in place at body temperature. Knowing where the transition occurs, and how it shifts with formulation, is therefore essential.

Conventional characterisation relies on UV-vis turbidimetry, dynamic light scattering (DLS), differential scanning calorimetry or rheology [6, 7]. Each requires separate specialised instrumentation, and rheological shear can itself disturb fragile early-stage network structures. The presented platform is uniquely

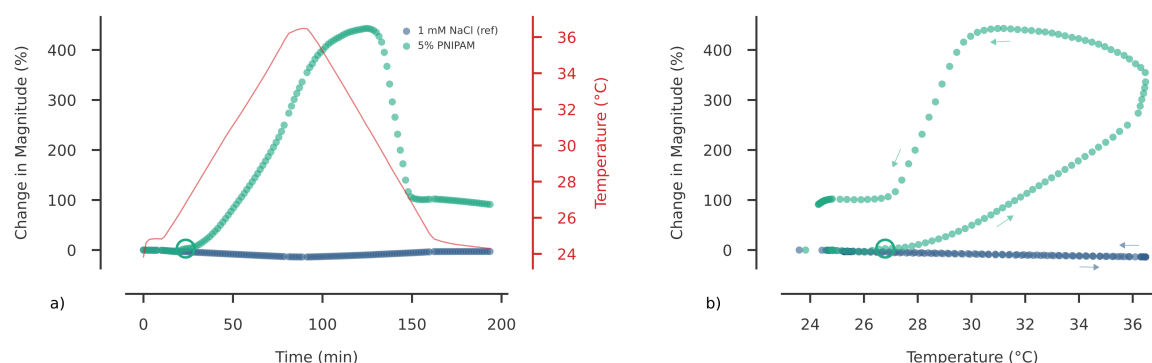


Figure 2: Electrical identification of the thermal inflection point. Relative impedance change at 464 Hz for 5 % (w/v) PNIPAM against a 1 mM NaCl reference, plotted against (a) time and (b) temperature.

suited to this application because the same well can be thermally actuated while its impedance is measured, so the transition is driven and observed in one operation.

Method

PNIPAM (M_w 300,000 g/mol) was dissolved in 1 mM NaCl at 3.5, 5, 7.5 and 9 % (w/v). The low electrolyte background provides mobile ions for the measurement without masking the polymer signature. Wells were filled with 200 μ L, equilibrated at 22 $^{\circ}$ C, then ramped at 0.2 $^{\circ}$ C/min to approximately 36 $^{\circ}$ C, held, and cooled at the same rate. Impedance was swept from 1 Hz to 1 MHz, and 464 Hz was selected for real-time tracking. A reference thermocouple held 0.5 mm above the electrode surface recorded the true sample temperature.

Results

On a pure 1 mM NaCl control the impedance follows the imposed thermal trajectory smoothly and monotonically, confirming that the thermal elements provide stable control without interfering with the impedance read-out. A PNIPAM formulation tracks that same baseline at low temperature but departs from it at a well-defined threshold, allowing an electrical thermal inflection point (T_{inf}) to be extracted from the relative impedance change (Fig. 2).

Across the concentration series the inflection point shifts systematically towards lower temperatures as polymer content increases (Fig. 3). These thresholds lie below the macroscopic cloud point but agree with independent DLS measurements, which suggests that the electrical read-out detects the early onset of polymer clustering rather than bulk gelation.

Considerations and outlook

The measurement is differential rather than absolute. T_{inf} is extracted from the departure of the sample trace from a reference electrolyte measured in a neighbouring well under an identical thermal programme, so slow drift in the thermal element or the base station affects both equally and cancels.

Some limits follow from the current implementation. A low background electrolyte is needed, since a high conductivity would mask the modest impedance change produced by polymer clustering, which puts physiological buffers out of reach for now. Cooling is passive, so only transitions above ambient temperature can be resolved, and heat lost through the plate body still requires an external thermocouple to establish the true sample temperature. Moving the same sensing and heating pair into a microfluidic channel would reduce sample volume and thermal mass, shrink these internal gradients and allow considerably faster thermal equilibration.

VERSATILITY: FURTHER APPLICATIONS

The same architecture, with the relevant read-out channels enabled, has been applied to a range of other applications.

Liquid identification

This was the first proof of principle in which both read-outs were used at the same time. Thermal and electrical data recorded simultaneously on glycerol and NaCl dilutions gave each liquid a distinct combined signature, which was then used to identify different fruit juices [8].

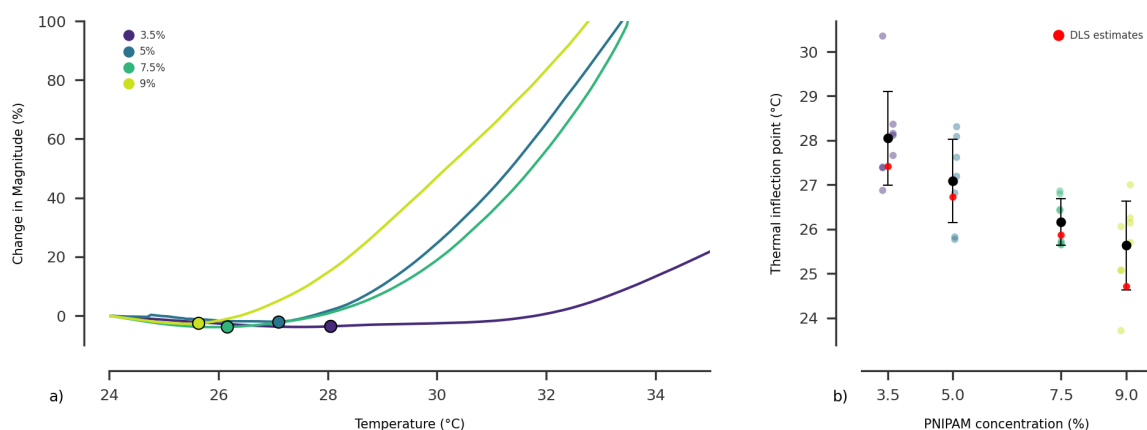


Figure 3: Concentration dependence. (a) Mean impedance change against temperature for four PNIPAM concentrations (average of eight cycles); (b) extracted inflection points compared against DLS estimates.

Cell proliferation and metabolic activity

Thermal sensors integrated into a custom microplate followed *Saccharomyces cerevisiae* growth in real time and without labels. The sensors resolved changes in cell number and in metabolic activity concurrently, replacing an end-point, reagent-based assay [9].

Cell viability and counting

Thermal sensing mainly reports biomass, while impedance is more sensitive to membrane integrity, so the two channels respond differently to cell number and viability. Combining them allowed both parameters to be predicted independently, with the accuracy improving at higher (bulk) cell concentrations [10].

Decoupling biomass from medium conductivity

In bioprocessing, medium conductivity and biomass growth are mixed together in any purely electrical measurement. The thermal signal proved a reliable proxy for cell count that is largely unaffected by ionic strength, and combining both channels recov-

ered the medium composition independently of the cell content, confirmed by dynamic spiking experiments (under review).

Polymer film degradation

Scaled to a 48-well format, the thermal channel measured polymer film thickness directly. This allowed the enzymatic degradation of polycaprolactone films to be followed in real time and different enzyme concentrations to be compared within a single run [11].

CONCLUSION

Six applications, spanning liquid classification, live-cell monitoring, bioprocess control, polymer degradation and soft-material screening, have been realised on one hardware concept. The versatility comes from combining two read-outs that depend on different transport mechanisms, and from being able to use the thermal elements as an actuator as well as a sensor. The hydrogel case shows what that combination adds: a stimulus and its response measured in the same well, which is the basic ingredient for feedback-controlled fluid handling.

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DETECTING A POLYMER PHASE TRANSITION INSIDE A MICROFLUIDIC CHANNEL WITH A SELF-SENSING PCB HEATER

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ABSTRACT

In this work it is shown that a heater in the floor of a microfluidic channel, on a custom-designed printed circuit board, can detect a phase transition in the fluid above it. The heater doubles as a thermometer: a current pulse warms it by a few kelvin, and how quickly it heats up reports how easily the fluid takes up heat. In aqueous poly(N-isopropylacrylamide) the volume phase transition temperature appears as a sharp dip, that returns to baseline afterwards. Its depth grows with polymer content, reaching 7.7, 13.3 and 17.8 % for 5, 10 and 15 % w/v. The dip is found both with the chip heated in an incubator and with the heater driving the ramp itself, so that no external heater or temperature controller is needed. It arises because the transition is endothermic, absorbing part of the delivered heat while it proceeds.

KEYWORDS

Transient plane source, thermal effusivity, thin-film heater, lab-on-chip, PNIPAM, volume phase transition temperature

INTRODUCTION

A phase transition reorganises a material at a characteristic temperature and, in doing so, takes up or gives out heat. That heat is what distinguishes a genuine transition from a gradual change in properties, and the temperature at which it appears is what fixes when a formulation gels, a protein unfolds, or a polymer collapses out of solution. Detecting a transition therefore means detecting either the heat that accompanies it or the structural change itself. Several methods are established for measuring them. Calorimetry determines the transition enthalpy directly from a millilitre sample in a dedicated instrument and remains the reference for thermodynamic characterisation [1]. Miniaturised calorimeters bring the required sample volume down towards the microlitre scale [2]. Optical methods, such as turbidity and microscopy, follow the transition in place in transparent chips and fluids and give the transition temperature directly. Here we measure

the heat uptake from inside the channel itself. A planar heater in the channel floor delivers a short pulse and follows its own temperature rise, which is governed by how readily the surrounding fluid absorbs and conducts the delivered heat [3]. Pulsed single-element sensing of this kind has already been used to measure thermal conductivity and flow rate inside a microchannel [4]. The element is a copper trace on a printed circuit board [5], acting as heater and resistance thermometer at once. We apply this to aqueous poly(N-isopropylacrylamide) (PNIPAM), whose volume phase transition temperature lies near 32 °C [6,7]. It appears as a sharp anomaly in the pulse response, whose depth grows with polymer concentration. The anomaly is resolved both with the chip heated externally and with the heater driving the ramp itself, and it returns to baseline once the transition is complete, showing that the measurement follows the transition while it proceeds rather than the states either side of it.

SENSOR AND MEASUREMENT PRINCIPLE

Chip and instrumentation

The chip is a stack of a PMMA base, a printed circuit board carrying an array of copper heaters, an adhesive layer in which the channels are cut, and a PMMA cover pierced by inlet and outlet holes (Fig. 1). Each heater forms part of the floor of its own channel. The device carries six parallel channels, each 1.5 mm wide and 6 mm long, with a height of 150 µm set by the adhesive layer. The heaters have a footprint of 9 mm² in copper and are plated in gold. The heaters are separated from the liquid by a coverlayer present on the PCB. Each heater is driven and read by a source-measure unit (Keysight B2900 series) in a four-wire configuration, with current forced on one pair of contacts and current and voltage sensed on another.

The measurement

The resistance of copper varies linearly and repro-

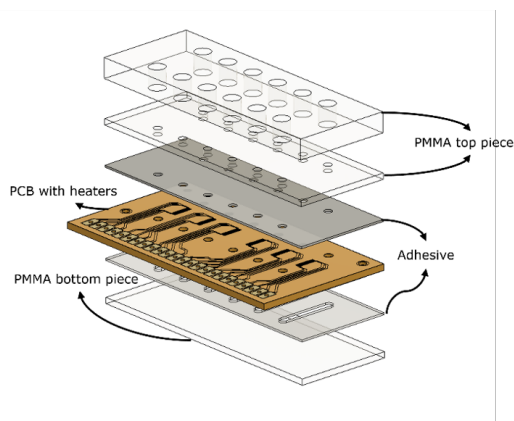


Figure 1: Exploded view of the chip. Copper heaters on the PCB form the floor of channels cut into the adhesive layer; the PMMA cover carries the inlet and outlet holes.

ducibly with temperature,

$$R(T) = R_0 [1 + \alpha (T - T_0)], \quad (1)$$

with $\alpha = 3.81 \times 10^{-3} \text{ K}^{-1}$ calibrated for these heaters and R_0 the resistance recorded for each heater at a reference temperature T_0 . The same four-wire measurement that delivers the pulse therefore also reads the trace's temperature throughout it: the resistance immediately before the pulse gives the temperature of the fluid, and the resistance during the pulse gives the temperature rise. Inverting the expression shows what limits the absolute scale, since a fractional error in R_0 propagates. Absolute temperatures below are referenced to a thermocouple. The same element can also set the temperature it measures: between pulses a standing current is held through the heater and adjusted by a PID loop using the heater's own resistance as feedback. In the incubator experiments the loop was disabled and the surrounding enclosure set the temperature, while a thermocouple measured the actual temperature inside. Two chips of the same design were used, one for each mode. How quickly the rise develops depends on how readily the material above the trace absorbs and conducts the delivered heat. A fluid that takes up heat well holds the trace close to its starting temperature; a poorer one lets it run away. Plotted against the square root of time the rise follows a straight line, and the steepness of that line is the measurement: a shallower line means a fluid absorbing heat more readily.

EXPERIMENTAL

PNIPAM (Scientific Polymer Products, average M_w 300 000 g mol^{-1}) was dissolved in deionised water at 5, 10 and 15 % w/v. Channels were filled using a syringe pump; after filling, the tubing was disconnected

and the ports taped shut to prevent evaporation. Measurements were made in stagnant liquid. Pulses were 50 mW and 0.5 s throughout, applied every 45 s in the incubator experiment and every 20 s in the on-chip experiment, where they alternated in direction: the upward step is fixed at 50 mW while the downward step is set by the standing power at that instant, to a maximum of 50 mW. Two thermal protocols were used, on two chips of the same design. In the incubator protocol the enclosure was set to 45 °C, allowed to settle, then set to 18 °C and left to cool passively, giving an unforced ramp of 0.083 K min^{-1} through the transition over 18.7 h; the three concentrations occupied three parallel channels started within 15 s of each other and so share one thermal history. In the on-chip protocol the sensing heater also drives the temperature, ramping 23–40–23 °C over 3600 s in each direction, or 0.28 K min^{-1} , roughly three times faster. Each pulse was reduced independently: the temperature rise was fitted against the square root of time over 0.2–0.4 s and the fitted steepness recorded together with the pre-pulse temperature. A low-order polynomial baseline was then fitted to the steepness across the temperature range, with the transition window excluded, and results are reported as the percentage deviation from that baseline. A negative deviation therefore corresponds to a fluid taking up heat more readily.

RESULTS

Single transients can resolve the transition directly. Over the fit window the temperature rise is linear in the square root of time. Figure 2(a) compares two pulses from the same channel: at 30.1 °C, inside the transition, the line is 16.6 % shallower than at 33.9 °C above it. Across the flat regions of the ramp the scatter in the fitted steepness is 0.37–0.48 %, which sets the noise floor for everything that follows. Over a full cooling ramp the transition appears as a sharp anomaly (Fig. 2(b)). The deviation is flat within a few tenths of a percent from 18 to 28 °C and again above 33 °C, with a notch of 7.7, 13.3 and 17.8 % for 5, 10 and 15 % w/v, of width 1.14, 1.66 and 1.78 K. The amplitude grows monotonically with polymer content, confirming the signal originates in the polymer rather than the sensor, while the transition temperature is essentially independent of concentration. Referenced to a shared thermocouple the three channels place the transition at 30.09, 30.09 and 29.98 °C, agreeing to 0.11 K across three simultaneous measurements in three parallel channels. The chip can also perform the experi-

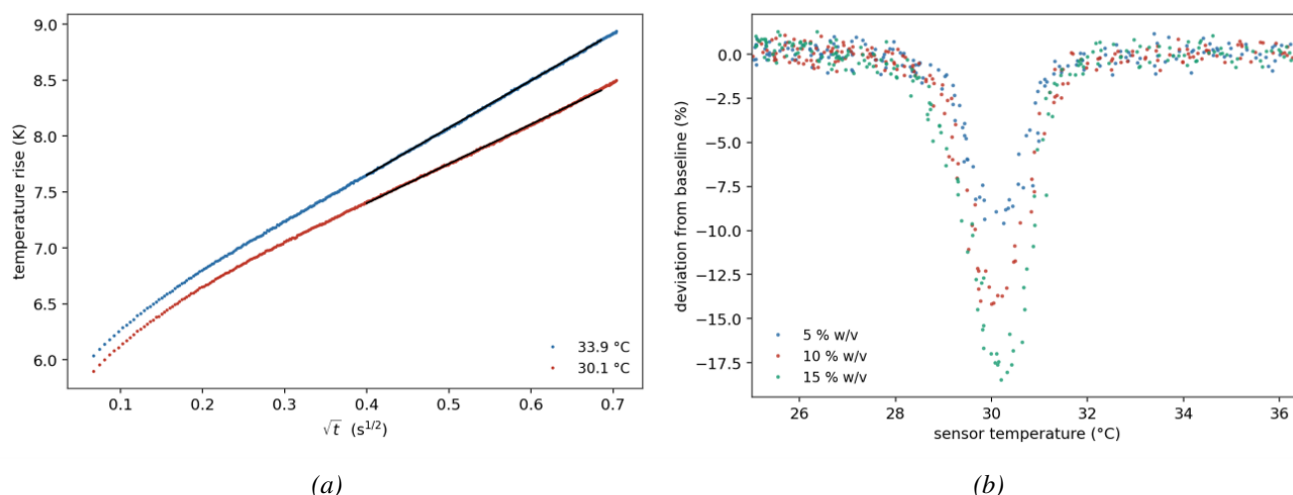


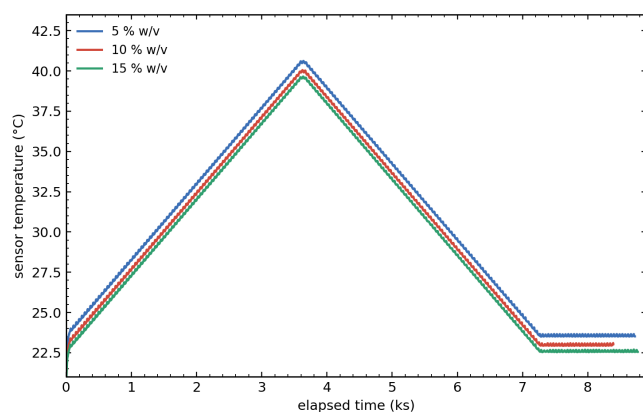
Figure 2: Incubator protocol: the chip measures while an external enclosure cools passively through the transition. (a) Single pulse transients at two points on the ramp: inside the transition (30.1 °C) the line is 16.6 % shallower than above it (33.9 °C). (b) Deviation of the fitted steepness from baseline for three concentrations measured simultaneously in parallel channels. Note the vertical scale differs from Fig. 3(b).

ment unaided. In Fig. 3(a) the temperature is set by the same traces that sense it and reconstructed entirely from the pre-pulse resistance, with no external heater, controller or thermometer in the loop: the three channels are ramped from about 22 °C to 40 °C and back, and the ramp is recovered point by point from the pulses themselves. The three traces run parallel but offset by up to about 1 K. Since all three channels sit on one board and share one thermal environment, that offset reflects the per-channel reference resistance rather than a real temperature difference, and is of the size expected from the sensitivity given above. The transition is resolved on all three channels (Fig. 3(b)). The deviation is flat to within about a percent below 30 °C, falls to roughly −5, −10 and −11 % for 5, 10 and 15 % w/v, and reaches its minimum near 32 °C in each case. As in the incubator experiment the depth grows monotonically with polymer content while the position is almost independent of concentration. The recovery above the transition is slower here: the deviation climbs back from its minimum but is still about a percent below baseline at the top of the range, so the return is not complete within the temperatures covered.

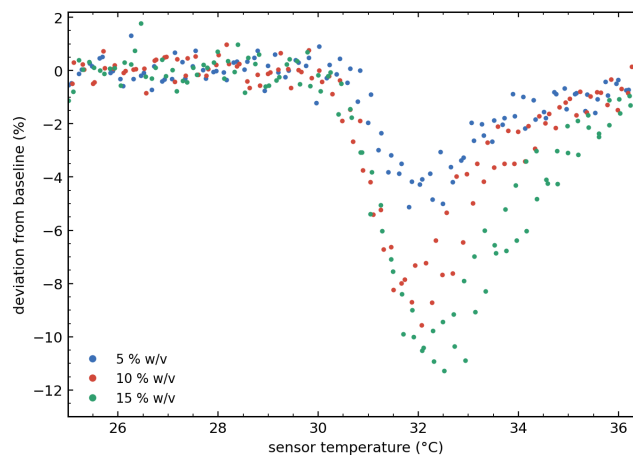
DISCUSSION

The PNIPAM transition absorbs heat as it proceeds [8]. While it is underway, part of every joule delivered goes into driving the transition rather than into raising the temperature, so the fluid behaves as though its heat capacity were far larger than it actually is and the sensor registers a correspondingly greater capacity to

absorb heat. The strongest support for this reading is the shape of the anomaly in the incubator experiment, where the deviation is confined to the transition and returns to baseline to within the scatter of the measurement once it is complete. A difference between the collapsed and the hydrated state would persist above the transition, and would have to reproduce the hydrated state to better than half a percent to escape detection. In the on-chip experiment the recovery is slower and does not complete within the range covered, so that dataset is consistent with the same picture without independently confirming it. The response is partial rather than complete because the channel is thin. Within a single pulse the fluid closest to the trace is driven through its transition and has no enthalpy left to absorb, so only part of the enthalpy available in the channel contributes to the measured amplitude. The approach is not only applicable to PNIPAM. Any transition that takes up or releases heat should be visible, from gelation to protein aggregation to the onset of crystallisation. It requires no optical access, so it is compatible with turbid, opaque or concentrated fluids and with chips built from materials that are not transparent. Three limitations should be stated. The channel ceiling takes part in every measurement, so the reported quantity is an effective value for the filled channel and results are given as relative changes. Absolute temperature relies on an external reference, because the scale is anchored at a single reference resistance whose error propagates directly into it, as the offsets between channels in Fig. 3(a) show. And only part of the transition enthalpy is captured within a pulse, so



(a)



(b)

Figure 3: On-chip protocol: the same heaters drive the ramp and sense it. (a) Temperature of the three channels reconstructed entirely from the pre-pulse resistance. (b) Deviation of the fitted steepness from baseline for the same three channels. Note the vertical scale differs from Fig. 2(b).

amplitudes are not absolute; no independent calorimetric measurement has been made yet on these samples.

CONCLUSION

A copper trace forming the floor of a microfluidic channel resolves a phase transition in the fluid above it from half-second pulses, without labels and without optical access. In PNIPAM the transition appears as an anomaly, reaching 17.8 % at 15 % w/v growing with concentration, and it is resolved with the chip heated externally and with the heater driving the ramp itself. That the anomaly is confined to the transition and returns to baseline afterwards identifies the heat taken up while the transition proceeds as the origin of the signal, and points to thermal sensing as a route to following phase behaviour inside standard printed circuit board hardware.

ACKNOWLEDGEMENTS

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AUTOMATED MICROFLUIDIC MICROTITER PLATES FOR ORGAN ON CHIP AND REAL TIME SENSOR INTEGRATION

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ABSTRACT

This paper describes a novel approach in microfluidic flow control, based on the integration of microtiter plates and on-board microfluidic pumping. The automated microfluidic microtiter plates enable on-board flow generation and control with a scalable architecture compatible with high throughput fluid handling, imaging and a plug-and-play interfacing system. We demonstrated the compatibility of this platform for implementation of multistep diagnostics workflows (e.g. ELISA), two chamber organ-on-chip culture modules and integration of in-line, real time photonic sensing.

KEYWORDS

Microfluidics, Automation, Microtiter Plates, ELISA, Organ On Chip, Photonic Sensors

INTRODUCTION

Successful implementation of microfluidic systems in commercial products increasingly requires on-board flow control. This is particularly relevant for applications that either require multistep workflows involving multiple reagents (e.g. point of care or in vitro diagnostics), or to culture cells, tissues and organs-on-chip under physiologically relevant conditions.

ALine has previously developed a toolbox of microfluidic components as a platform for reliable on-board fluid handling and assay implementation in microfluidic consumables [1-2]. This approach involves the use of pneumatic functions (on-board pneumatic valves, pumps and vents), within disposable microfluidic devices controlled by an external unit. Valves are implemented by using a flexible membrane layer, which deflects and closes the fluidic path when positive pressure is applied (typically between 50-800mbar). When negative pressure is applied, the membrane deflects the opposite way and opens the fluidic path. Multiple valves can also be operated in sequence to provide on-board pumping with peristaltic actuation. The disposables typically include the use of multilayer laminates, produced with techniques that are compatible with scale up manufacturing and

commercialization (e.g. laser cutting, roll to roll die cutting, CNC machining and injection molding). Advantages of this approach include the ability to confine the reagents and samples in the disposable, without the need for instrument cleaning or washing cycles (“dry instrument”), and the ability to optimized the workflow by modifying the script used to control the on-board pneumatic components.

Current on-board flow integration suffers from a lack of standardization. A variety of flow control options have been implemented in commercial consumables, including on board pneumatic, mechanical, rotary and piezo valves/pumps. In most cases, the consumable architecture and dimensions are customized for the final application, and require a dedicated controller that is tailored to the final consumable footprint, and in many cases is not compatible with high throughput automation strategies and fluid delivery systems. (e.g. pipetting robots, liquid handlers, plate handling robots). The technologies described in this paper have the goal to address this gap and ease the adoption of microfluidic platforms in commercial settings.

MICROFLUIDIC MICROTITER PLATE ARCHITECTURE

This work describes the implementation of the ALine pneumatic fluid control in microtiter plate format, enabling the use of external high throughput fluid delivery systems (e.g. liquid handlers, pipetting robots and plate handling robots), while retaining the benefits of precise flow actuation within the consumable. To demonstrate this, we developed hybrid devices (Fig 1) that are constituted of two main components:

- (i) a bottomless 96-well microtiter plate (commercially available from Greiner Bio-One, Kremsmünster, Austria), which allows interfacing with standard liquid handlers for reagent pre-loading and waste disposal.
- (ii) a custom laminate designed and produced using ALine’s laser cutting and lamination processes for batch manufacturing [1], which includes on-board valves and pumps to generate and control precise flow patterns used to implement the desired workflows.

The designs and components used in this approach are compatible with product development and low volume prototyping, but they have been successfully scaled up for commercialization using a combination of injection molding and roll to roll die cutting processes.

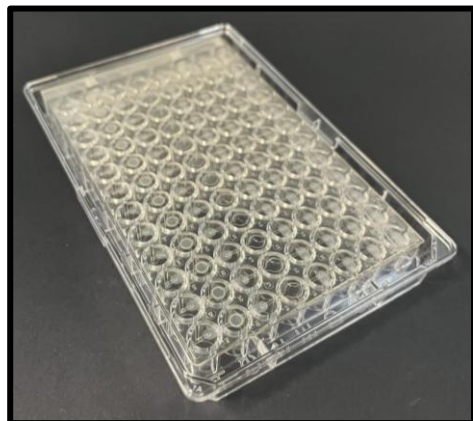


Figure 1: Microfluidic Microtiter Plate hybrid device, including a bottomless 96-well plate and a custom laminate with on board pumps and valves. The unit is shown upside down to showcase the on-board components located on the bottom side of the microtiter plate wells.

MULTISTEP ASSAY IN MICROFLUIDIC MICROTITER PLATE FORMAT

We developed an automated microtiter plate capable of implementing automated ELISA workflows. We first demonstrated ability to implement an ELISA workflow with up to four different reagents dispensed sequentially on a capture region (for ELISA applications). First, the liquid reagents (up to 200 microliters each) are pre-loaded into the microtiter plate wells using a pipettor or an external liquid handling robot. The on-board valves and pumps are then actuated according to a pre-programmed script, and sequentially dispensed to a capture region pre-coated with primary antibodies and into a waste reservoir. The fluidic sequence is described in Fig.2 and involves the following steps (i) sample dispensing and incubation, (ii) washing with sequential dispensing of wash buffer and air plugs, (iii) secondary antibody dispensing and incubation, (iv) washing and finally (v) substrate loading and incubation. Once the fluidic workflow is completed, the content of each capture region is imaged using a plate reader or a dedicated sensor to collect the ELISA signal and quantify the analyte. The setup is compatible with addition and removal of fluid from the microtiter plate wells during the protocol, expanding the capabilities to a larger number of reagents if the assay requires more complex workflows.

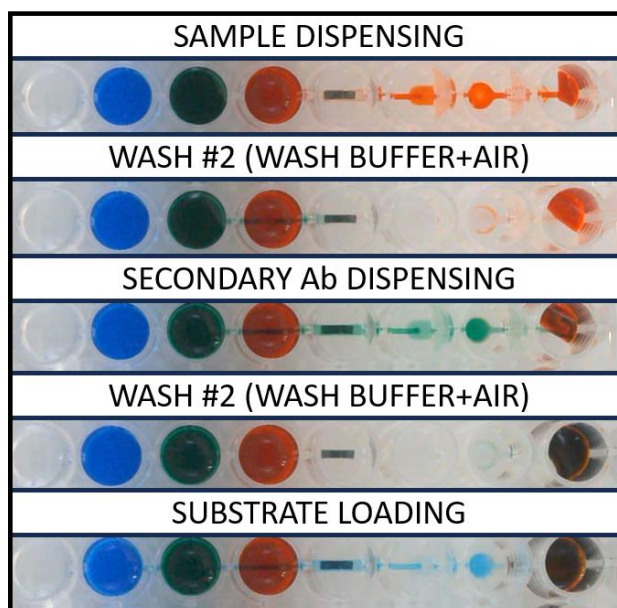


Figure 2. Step by step implementation of the ELISA workflow, single lane shown from 12-plex Microfluidic Microtiter plate.

CLAMPING MANIFOLD AND RIBBON CONNECTORS

We developed a tubing free plug and play holder to control the automated microfluidic microtiter plates. The ADEPT Mini (Fig.3) is a pneumatic controller that has been developed at ALine to supply the pressure and vacuum required to actuate the on-board valves. Pressure and vacuum are supplied to the ADEPT mini using an external set of diaphragm pumps, and the setup includes 12 pneumatic channels, each controlled independently for what pressure state is delivered to the microfluidic consumable. The system can be automated by loading a script into the ADEPT with the desired sequence of events, or using serial communication to control the status of each valve in real time. Previous versions of this controller relied on flexible tubing to interface with the microfluidic consumables.

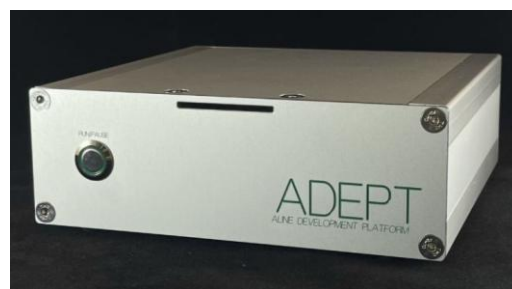


Figure 3: ADEPT Mini, a 12 channel pneumatic controller that can be used to supply pressure states to the on-board valves and pumps

To simplify interface and improve robustness of operation, we have developed a clamping manifold and ribbon connector system, shown in Fig. 4. This setup allows plug-and play pneumatic interface with the controller, while leaving the wells accessible for imaging in transmission using a plate reader of high-resolution microscope. The ribbon connector can be produced in different lengths to de-couple the location of the consumable from the controller, thus providing additional flexibility on the final setup, especially in the case of applications that require the use of an incubator.

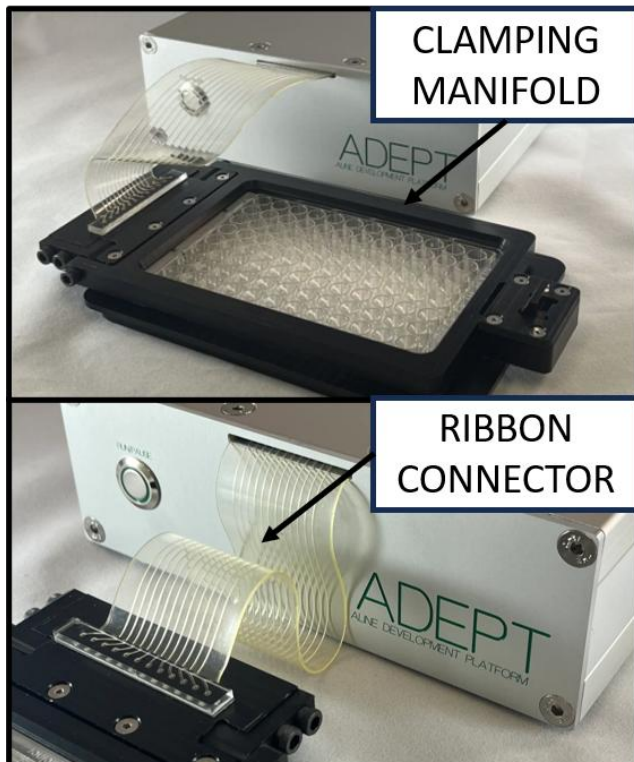


Figure 4 Clamping manifold and ribbon connector used to interface the microfluidic microtiter plate with the external connector.

INTEGRATION OF ORGAN ON CHIP CULTURE MODULES

We also demonstrated the integration of organ on chip culture modules in the automated microfluidic microtiter plate. To demonstrate the platform capabilities, we integrated 2-chamber organ on chip culture modules, in which a porous membrane is used to separate the cells/tissues cultured in each chamber. The on-board pumps and valves allow controlled delivery of reagents (culture media, drugs, etc.) to perform long term culture experiments in an incubator. Fig. 5 shows a section of the microtiter plate containing three separate organ on chip culture modules. Each of the chambers in the culture modules

(top and bottom chamber) is controlled by an independent pump, which can be used to deliver up to four different reagents based on the desired workflow.

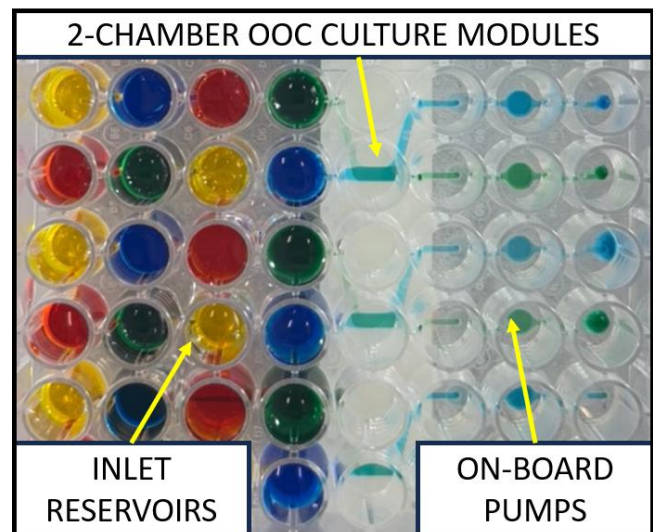


Figure 5. Microfluidic Microtiter Plate with integrated Organ-on-Chip culture module. Three separate organ on chip culture chambers shown, where each chamber can be loaded with up to four different reagents/culture media during the experiment.

This type of application requires the consumable device to be located in an incubator to control temperature and gas content. The use of the clamping manifold and ribbon connector allows real time control of the pressure states in the microfluidic device, while the ADEPT Mini can be located outside of the incubator.

INTEGRATION OF REAL TIME PHOTONIC SENSORS

To provide real time detection, we also integrated Photonic sensors, developed and commercialized by Phlotonics, Inc. This approach [3] provides the ability to perform multiplex, real time detection of the contents of the reagents/samples being dispensed by the on-board pumps. Fig.6 shows a microtiter plate format that includes on-board sensor and an example of real time detection of four different biomarkers (Cel culture stabilizing factor, Early-Stage differentiation factor, Non-Antibody protein control and Antibody control). For the first 7 minutes the system establishes a baseline for all four biomarkers. The sample is then flown onto the sensor, showing binding (signal growth) for the two biomarkers of interest, while the controls do now stay stable over

time. At the 14 minutes mark, the secondary solution is delivered to the sensor, and signal is measured over time showing a further increase of the two biomarkers of interest. Using the on-board microfluidic pumps allow automation of this protocol, with controlled flow rates and volumes dispensed.

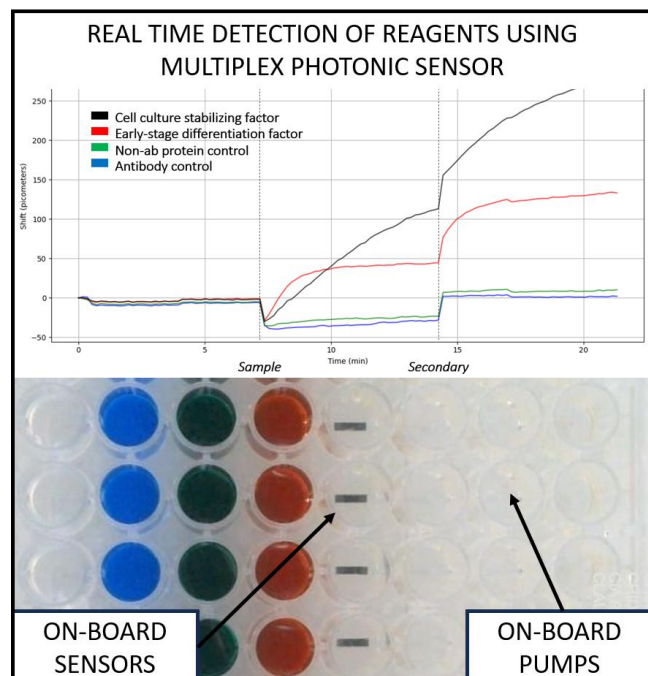


Figure 6. Microfluidic Microtiter Plate with integrated photonic sensors and example of real time detection trace. Four lanes shown of a 12-plex Microfluidic Microtiter plate

CONCLUSIONS

The automated microfluidic microtiter plates enable on-board flow control with a scalable architecture, compatible with high throughput fluid handling and, imaging. This approach retains the key advantages of microfluidics (e.g. precise fluid control, reduced volumes), while addressing some of the challenges that limit its widespread adoption, such as the need for tubing and customized controllers (chip in a lab paradox). We demonstrated compatibility of this platform with key applications that include multistep workflows used in diagnostics (ELISA), drug development (cell culture / organ on chip) and biomanufacturing (real time sensing for antibody production). We expect this technology to expand the applicability of microfluidic platforms into high throughput systems that are compatible with automation, supporting the next generation platforms for biotechnology research and drug development.

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SYSTEMIC AUTONOMOUS CHARACTERISATION OF INLINE-MULTI-MODAL MICROFLUIDIC DEVICES FOR MACHINE LEARNING TRAINING

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ABSTRACT

Machine learning for multi-modal microfluidic sensors requires large, accurately labeled datasets. However, generating them is time-consuming, because many operating conditions must be varied and stabilized. This work presents an autonomous acquisition system for inline multi-modal microfluidic sensor chips that applies gas or liquid mixtures while controlling flow, pressure, temperature, composition, and actuation. The platform combines SMUs, high-speed TiePie oscilloscopes, and ZSSC3241-based bridge readout with industry-standard instruments for label generation. A custom Python program synchronizes all devices with microsecond accuracy and logs structured data. Week-long stable operation and precise measurements demonstrate suitability for efficient machine-learning dataset generation and robust sensor characterization.

INTRODUCTION

The application of machine learning (ML) on multi-modal sensors is an increasingly reported-on subject [1]. It allows for the analysis of a combination of sensors to extract correlations in sensor signals. To find these correlations, ML algorithms require extensive datasets comprising: acquisition of sensor data at various setpoints, precise ground-truth measurements for labeling and clean-up and preparation of labels and data [2].

Inline Multi-modal microfluidic sensor devices may contain sensors like pressure sensors, Coriolis mass-flow sensors, thermal flow sensors, and temperature sensors [3][4]. During characterization of these sensors, all measurement quantities can be varied, e.g. flow, pressure, temperature, actuation power, fluid composition. Varying these quantities results in many unique setpoints. Accounting for stabilization (1 to 30 minutes) and acquisition durations (0.1 to 5 minutes), full dataset generation may take several days to weeks [4].

To fulfil the need for large, accurate and well-labeled datasets, an autonomous data acquisition system for microfluidic chips has been designed, realized and tested. The system can apply a mix of gases or a mix of liquids to a microfluidic chip. During measurements, fluid flow rate, mix ratios, fluid pressures, actuation parameters and temperatures can be varied. At every unique setpoint, both steady-state and dynamic measurements are available.

SYSTEM DESIGN

Sensor data is acquired using:

- three U2722A Source Measure Units (SMUs) totalling 12 channels for 4-point probe resistive measurements,
- three TiePie HS5/6 oscilloscopes: 10 ADC channels, 2 DAC channels for high speed signal acquisition,
- custom hardware using the Renesas ZSSC3241 sensor signal conditioner IC for resistive bridge sensors.

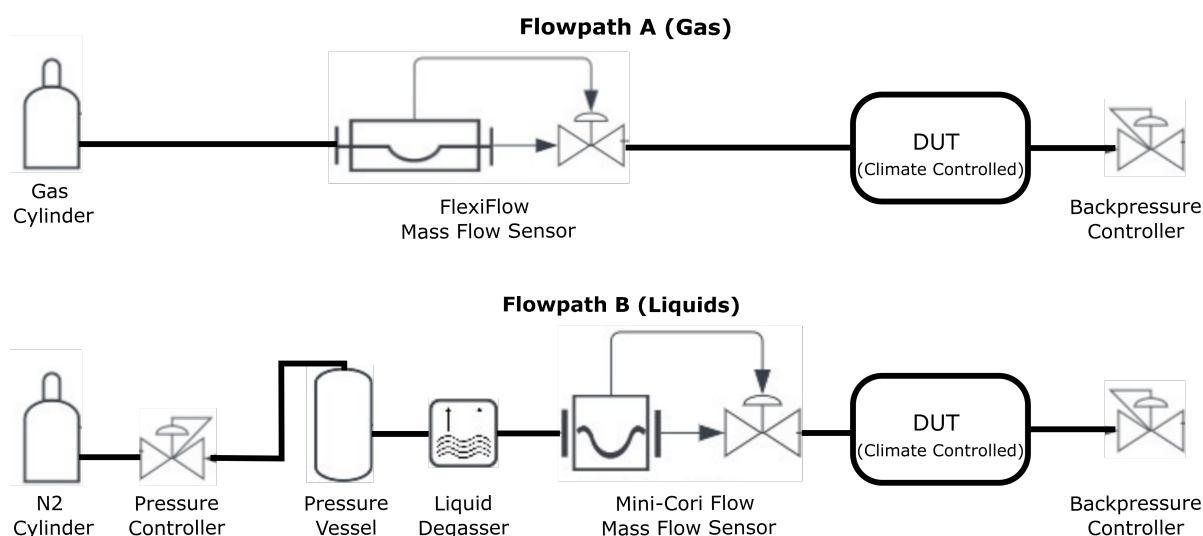


Figure 1: Layout schematics for the gas and liquid flow paths.

System control and data labels are executed and acquired using the following instruments:

- four Bronkhorst EL-PRESS (back)pressure controllers and sensors,
- two Bronkhorst Flex-Flow mass-flow controllers,
- two Bronkhorst Mini-Cori mass-flow controllers,
- two Keller M5HB high-bandwidth pressure sensors,
- one NI6211 DAQ,
- one four-channel PT-104 Temperature Data Logger.

The layout schematics for the gas and liquid flow paths are depicted in Figure 1. The general disposition of the setup is depicted in Figure 2.

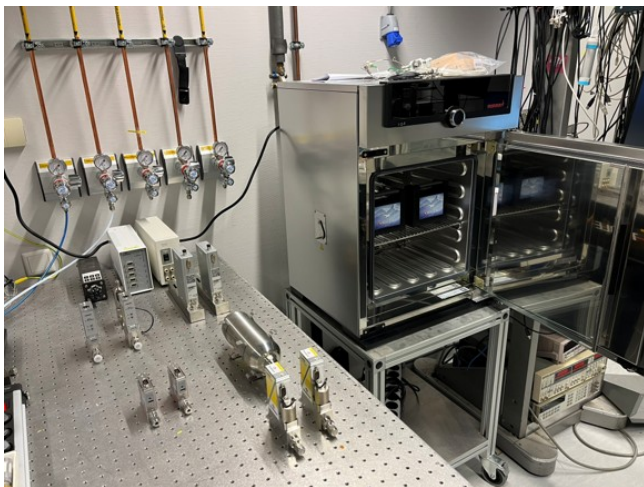


Figure 2: Component overview of the setup. Gas supply lines (top left), Instruments (bottom left), climate-controlled environment (right).

A custom Python program manages the synchronous readout of all instruments and allows for programming of measurement cycles. At every sample interval, all instruments are sampled with microsecond accuracy, and all measurement data, settings and labels are logged in a structured matlab dictionary.

The versatile acquisition instruments combined with the industry standard instruments for label generation have proven to provide ample basis for extensive dataset generation. The presented specifications and abilities allow for accurate and precise characterization and dataset generation of inline-multi-modal microfluidic sensor devices for use with machine learning training.

MEASUREMENT CAPABILITIES

The U2722A SMUs allow for 4-point probe resistive measurements at a maximum of 30 Hz. The units are fully programmable through VISA commands. The Python control software allows programming of the following parameters:

- Current Range
- Voltage Range
- Integration Time
- Moving Average Filter

All settings can be controlled through the window depicted in Figure 3 or through scripting.

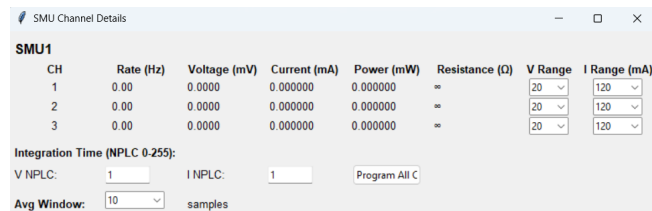


Figure 3: SMU control window. Measurements are updated live. Settings can be adjusted manually or in script.

The TiePie HS5 USB oscilloscope offers one arbitrary waveform generator (AWG) and three high-speed DAQ channels. The TiePie HS6 USB oscilloscope offers four high-speed DAQ channels. Two HS5 and one HS6 units are combined to offer 10 ADC channels and 2 DAC channels. The units are interconnected on a hardware level, enabling sample-level synchronized acquisition over all channels and sample-level synchronized triggering on the AWG channels.

TCR Measurements

Through continuous acquisition of resistances with varying temperatures, a linear temperature coefficient of resistance of the on-chip resistors can be determined. By injecting 100 μ A and recording currents and voltages, the resistors can be characterized without self-heating.

Constant Power Actuation

Utilizing the 30 Hz update rate of the SMU, a proportional (P) type control loop was implemented for constant power actuation. This allows the setup to actuate a resistor to a programmable power level, for example, to be used in anemometric measurements. The control loop compares the measured power P with the desired power $\hat{P}$, and adjusts the output P_{out} such that

$$P_{out} = K_p(\hat{P} - P) + P_0 \quad (1)$$

approaches the desired power with minimal error.

Constant Temperature Actuation

A P type control loop was implemented to enable constant temperature actuation of on-chip resistors. This allows any resistor to be used as an on-chip heater. The progressive controller acts identically as described in Equation 1. The controller requires input of the resistance R_0 at T_0 (i.e. 20°C), the TCR, and the measured resistance R of the connected resistor. The temperature T is calculated by the controller as

$$T = T_0 + \left(\frac{R}{R_0} - 1 \right) \cdot TCR^{-1}, \quad (2)$$

and is reported live in the SMU window of the control software for reporting and monitoring.

Resistive Bridge Measurements

Resistive bridge measurements are enabled through a custom acquisition board, built using a Renesas ZSSC3241 sensor signal conditioner IC for resistive bridge sensors. This system is shown in Figure 4. The Renesas IC offers a wide range of signal conditioning options. Most importantly, it provides a well documented analog and digital signal path when the advanced calibration features are turned off. This is critical to enable the calculation of the original voltage signals from the digital output of the sensor.

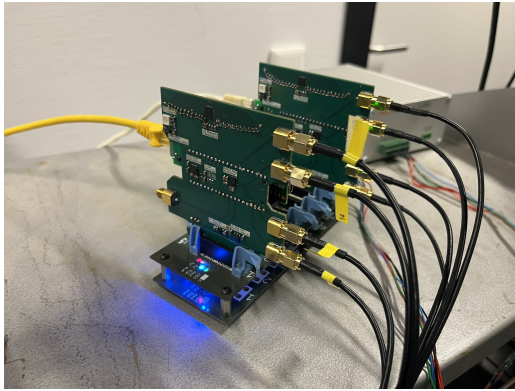


Figure 4: Custom Wheatstone bridge readout circuit. Two circuits are depicted. Coaxial connections to chip (right), Digital readout over Ethernet (right).

The analog signal path, described in Figure 5, allows for multiple adjustments to the wheatstone bridge output. It has several features optimized for use with custom sensors, e.g. an input voltage shift to compensate for unbalanced bridges due to manufacturing tolerances and an ADC shift to make sure that sensors with large offsets still fall within ADC range. Additionally, the sensor features an analog output, leveraging the high bandwidth of the sensor and enabling high-frequency synchronized acquisition using a high-speed DAQ.

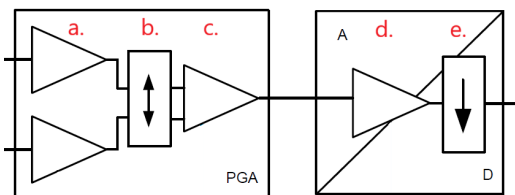


Figure 5: Signal path ZSSC3241. a: pre-gain stage, b: input voltage shift, c: main gain stage, d: ADC gain stage, e: ADC shift.

Dynamic Capacitive Measurements

Using the TiePie ADC and DAC channels in combination with a charge-amplifier, capacitive measurements can be performed. A 1 MHz carrier signal is generated. This signal is fed through the to-be-measured capacitor. The charge is monitored and converted to a voltage using a charge-amp, which produces a voltage output proportional to the integrated value of the input current. The output voltage frequency, phase shift and amplitude can be used to analyze dynamical mechanical chip behaviour.

Frequency Analysis / System Identification

Using the exact synchronization of the TiePie ADC and DAC channels, system identification or frequency analysis of mechanical sensors is possible. A chirp signal, depicted in Figure 6, is generated in script and produced by the AWG to actuate the microsensor. The microsensor is actuated through Lorentz actuation. The resulting displacement of the sensor is read back by Lorentz induction or capacitive measurement on a TiePie input channel.

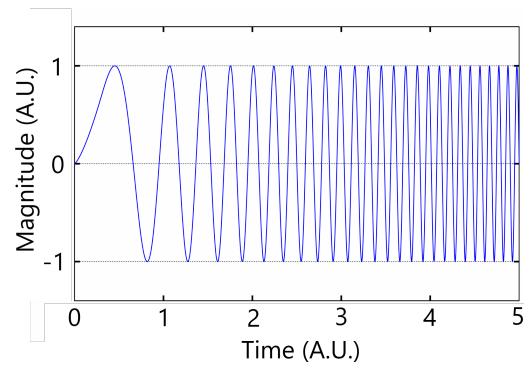


Figure 6: A linear chirp signal that contains all frequencies between frequency F_{lower} and F_{upper}

The actuation and readout are synchronized in time down to one sample-time accuracy. To obtain the system transfer function, the cross spectral density from output to input is divided by the input auto spectral density.

RESULTS

The measurement setup was shown to be stable for long run-times up to two weeks. All features of the setup have been tested and verified. Using these features, three example measurements have been performed and are reported on in this section.

TCR Measurements

The temperature coefficient of resistance of multiple known resistors was characterized using the setup. The resulting measurements are depicted in Figure 7. The results were ob-

tained at an actuation power of 50 μ W. A TCR of 2200.7 PPM/C was measured by linear fit of the measurement results. The specification of the used resistor was 2200 PPM/C. The resulting resistance measurements showed a standard deviation of 2.7 m Ω .

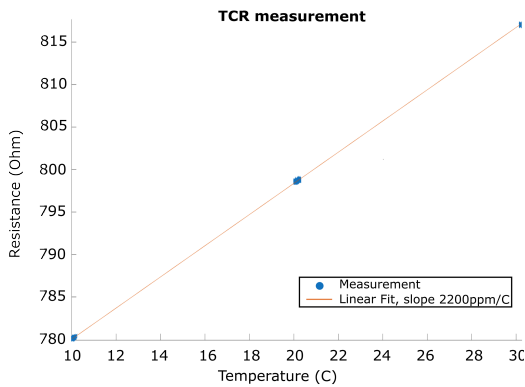


Figure 7: Temperature Coefficient of Resistance measurements of platinum MEMS resistors, obtained using the U2722A SMU and the temperature-controlled environment.

Resistive Bridge Measurements

Table 1: Overview of measurement results of on-chip strain-gauge measurements.

	Inlet Sensor
Sensitivity	79.2 μ V V ⁻¹ bar ⁻¹
Standard Deviation	1.7 mbar

Using the ZSSC2431 IC, Measurements were performed on an on-chip strain gauge. The pressure applied to the strain gauge was varied from 0 bar to 7 bar, and the bridge voltage was determined from the digital output of the measurement IC. To compare, a FEM model of the strain gauge was made. Both results are shown in Figure 8. The resulting parameters are shown in Table 1

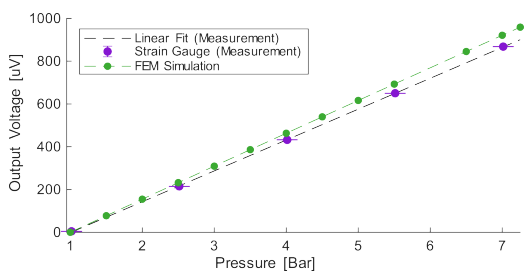


Figure 8: Obtained response from an on-chip strain gauge.

Frequency Analysis / System Identification

A frequency analysis was performed on a mechanical microsensor. The first two resonance modes of this sensor are known to be approximately 1950 Hz and 3300 Hz. The system identification provided the transfer function from Lorenz ac-

tuation to the induction voltage on a Lorenz track on the chip. The resulting spectrum is shown in Figure 9, and confirms the location of the resonance modes are where they are expected for the used sample.

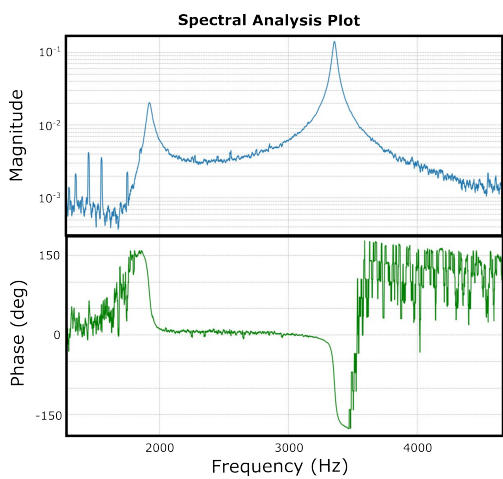


Figure 9: Dynamic spectrum with sub-Hz resolution, obtained from a MEMS based Micro-Coriolis sensor by Lorenz actuation and Lorenz track readout.

CONCLUSION

The measurement setup was shown to be stable for long run-times up to two weeks. The SMU’s have been shown to reach standard deviations of 2.7 m Ω in resistance measurements at an actuation power of 50 μ W to prevent self-heating, shown in Figure 7. The TiePie ADC channels acquire data at 16 bit at 1 GSa/s in ranges from $\pm$ 200 mV to $\pm$ 80 V. The DAC channels support arbitrary waveform generation from 0.5 nHz to 30 MHz. Utilising the sample-level synchronisation TiePie channels allows for lock-in amplifier-type capabilities on all 8 ADC channels, and high-resolution spectral analysis, depicted in Figure 9. The Renesas ZSSC3241 is shown to be capable of accommodating nearly all MEMS resistive bridge configuration types.

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RAPID PROTOTYPING MICROFLUIDICS WITH 3D PRINTED FLUIDIC CHANNELS

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ABSTRACT

Cleanroom-based microfabrication and 3D printing can be used in concert to enable rapid prototyping in microfluidics. The housing of the microfluidic device can be used as a test environment, or as an integral component to the microfluidic device itself. In this work, the test setup of several 2D directional anemometers is discussed, showing the benefits of using 3D printing during early development stages. Additionally, a viscous fluid flow sensor is designed and realised using a hybrid structure based on MEMS fabrication techniques and 3D printing. In this way, rapid prototyping is enabled in a field of research where fabrication procedures can be lengthy and critical.

KEYWORDS

3D printing, Additive Manufacturing, Microfluidics, Flow Sensor, Viscosity.

INTRODUCTION

Microfabrication is an enabling technology for many fluidic sensors, allowing for their improvement and miniaturisation by offering a wide array of materials and geometries. Microfabricated sensors have several advantages over meso- and macroscale sensors including lower measurement volumes for biosensors [1], lower power draws [2], and multisensor integration with a small footprint [3].

Novel sensing techniques are enabled by microscale devices, such as the inclusion of a thermal shunt for calorimetric flow sensing range extension [4], or out-of-plane drag force sensing with integrated thermal flow sensors [5]. A major drawback of microfabrication in microfluidics is the time-consuming nature of most process flows and fabrication procedures. This is especially relevant to microfluidic sensors with integrated channels, where the fabrication of the channel regularly requires more processing steps than the fabrication of electrodes and wiring of the sensor. A second drawback of microfabrication in the world of microfluidics is the limited channel size, making it extremely challenging to sense in highly viscous media, or with high flow rates, which require much larger channels.

3D printing has been used in sensor fabrication in both the micro and mesoscale [6]. Unfortunately, 3D

printed sensors suffer from many negative factors including creep, moisture sensitivity, hysteresis and drift.

We propose that 3D printing can still aid in the development of microfluidic sensors despite these shortcomings. Instead of being used for the fabrication of the sensor structure itself, it is used as the housing of microfluidic sensors in both application and test setups. The requirements of the housing are that it allows for a bulk of fluid to be injected into channels or cavities that pass by a sensing structure. Furthermore, the housing often should support a means of electronic or optical interfacing with the sensing elements and fluidic structure.

The primary advantage of this method is that it allows for rapid prototyping during the development of novel sensing structures and concepts. Modern immersion printing techniques enable sub-mm (even 10 μm) resolution, allowing for geometric freedom in the channel size when it comes to viscous microfluidics.

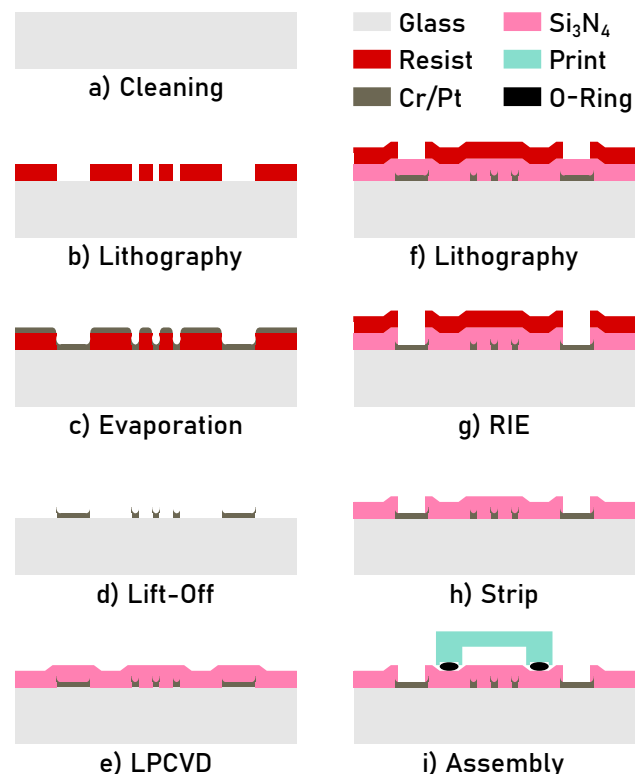


Figure 1: Lift-off process flow with a 3D printed cap.

SENSOR DESIGN

To demonstrate this hybrid fabrication technique, an anemometric test set-up and a viscous fluid validation set-up have been realised.

The investigated anemometric sensors are a dual-mode thermal wind sensor and a hybrid mechanical and thermal cantilever-based anemometer. Both sensors are capable of determining the wind direction and speed [5, 7]. The dual-mode sensor was fabricated using industrial 65-nm Complementary Metal-Oxide-Semiconductor (CMOS) technology. Due to the limitations imposed by the industrial fabrication, the sensor is a monolithic device, without any cavities, free hanging structures or membranes. The sensor uses the top two metallisation layers of the CMOS stack to create thermopiles that are routed around a central heater, enabling a differential calorimetric flow sensing principle. The hybrid mechanical and thermal sensor was made using Micro-ElectroMechanical Systems (MEMS) techniques such as KOH bulk wet etching and uses strain mismatched SiRN layers to cause out-of-plane cantilever bending [5]. The cantilevers stick out above the sensor, allowing for mechanical interaction with the fluid. The added benefit is that the thermal sensing element is placed in the flow beyond the boundary layer.

The viscous fluid sensors are hot-element thermal flow sensors capable of determining the flow speed of (viscous) fluids. The hot-elements are deposited on a glass substrate. The sensing chips contain 10 hot-elements, arranged in two rows of 5. Each hot-element is interfaced via 4-point measurement with integrated Kelvin probes to measure the change in resistance of the hot-element.

The fabrication procedure shown in Figure 1 begins with a clean glass MEMpax® wafer (Figure 1a) upon which a positive photoresist is spun and patterned (Figure 1b). After development, a stack of a 5 nm Cr adhesion layer and 200 nm Pt device layer are deposited using evaporation (Figure 1c). A lift-off is performed in an acetone sonicator bath (Figure 1d). Post wafer inspection, a 500 nm layer of Si₃N₄ is deposited using Low Pressure Chemical Vapour Deposition (LPCVD) (Figure 1e). Using a new layer of photoresist, contact holes are etched through Si₃N₄ using Reactive Ion Etching (RIE) (Figure 1f & Figure 1g), after which the photoresist is stripped using an ozone plasma stripper (Figure 1h). The finished wafers are then diced using a disco dicer and placed in the assembly (Figure 1i).

ELECTRICAL INTERFACING

Both the anemometric and viscous fluid sensors are interfaced with intermediate Printed Circuit

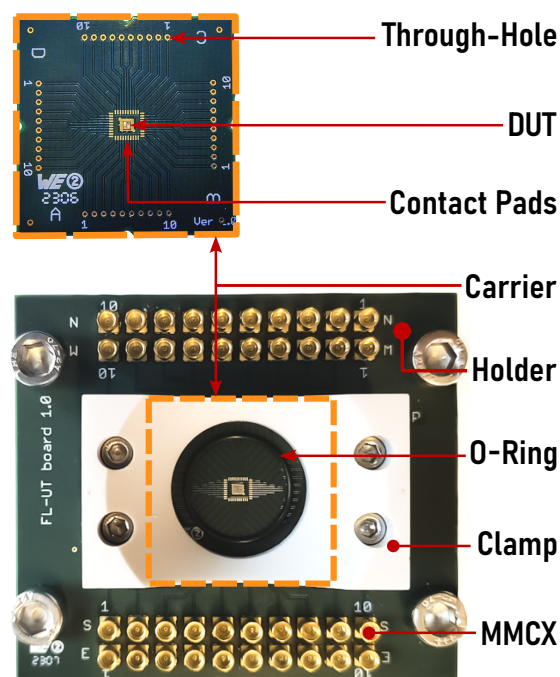


Figure 2: Photographs of the carrier and holder PCBs.

Boards (PCBs). The millimetre-scale anemometric chips are mounted on a square carrier PCB, with wire bonds connecting up to 40 contact pads [5, 7]. The carrier PCB can then be pressed onto four separate pogo pin connectors (10-pin), which are connected to the holder PCB as shown in Figure 2. A 3D printed clamp presses the chip onto the pogo pins in order to make good electrical contact. Micro-miniature coaxial (MMCX) connectors are used to connect the measurement setup to external bench top equipment.

The viscous fluid measurement chip is much larger than the anemometric chips. Additionally, to enable optical readout techniques, the chip should not be mounted directly on a closed PCB. Therefore, the chip is instead clamped in place by the housing, with pogo pins pressed against the contact pads of the fluidic chip. This avoids having to wire bond and mount each chip to a PCB, which allows for the reuse of PCBs. Furthermore, this allows for the chip to be swapped out for another device, without requiring any wire bonding.

As a result, the readout PCB is designed to contain two 2 × 10-pin pogo pin strips, which connect to 40 SubMiniature version A (SMA) connectors. At the centre of the PCB, there is an opening, which allows for alignment of the PCB onto the contact pads of the chip.

FLUIDIC HOUSING

Both sensor types rely on the movement of a fluid across the top of the sensing plane. To apply such a flow, the two different 3D printed housings were designed to fit over the top of both chips. The 3D printed

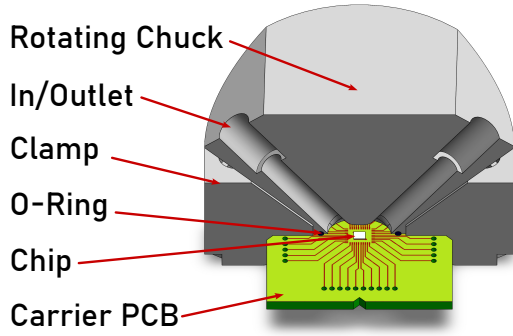


Figure 3: Schematic of the rotational anemometry measurement housing with PCB.

components were all made using immersion printing (Elegoo 16k Saturn 4 Ultra), with Phrozen 8K aqua resin.

The 3D printed measurement housing for the anemometric chips is made in two parts, the aforementioned clamp (Figure 2) and the rotating chuck [5, 7]. The carrier PCB of the anemometers is used as one of the sidewalls of the housing's fluidic cavity. The central cavity of the rotating chuck is placed over the top of the planar sensor (Figure 3), creating a seal with the carrier PCB by means of an o-ring. This allows for the 3D printed chuck to be rotated, which changes the direction of the airflow over the top of the different anemometers.

The housing of the viscous flow chip consists of three 3D printed parts, as well as the chip and the readout-PCB (Figure 4). The central component is the fluidic chuck, which has a fluidic channel connected to an in- and output. The chip is pressed against the fluidic chuck by the chip clamp using four tightening bolts. This seals the fluidic channel, making the chip a part of the housing. Between the chip and the fluidic chuck

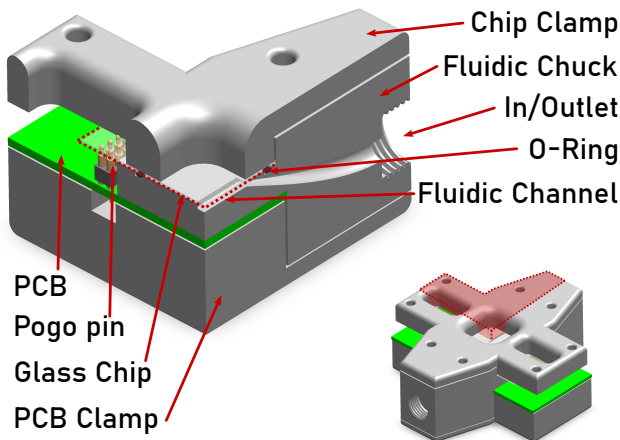


Figure 4: 3D printed viscous flow test set up. The central cavity is sealed by the glass chip. The PCB serves as a representation, as different PCB layouts are possible.

is an o-ring that prevents any leakage. The readout-PCB slots into the back of the fluidic chuck, and is held in place by the PCB-chuck. Once tightened, the PCB makes contact with the chip using the pogo pin strips.

FLUIDIC RESISTANCE

Different microfluidic technologies have different lengthscales and therefore have differing typical fluidic resistance values. The fluidic resistance (R_f) is proportional to the length of the channel (L) and inversely proportional to the hydraulic diameter of the channel (D_h). The fluidic resistance is also proportional to the Reynolds number of a given flow (Re):

$$R_f \propto \frac{Re \cdot L}{D_h}.$$

At a fixed flow rate, the hydraulic pressure varies with the viscosity of the fluid as Re is inversely proportional to the dynamic viscosity. The typical length scales of different microfluidic processes are summarised in Table 1. In Figure 5, the typical fluidic resistance of different microfluidic technologies is given as a function of viscosity.

Technology	D_h & L [mm]
CMOS metallisation	0.012
SCT	0.2
Glass	0.5
Viscous	2
Rotational	10

Table 1: Typical values for the hydraulic diameter and the channel lengths for microfluidic channels in CMOS microfluidics [8], Surface Channel Technology (SCT) [4], Glass [9], and for the 3D printed housing in this work.

For the anemometric rotational setup, the fluidic resistance should be as low as possible. A fluidic resis-

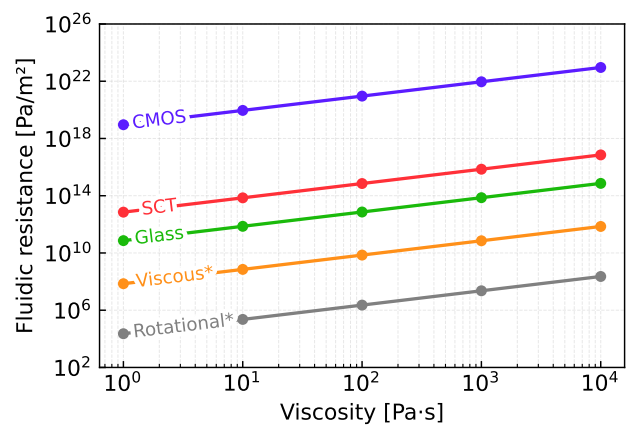


Figure 5: Typical fluidic resistance of different microfluidic technologies calculated from typical feature sizes. The viscosity ranges from the viscosity of air to typical values for honey. (*) 3D printed housings in this work.

tance that is too high would cause the air to compress, which would significantly change the thermal properties of the air. This would occur if, for a given flow rate, the flow speed would exceed around 100 m s^{-1} [10]. As the housing is designed to imitate open air flow, it is important not to compress the air significantly beyond atmospheric conditions.

The viscous housing and fluidic channel provide the second-lowest fluidic resistance over the viscosity range. This is especially relevant for highly viscous fluids such as honey. The hydraulic diameter can be reduced to the order of a few tens of micrometers, where low mass flows and analyte quantities are sought after.

DISCUSSION

The 3D printed housings presented in this work play an important role in early sensor development as well as rapid prototyping during fabrication.

The 3D printed rotational anemometer measurement housing has made it possible to measure and characterise different 2D anemometers over a 360° range. Without such a housing the sensors would have been measured in an academic or commercial wind tunnel, which would have incurred significant costs. In addition, the 3D printed rotational housing allows for different gases and automated measurement (the latter of which has indeed been done [5, 7]).

The 3D printed viscous fluid flow measurement housing provides a hybrid fabrication method for microfluidics. This hybrid fabrication assembly removes the need for a lengthy cleanroom fabrication process for the validation of a novel sensor, allowing for rapid prototyping of different channel diameters [11, 12]. The flexibility of the 3D printing technique paired with a straightforward cleanroom fabrication provides an attractive platform for the further development of microfluidic sensing techniques.

CONCLUSION & OUTLOOK

The interface between 3D printing and sensing technology is leveraged for the testing and development of thermal and mechanical wind and flow sensors. By keeping the microfabrication simple and using 3D printing for test set-ups, packaging and development, and early research can proceed at a rapid pace, minimising the risks of failed fabrication runs. This increases the likelihood of detecting problems early in the development of fluidic sensors.

CONTACT

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MICRO FLOWMETER WITH EXTENDED FLOW RANGE USING THE CTA PRINCIPLE FOR LAB-ON-A-CHIP APPLICATIONS

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ABSTRACT

An micro liquid flow sensor with an constant temperature anemometry measurement principle has been realised. The sensor is manufactured with surface channel technology. This consist of two suspended channels with two platinum resistors on each channel. This sensor is developed with lab-on-a chip application in mind. Therefore the sensor requirements are to measure flow up to 6 g/h and has a maximum pressure drop of 2 bar. Using one channel as the sensing part and the other as the heating element which was combined with an PID control loop, a Flow up to 20 g/h could be measured.

KEYWORDS

Micro Flow Sensor, Lab-On-A-Chip, Anemometry, Modular design, Organ-on-Chip

INTRODUCTION

Microfluidic flow sensing is an increasingly important technology within lab-on-a-chip and organ-on-chip environments. As these platforms continue to expand and integrate additional functionalities, accurate measurement and control of liquid flow become increasingly critical. Due to the small scale of these systems, the required flow rates are typically very low, generally in the range of 10 to 100 $\mu\text{L}/\text{min}$ for water, corresponding to approximately 6 g/h [1]. Furthermore, many applications involve biological materials, which impose an operating temperature constraint below 42°C [2]. Within the NXTGEN BioMed 3 a modular organ-on-chip system is being developed, in which components include pumps, flow sensors and biological testing sensors. For this modular application a dedicated flow sensor module is realised. To address these requirements, a thermal flow sensor based on Surface Channel Technology was investigated for this use case. Due to the overall system constraints, the flow module is limited to a size of 15x15 mm. This sensor architecture is shown in figure 1.

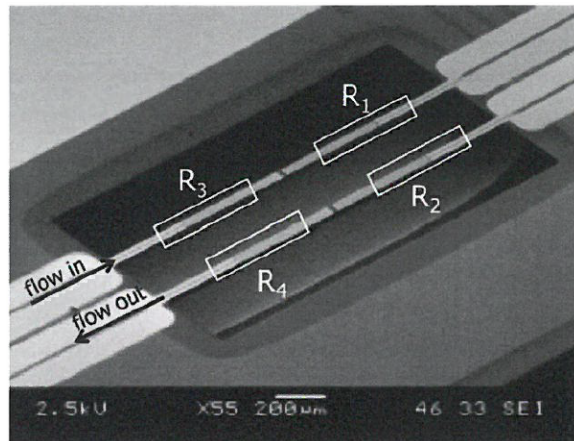


Figure 1: SEM image of the Surface Channels architecture used in the sensor [3]

Conventionally, the flow sensor operates according to a calorimetric measurement principle. While this approach is well suited for gas flow sensing, the significantly higher heat capacity of liquids results in a reduced and shifted operational flow range. To enable the same sensor to operate effectively within the desired low-flow range for liquid media, an alternative measurement principle was applied. Constant Temperature Anemometry (CTA) was implemented, in which a constant temperature difference between the upstream and downstream regions of the sensor is maintained. By adjusting this temperature difference, the operational flow range and sensitivity of the sensor can be tailored to the application requirements. In the case of the modular organ-on-chip platform the flow range should be within 0 to 6 g/h, and the pressure drop across the flow sensor should not exceed 2 bar.

METHODOLOGY

Firstly an experimental setup was realized to determine if the surface channel sensor could be applied in this setting. The experimental setup consisted of a Memmert IPP55 incubator, a Keithley DAQ6510 data acquisition unit, a Keithley 2500 Source Measurement Unit (SMU), a Bronkhorst High-Tech EL-PRESS pressure controller, a Bronkhorst High-Tech Mini Cori-Flow flow controller, and an INACOM Instruments degasser. The setup is shown in figure 2, with the schematic of the fluidic circuit.

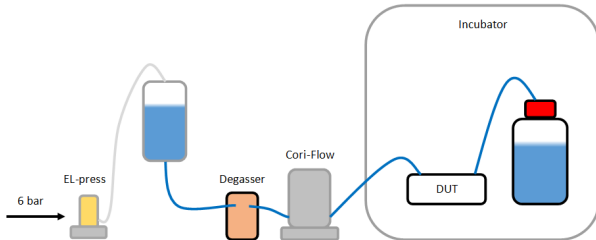
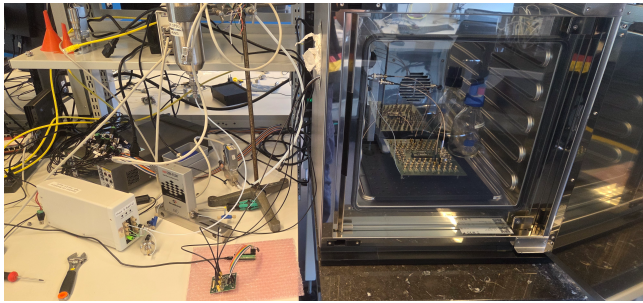


Figure 2: The top image shows the actual measurement setup. With underneath a schematic version of the measurement setup.

The Device Under Test (DUT) was placed inside the incubator to ensure a controlled ambient temperature. Deionized water (H_2O) was stored in a pressure vessel, with the EL-PRESS regulating the applied pressure. Prior to entering the DUT, the liquid was degassed to prevent bubble formation. The Mini Cori-Flow was used to control and measure the flow rate.

Initially the exploratory measurements were performed with a python script with a PID control loop. This loop regulated the output power of the Keithley SMU set to the heater. This was done to maintain a defined temperature difference of between the up and downstream elements. These measurements showed a measurable range above the desired 6 g/h. Tuning this temperature difference allows for optimizing the measurement range. By selecting a low temperature difference, this influences the lower range measurements by creating a low signal to noise ratio. Therefore when the measurement a lower flow range, a higher temperature difference is preferable.

After the initial measurements were performed and gave clarity in the feasibility of the measuring method. The step towards building a flow sensor module could be taken. Using this knowledge an intermediate control PCB was created. This PCB was designed to still be versatile so different sensor design could still be measured, while maintaining the same measurement principle. This intermediate PCB contained a small control loop for the heating element. Using this method the sensor had to be characterized for the specified operating parameters.

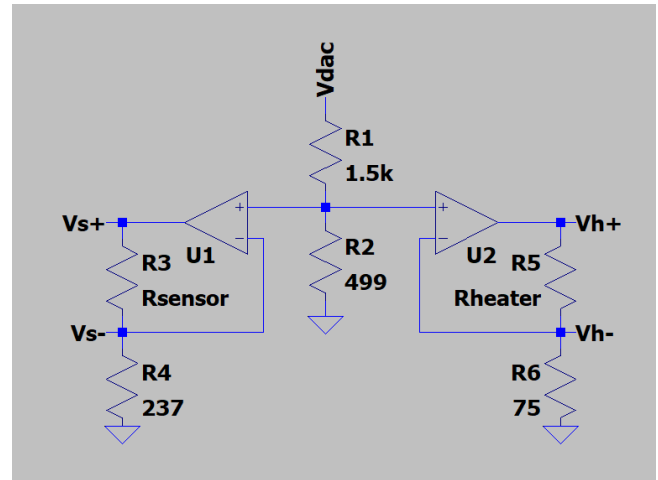


Figure 3: Schematic overview of the control circuit used on the intermediate PCB.

The DAC voltage goes to a resistor divider to get a voltage in the range of 0 to 0.625V. Then, this voltage is mirrored onto the shunt resistors by the operational amplifiers, setting the current in both branches. The shunt resistor in the heater branch is chosen such that the current goes up to 8mA. The resistor in the sensor branch is then chosen such that the power in the sensor is approximately 1/10th of the power in the heater branch.

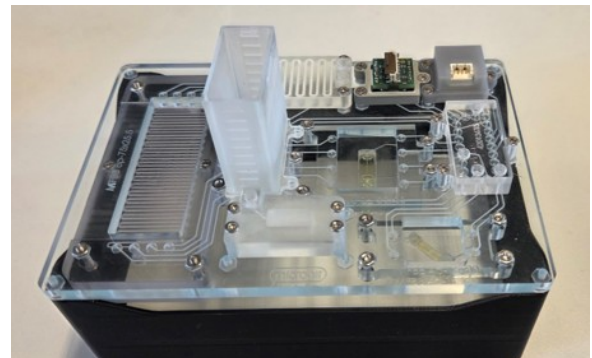


Figure 4: Prototype of the demonstrator resulting from the NXTGEN hightech Biomed3 project. Where in the top right corner a flow sensor and pump module are present.

Finally to create the flow sensor module for the demonstrator as seen in figure 4, a fluidic adapter was designed which enables a connection between the in and outlets on the demonstrator and the sensor. A PCB stack was created to allow for controlling via the intermediate control PCB. The module is seen in figure 5, where the transparent bottom is the fluidic adapter and the PCB stack with connector is visible on top.

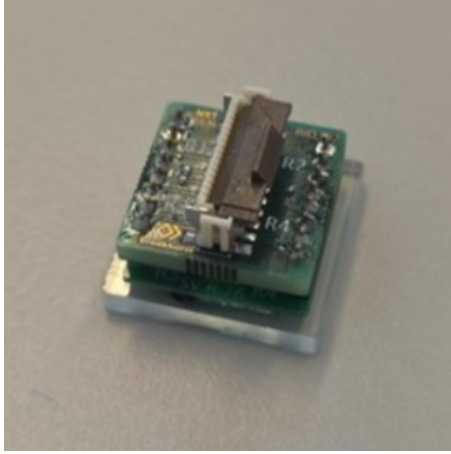


Figure 5: Assembled flow sensor module which can operate on the modular platform.

RESULTS

Initial experiments were conducted exclusively using H_2O as the working fluid. The resulting measurements are shown in Figure 6. These results demonstrate a practical operational flow range extending to at least 20 g/h, which significantly exceeds the target range of 6 g/h for lab-on-a-chip applications. This range was achieved while maintaining a temperature difference of only $1^\circ C$ between the upstream and downstream sensor elements, ensuring compliance with biological temperature constraints. By adjusting the temperature difference, the sensitivity of the sensor can be optimized for a specific flow range or fluid medium. This effect is illustrated in Figure 7, where a higher temperature difference of $5^\circ C$ was applied while measuring isopropyl alcohol (IPA), resulting in enhanced sensitivity.

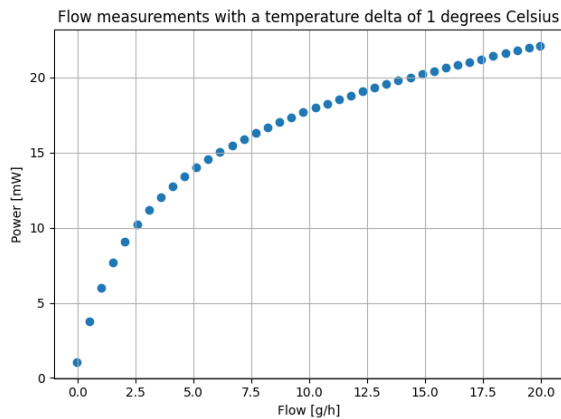


Figure 6: The result of the first measurement with H_2O . Where the temperature delta is set to 1 degrees Celsius.

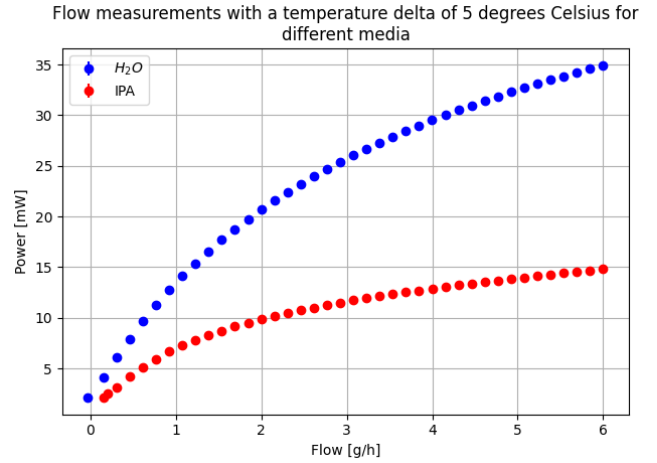


Figure 7: The result of measuring different media's through the sensor with the same actuation settings. In this measurement the temperature delta was set to 5 degrees Celsius.

Due to the different environmental applications the flow sensor was also tested at different temperatures. These temperatures are selected to be above the desired working temperatures of the resulting modular setup.

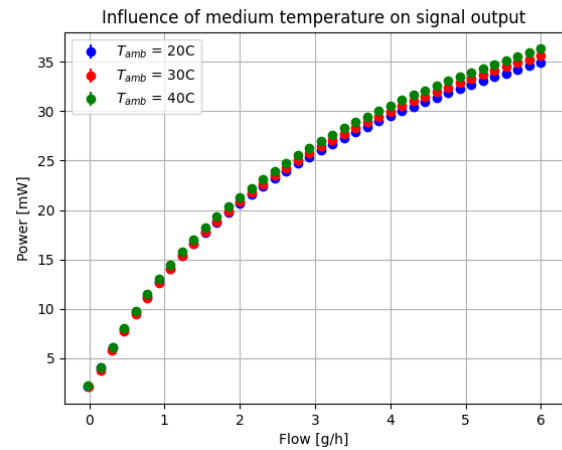


Figure 8: Difference in signal output due to the temperature of the medium flowing through the sensor.

These results show slight deviation at the higher flow speed of 6 g/h, this difference is around 3%.

Following these preliminary results, a stability and reproducibility assessment was conducted with an temperature setpoint of 3 degrees Celcius. The corresponding results are presented in Figure 9. The measurements exhibit an error within 1% full scale. This error was determined from experiments in which the flow setpoints were applied in a randomized order to assess repeatability. The marker color indicates temporal progression throughout the measurement sequence, with purple representing the start of the experiment and yellow indicating the final measurements.

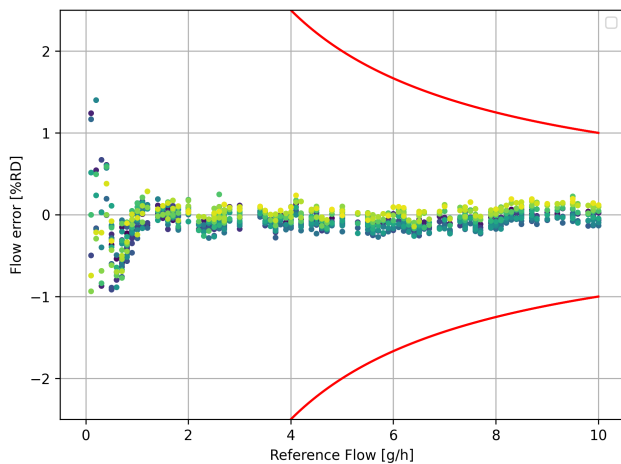


Figure 9: Error reading full scale, where the purple markers show the beginning of the measurement, this transitions to yellow which marks the end of the measurement.

CONCLUSION

This study demonstrates the feasibility of applying a thermal flow sensor based on Surface Channel Technology for low-flow liquid sensing in lab-on-a-chip applications. By employing Constant Temperature Anemometry, the operational flow range and sensitivity of the sensor can be effectively adapted to accommodate liquids while maintaining biologically compatible temperature limits. Experimental results confirm reliable operation well beyond the targeted flow range of 6 g/h, even at small temperature differences. An flow sensor module was realized for the demonstrator in the NXTGEN BioMed 3 project. Furthermore, the ability to tune the temperature differential allows optimization of sensor performance for different fluids, highlighting the versatility of the proposed approach for microfluidic flow measurement.

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ANALYTICAL RESPONSE ANALYSIS FOR THE DESIGN OF CALORIMETRIC THERMAL FLOW SENSORS

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Introduction

Measuring inline fluid flow rates is essential in various fields, for example, in lab-on-a-chip, liquid chromatography, the semiconductor industry, and flow chemistry. This work focuses on calorimetric thermal flow sensors. These sensors have the advantage of a high sensitivity in the low flow range, the ability to detect the flow direction, and the sensor response scaling proportionally with the specific heat of the fluid, given that the fluid is fully heated through in the radial direction. To aid the design of calorimetric thermal flow sensors, accurate analytical models are important.

A number of analytical models have been reported [1–6]. The models in [1,4,6] use boundary conditions which prevent heat from exiting the sensor. Additionally, the models in [4,6] do not model the temperature distribution at the heater section. In [2,3], the derivation of the model and the boundary conditions are not discussed. Moreover, all models [1–6] assume infinitely small temperature sensors, i.e. single points, and do not derive the linear approximation for small mass flow rates, as presented in textbooks [7,8].

This work proposes a complete analytical model with an explicit derivation to aid future flow sensor designs and to provide more insight into the operating principle of flow sensors. The Model section shows the derivation of the model, and the Results section analyses the effect of the model parameters on the sensor response.

Model

A typical calorimetric thermal flow sensor consists of two temperature sensors located symmetrically up- and downstream of a central heater element. The response of a calorimetric thermal flow sensor is obtained by taking the temperature difference between the up- and downstream temperature sensors. The governing differential equation is derived by studying the heat flux balance in a channel segment with length dx , as shown in Figure 1a. To analyse the operating principle of a calorimetric thermal flow sensor, the differential equation is applied to an infinitely long channel with three consecutive channel sections, as shown in Figure 1b. The heater section (②) has finite length l_h and the upstream (①) and downstream (③) sections have finite lengths l_T . The derivation is based on the work of Jouwsma [2,3]. In this work, the derivation—including the boundary conditions—is provided, and the model allows for $l_h \neq l_T$. Three assumptions are made: the flow is laminar, there is no temperature gradient in the y -direction—i.e. the thermal contact between the channel wall and the fluid is ideal—and the thermal conduction in the x -direction is dominated by the conduction in the channel wall.

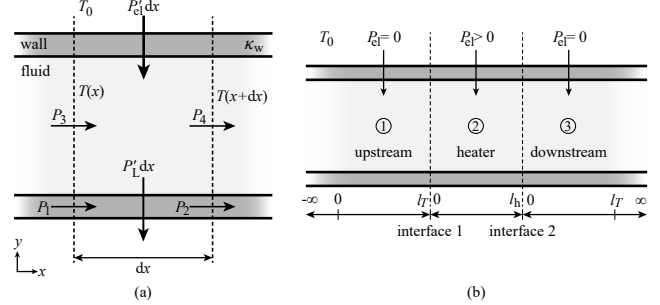


Figure 1: Heat balance of a channel segment with length dx (a) and an infinitely long channel with three channel sections (b), in which the temperature sensors in sections ① and ③ have length l_T and the heater section has length l_h . The thermal conductivity of the channel wall is κ_w .

Table 1: Meaning of the symbols and their units.

P	power	[mW]
T	temperature	[K]
c_p	specific heat capacity	[J/(kg·K)]
ϕ	mass flow rate	[kg/s]
κ_w	thermal conductivity, channel wall	[W/(m·K)]
$A_{c,w}$	cross-sectional area, channel wall	[μm^2]
Λ	heat loss parameter per unit length	[W/(m·K)]
l	length	[mm]

The symbols are defined in Table 1. From Fig. 1a, we obtain the heat balance:

$$P'_{el} dx = \underbrace{(P_2 - P_1)}_{\Delta P_w} + \underbrace{(P_4 - P_3)}_{\Delta P_f}, \quad (1)$$

where P'_{el} is the electrical input power per unit length, ΔP_w is the conduction through the channel wall defined as:

$$\Delta P_w = -\kappa_w A_{c,w} \left[\frac{dT(x+dx)}{dx} - \frac{dT(x)}{dx} \right] = -\kappa_w A_{c,w} \frac{d^2 T}{dx^2} dx. \quad (2)$$

P'_L is the heat loss per unit length:

$$P'_L = \Lambda(T(x) - T_0), \quad (3)$$

where Λ is the heat loss coefficient per unit length and T_0 the ambient temperature.

ΔP_f is the heat transport in the fluid:

$$\Delta P_f = c_p \phi [T(x+dx) - T(x)] = c_p \phi \frac{dT}{dx} dx. \quad (4)$$

Substituting Eq. 2 to 4 into Eq. 1 yields:

$$\frac{d^2 T}{dx^2} - \underbrace{\frac{c_p \phi}{\kappa_w A_{c,w}}}_{\alpha} \frac{dT}{dx} - \underbrace{\frac{\Lambda}{\kappa_w A_{c,w}}}_{\beta^2} (T - T_0) + \frac{P'_{el}}{\kappa_w A_{c,w}} = 0. \quad (5)$$

For concision, we introduce two parameters: α , which is directly proportional to the mass flow rate and for which $\alpha \geq 0$ holds, and β^2 for which $\beta > 0$ holds. Eq. 5 is an ordinary differential equation with the solution:

$$T - T_0 = C_1 e^{\lambda_1 x} + C_2 e^{\lambda_2 x} + \frac{P'_{el}}{\Lambda}, \quad (6)$$

where:

$$\lambda_{1,2} = \frac{\alpha}{2} \pm \beta \sqrt{1 + \left(\frac{\alpha}{2\beta}\right)^2}. \quad (7)$$

This result is the general solution to the situation of Fig. 1a. Additionally, since $\beta > 0$, Eq. 7 yields that $\lambda_1 > 0$ and $\lambda_2 < 0$, always.

Fig. 1b is used to apply the solution to the configuration of a calorimetric thermal flow sensor. This configuration yields a set of three temperature distributions for sections ①, ②, and ③, respectively:

$$T_1 - T_0 = A_1 e^{\lambda_1 x} + B_1 e^{\lambda_2 x}, \quad (8)$$

$$T_2 - T_0 = A_2 e^{\lambda_1 x} + B_2 e^{\lambda_2 x} + \frac{P'_{el}}{\Lambda}, \quad (9)$$

$$T_3 - T_0 = A_3 e^{\lambda_1 x} + B_3 e^{\lambda_2 x}. \quad (10)$$

To obtain an expression for each of the six constants (A_{1-3} and B_{1-3}), we need six boundary conditions. Since sections ① and ③ are infinitely long, temperatures T_1 and T_3 must decay to T_0 . Taking the limits to $\pm\infty$ yield the first two boundary conditions:

$$\lim_{x \rightarrow -\infty} T_1 - T_0 = 0 \Rightarrow B_1 = 0, \quad (11)$$

$$\lim_{x \rightarrow \infty} T_3 - T_0 = 0 \Rightarrow A_3 = 0. \quad (12)$$

To find the remaining four coefficients, we use four continuity boundary conditions. At both interfaces we have a condition for the continuity of the temperature T and a condition for the continuity of the heat flux dT/dx . At interface 1 we have:

$$T_1 - T_0 \Big|_{x=l_T} = T_2 - T_0 \Big|_{x=0} \Rightarrow A_1 e^{\lambda_1 l_T} = A_2 + B_2 + \frac{P'_{el}}{\Lambda}, \quad (13)$$

$$\begin{aligned} \frac{d}{dx} (T_1 - T_0) \Big|_{x=l_T} &= \frac{d}{dx} (T_2 - T_0) \Big|_{x=0} \\ &\Rightarrow A_1 \lambda_1 e^{\lambda_1 l_T} = A_2 \lambda_1 + B_2 \lambda_2. \end{aligned} \quad (14)$$

Similarly, at interface 2 we have:

$$\begin{aligned} T_2 - T_0 \Big|_{x=l_h} &= T_3 - T_0 \Big|_{x=0} \\ &\Rightarrow A_2 e^{\lambda_1 l_h} + B_2 e^{\lambda_2 l_h} + \frac{P'_{el}}{\Lambda} = B_3, \end{aligned} \quad (15)$$

$$\begin{aligned} \frac{d}{dx} (T_2 - T_0) \Big|_{x=l_h} &= \frac{d}{dx} (T_3 - T_0) \Big|_{x=0} \\ &\Rightarrow A_2 \lambda_1 e^{\lambda_1 l_h} + B_2 \lambda_2 e^{\lambda_2 l_h} = B_3 \lambda_2. \end{aligned} \quad (16)$$

The set of Eq. 13 - 16 can be solved, yielding:

$$A_1 = \frac{P'_{el} \lambda_2}{\Lambda(\lambda_1 - \lambda_2)} (e^{-\lambda_1 l_h} - 1) e^{-\lambda_1 l_T}, \quad (17)$$

$$A_2 = \frac{P'_{el} \lambda_2}{\Lambda(\lambda_1 - \lambda_2)} e^{-\lambda_1 l_h}, \quad (18)$$

$$B_2 = \frac{-P'_{el} \lambda_1}{\Lambda(\lambda_1 - \lambda_2)}, \quad (19)$$

$$B_3 = \frac{P'_{el} \lambda_1}{\Lambda(\lambda_1 - \lambda_2)} (1 - e^{\lambda_2 l_h}). \quad (20)$$

For the calorimetric readout, we need the temperature difference between the up- and downstream sections. The temperature sensors are located around the heater section and have finite length l_T , as indicated in Fig. 1. We can calculate the difference between the averages of the recorded temperature increase relative to ambient:

$$T_{31} = \overline{T_3 - T_0} \Big|_{x=0}^{x=l_T} - \overline{T_1 - T_0} \Big|_{x=0}^{x=l_T}, \quad (21)$$

where:

$$\begin{aligned} \overline{T_3 - T_0} \Big|_{x=0}^{x=l_T} &= \frac{1}{l_T} \int_0^{l_T} B_3 e^{\lambda_2 x} dx \\ &= \frac{P'_{el}}{\Lambda \lambda_2 l_T} \frac{-\lambda_1}{\lambda_1 - \lambda_2} (1 - e^{\lambda_2 l_h})(1 - e^{\lambda_2 l_T}), \end{aligned} \quad (22)$$

$$\begin{aligned} \overline{T_1 - T_0} \Big|_{x=0}^{x=l_T} &= \frac{1}{l_T} \int_0^{l_T} A_1 e^{\lambda_1 x} dx \\ &= \frac{P'_{el}}{\Lambda \lambda_1 l_T} \frac{-\lambda_2}{\lambda_1 - \lambda_2} (1 - e^{-\lambda_1 l_h})(1 - e^{-\lambda_1 l_T}). \end{aligned} \quad (23)$$

Substituting Eq. 22 and 23 into Eq. 21 gives the expression:

$$\begin{aligned} T_{31} &= \frac{-P'_{el}}{\Lambda(\lambda_1 - \lambda_2) l_T} \left[\frac{\lambda_1}{\lambda_2} (1 - e^{\lambda_2 l_h})(1 - e^{\lambda_2 l_T}) \right. \\ &\quad \left. - \frac{\lambda_2}{\lambda_1} (1 - e^{-\lambda_1 l_h})(1 - e^{-\lambda_1 l_T}) \right]. \end{aligned} \quad (24)$$

Since the calorimetric response of a thermal flow sensor is in the lower flow regime, we examine the effect of small mass flow changes to the zero flow scenario. Therefore, we linearise the four exponent terms in Eq. 24 by using a Taylor expansion up to the third order and we expand the brackets:

$$(1 - e^{-\lambda_2 l_h})(1 - e^{-\lambda_2 l_T}) = \lambda_2^2 l_h l_T + \frac{1}{2} \lambda_2^3 l_h l_T (l_h + l_T) + \mathcal{O}(\lambda_2^4), \quad (25)$$

$$(1 - e^{-\lambda_1 l_h})(1 - e^{-\lambda_1 l_T}) = \lambda_1^2 l_h l_T - \frac{1}{2} \lambda_1^3 l_h l_T (l_h + l_T) + \mathcal{O}(\lambda_1^4). \quad (26)$$

Eq. 25 and 26 are inserted into Eq. 24 to obtain the approximation:

$$\tilde{T}_{31} = \frac{-P'_{el}}{2\Lambda(\lambda_1 - \lambda_2)l_T} \lambda_1 \lambda_2 (\lambda_1 + \lambda_2) l_h l_T (l_h + l_T). \quad (27)$$

For small changes in mass flow, heat loss is considered dominant. Hence, we assume $\alpha \ll \beta$. This implies:

$$\lambda_1 \approx \frac{\alpha}{2} + \beta, \quad \lambda_2 \approx \frac{\alpha}{2} - \beta, \quad \lambda_1 - \lambda_2 = 2\beta, \\ \lambda_1 + \lambda_2 = \alpha, \quad \lambda_1 \lambda_2 \approx -\beta^2. \quad (28)$$

Inserting these approximations into Eq. 27 gives:

$$\tilde{T}_{31} = \frac{1}{4} (l_h + l_T) \frac{\beta}{4\Lambda} P'_{el} l_h \alpha. \quad (29)$$

Using the definitions of α , β , and the total input power $P_{el} = P'_{el} l_h$, we obtain an approximation for small mass flow rates:

$$\tilde{T}_{31} = \gamma P_{el} c_p \phi, \quad \gamma = \frac{l_h + l_T}{4\kappa_w A_{c,w} \sqrt{\Lambda \kappa_w A_{c,w}}}, \quad (30)$$

where γ is a constant that includes the geometric and thermal properties of the sensor. The linear approximation yields two notable results. Firstly, a calorimetric thermal flow sensor has a linear response for small mass flow rates. Secondly, the specific heat capacity can be used as a conversion factor to adjust the sensor response for different fluids and fluid mixtures.

Results

Figure 2 plots the normalised temperature distribution in the three sections for six different flow rates, including zero flow, for the parameter values provided in Table 2. Two observations are made regarding the flow range. Firstly, for increasing flow rates, the temperature in the heater section

reduces. This causes the temperature difference between ③ and ① to decrease as well, limiting the flow range. Secondly, for large flow rates, the temperature recorded in ① reaches 0, from which the sensor effectively becomes an anemometric thermal flow sensor. Hence, yielding the maximum flow range if the heater temperature is not maintained.

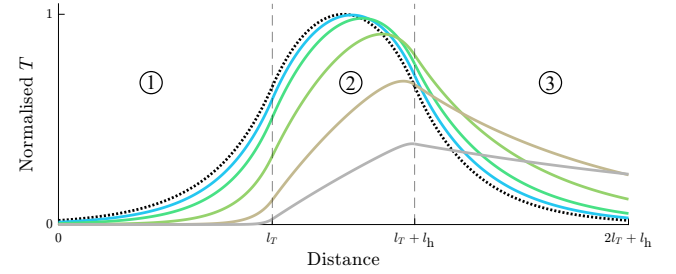


Figure 2: Normalised plots of: $T_1 - T_0$ (Eq. 8), $T_2 - T_0$ (Eq. 9) shifted by l_T , and $T_3 - T_0$ (Eq. 10) shifted by $l_h + l_T$ at zero flow (dotted curve) and for five logarithmically increasing mass flow rates (light blue to grey curves).

Table 2: Adopted model parameter values.

Parameter	Value	
l_h	1	[mm]
l_T	1.5	[mm]
c_p	4180	[J/(kg·K)]
κ_w	8	[W/(m·K)]
A	$\pi(95^2 - 87^2)$	[μm^2]
Λ	0.2	[W/(m·K)]
P'_{el}	1	[mW/mm]

Fig. 3a shows the normalised temperature difference T_{31} for various values of the wall conduction parameter $\kappa_w A_{c,w}$. The thermal conduction through the wall opposes the convective component, hence the minus sign in Eq. 2. Increasing the wall conduction results in higher temperatures at sections ① and ③ for zero flow. Therefore, a larger convective component is needed to reduce the temperature to 0 in section ①, yielding a larger flow range. However, a trade-off occurs in the sensitivity of the sensor, as the heat flux through the channel wall disperses the temperature profile. Fig. 3b shows a zoom in to compare the exact analytical solution to the linear approximation $\tilde{T}_{31}$ up to 10% deviation.

Similarly, Fig. 3c and Fig. 3d show the normalised T_{31} for six different values of the heat loss coefficient Λ and a zoom in to evaluate the linear approximation. Since the heat loss scales with the temperature difference, the effect of the value of Λ is comparable to that of the wall conduction parameter: a trade-off between sensitivity and flow range. However, since the analytical model is based on the assumption that there is no temperature gradient in the y-direction, for large P_L —which is defined in the y-direction—the model becomes less accurate. Moreover, in practice, the heat loss cannot be tuned independently from the wall conduction. Large heat losses to the environment also spread out in the x-direction,

which reduces the sensitivity significantly and increases the power consumption.

In addition, Fig. 3e and Fig. 3f show the normalised T_{31} for six different values of the electrical input power per unit length P'_{el} and a zoom in to plot the linear approximation. The value of P'_{el} affects the sensitivity linearly.

Furthermore, the thermal contact between the channel wall and the fluid should be maximal to maintain a minimal vertical temperature gradient and hence the largest flow range.

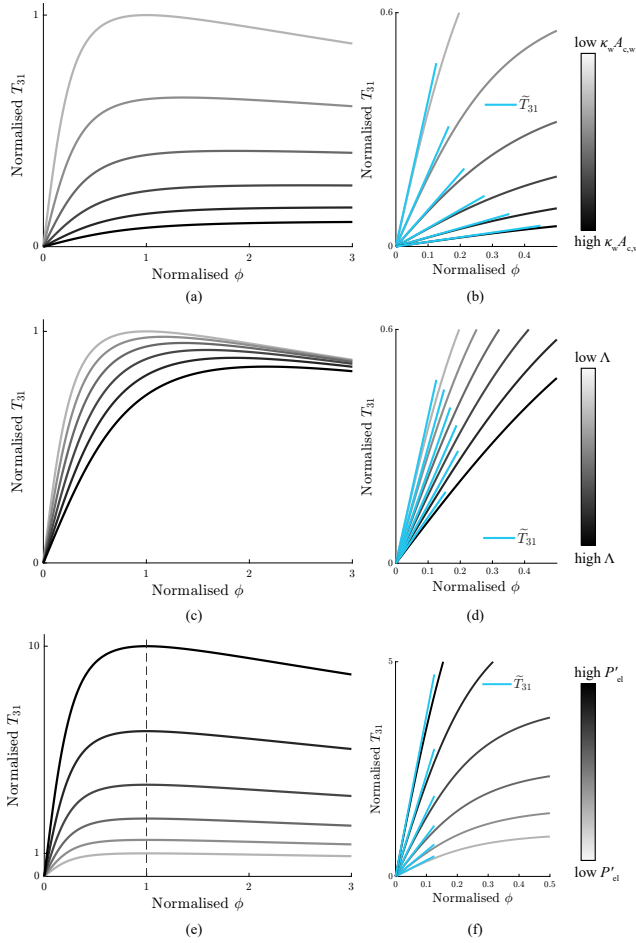


Figure 3: Normalised plots of T_{31} (Eq. 24) for six values of $\kappa_w A_{c,w}$ (a), Λ (c), and P'_{el} (e), with a zoom in for comparison with the linear approximation $\tilde{T}_{31}$ (Eq. 30) in (b), (d), and (f), respectively. The values of $\kappa_w A_{c,w}$, Λ , and P'_{el} are varied logarithmically by one order of magnitude. The curves are normalised to the maximum of T_{31} of the lightest curve. The linear approximation is plotted up to 10% deviation from T_{31} . Note, the lightest curves in Fig. 3a, Fig. 3c, and 3e are identical. Furthermore, the vertical dashed line indicates the maximum T_{31} , which holds for each curve in Fig. 3e.

Conclusion and outlook

This work reports on the analytical response analysis for the design of calorimetric thermal flow sensors. The assumptions and the boundary conditions of the model are explicitly stated, and a complete mathematical derivation is presented. The sensor model averages the temperature over a given, non-zero temperature sensor length. Moreover, the model describes the temperature distribution at the heater section and allows the heater length to be set independently of the length of the temperature sensors. Through the analytical analysis it is possible to visualise the effect of individual model parameters on the sensor response: the values of $\kappa_w A_{c,w}$ and Λ show a similar trade-off between the flow range and the sensitivity, whereas P'_{el} only affects the sensitivity. The analytical model can be used to gain more insight into the operating principle of calorimetric thermal flow sensors and can help to optimise the sensor performance for specific applications.

For future work, the model can be extended to allow for dissimilar lengths of the temperature sensors. Furthermore, asymmetrical positions of the temperature sensors are possible when choosing the upper and lower bounds of the integral away from the heater section. However, these additions can make the model significantly more complex.

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INVESTIGATION OF DAMPING MECHANISMS IN A MICRO CORIOLIS MASS FLOW SENSOR FOR VISCOSITY SENSING USING QUALITY FACTOR ANALYSIS

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ABSTRACT

This work investigates quality-factor (Q) analysis of a micro Coriolis mass flow sensor for viscosity sensing. Pressure-dependent measurements characterize air damping, while liquid-filled channel measurements reveal additional fluid-related damping. Experiments with water, IPA, and acetone show Q variations consistent with the expected influence of viscosity. The results demonstrate the potential of Q-factor analysis to extend micro Coriolis sensors toward simultaneous mass flow, density, and viscosity measurement.

KEYWORDS

Micro Coriolis mass flow sensor; quality factor; viscosity sensing; microfluidics

INTRODUCTION

Accurate characterization of fluid properties is essential in applications such as process monitoring, flow chemistry, and lab-on-chip systems. In addition to mass flow rate and density, viscosity provides important information on fluid composition and state. Simultaneous measurement of these properties within a single sensing platform can therefore provide a more comprehensive characterization of a fluid while reducing the need for multiple independent sensors.

Micro Coriolis mass flow sensors are particularly attractive for multi-parameter fluid sensing because they combine fluid transport and mechanical resonant sensing within a single suspended microchannel structure [1]. Mass flow rate can be determined from the Coriolis response generated by fluid flowing through the vibrating channel, while fluid density can be derived from the density-dependent resonance frequency. Extending the same sensing channel toward viscosity measurement would enable mass flow rate, density, and viscosity to be obtained using a single microfluidic resonator.

One potential approach is to extract fluid viscosity information from the quality factor (Q) of the fluid-filled resonator [2]. However, Q is not determined by viscosity alone, but by the combined energy dissipation arising from air damping, intrinsic losses, and fluid-related damping [3]. Furthermore, changes in fluid density affect the effective mass of the resonator and consequently affect Q. Therefore, the individual contributions to the measured quality factor must first

be understood before Q can be quantitatively related to viscosity.

In this work, the damping behavior of a micro Coriolis mass flow sensor is investigated through pressure-dependent and liquid-dependent Q measurements. Pressure sweeps are first used to characterize and suppress air damping, followed by liquid-filled measurements to investigate fluid-related energy dissipation. A simplified mass-loading model is subsequently used to estimate the contribution of fluid density, providing a basis for evaluating the remaining Q variation as a potential indicator of viscosity-dependent damping.

PRINCIPLE OF THE MICRO CORIOLIS MASS FLOW SENSOR

The micro Coriolis mass flow sensor consists of a suspended fluidic microchannel with two relevant vibration modes: an actuation (twist) mode and a detection (swing) mode. During operation, the channel is actively driven in the twist mode. As illustrated in Figure 1, when fluid with a mass flow rate ($\vec{\Phi}_m$) flow through the vibrating channel, the combination of the fluid motion and the angular velocity ($\vec{\omega}_{act}$) of the channel generates a Coriolis force ($\vec{F}_C$) perpendicular to the actuation motion. For the rectangular channel geometry, the Coriolis force is given by

$$\vec{F}_C = -2L_x(\vec{\omega}_{act} \times \vec{\Phi}_m)$$

where L_x is the channel length perpendicular to the rotational axis [3]. The Coriolis forces acting on opposite sides of the channel generate a secondary vibration of the suspended structure, corresponding to the detection or swing mode. Since the magnitude of the Coriolis response is directly proportional to the mass flow rate, the twist mode provides the primary actuation while the swing mode enables mass flow detection (Figure 2).

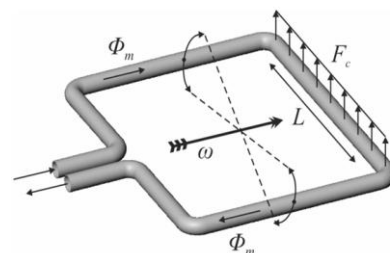


Figure 1: Operating principle of the micro Coriolis mass flow sensor, showing the twist actuation, fluid mass flow, and resulting Coriolis force.

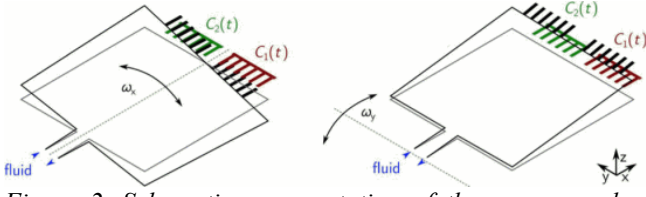


Figure 2. Schematic representation of the sensor modes. Left: Actuation/twist mode. Right: Detection/swing mode [4].

In addition to mass flow measurement, the resonant behavior of the suspended channel provides information on fluid properties. Filling the channel with different fluids can change its effective mass and consequently shift its resonance frequency, which can be used to determine fluid density. The resonator can be approximated as a second-order mass-spring-damper system,

$$M\ddot{x} + D\dot{x} + kx = F$$

with the quality factor expressed as

$$Q = \frac{\sqrt{m_{eff}k}}{c_{eff}} = \frac{m_{eff}\omega_0}{c_{eff}}$$

where m_{eff} , k , c_{eff} , and ω_0 are the effective mass, stiffness, effective damping coefficient, and resonance angular frequency, respectively.

In this work, the quality factor of the twist mode is investigated under zero-flow conditions, allowing the damping behavior of the resonator to be studied independently of the Coriolis-induced swing response. Fluid density influences Q through mass loading, whereas viscosity is expected to contribute to fluid-related energy dissipation and therefore to c_{eff} . The measured damping additionally contains contributions from the surrounding gas and intrinsic losses of the resonator. Separating these contributions is therefore necessary before estimating fluid viscosity by changes in Q .

SENSOR AND EXPERIMENTAL SETUP

Two micro Coriolis sensor designs with different channel dimensions were investigated. The suspended rectangular channels have in-plane dimensions of 5 mm × 2.5 mm (Chip 1) and 4 mm × 1.75 mm (Chip 2), respectively (Figure 3) [6]. Cross-sectional SEM images show the hollow microchannel structure, with channel cross-sections of approximately 42.7 μm × 32.8 μm for Chip 1 and 46.4 μm × 28.4 μm for Chip 2, and a wall thickness of approximately 0.8 μm (Figure 4). The two geometries were used to investigate the influence of sensor dimensions on pressure-dependent damping behavior.

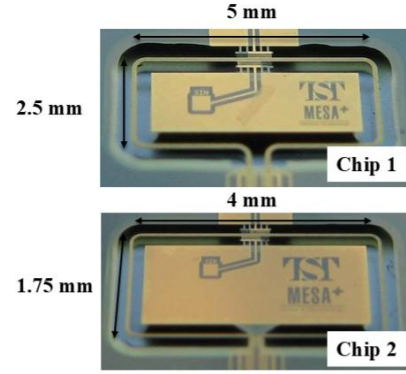


Figure 3. Photographs of two measured chips with channel length and width [5].

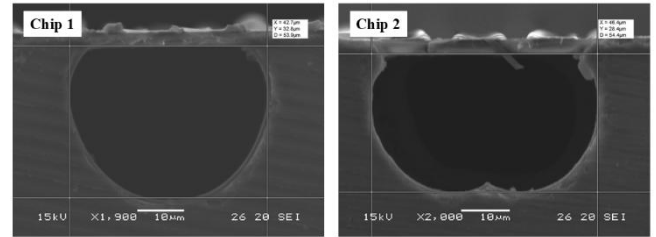


Figure 4. SEM images of the cross-section of two channels, provided by Jarno Groenesteijn.

Table 1. Overview of the mechanical parameters of the two defined channels and their cross-sections.

Parameters	Chip 1	Chip 2
Channel length (mm)	5.0	4.0
Channel width (mm)	2.50	1.75
Diameter (μm)	42.7	46.4
Height (μm)	32.8	28.4
Wall thickness (μm)	0.8	0.8
Flap width (μm)	72.0	72.0

The sensor chip was mounted on a dedicated printed circuit board (PCB) equipped with permanent magnets for Lorentz force actuation (Figure 5). An alternating current through the integrated metal tracks generates a Lorentz force in the magnetic field, actuating the suspended channel in its fundamental twist mode. The vibration response was measured using a laser Doppler vibrometer (LDV). The resonance frequency and quality factor were obtained from the measured frequency response. The Q values reported by the LDV software were independently verified by Lorentzian fitting of the resonance peaks, yielding consistent results.

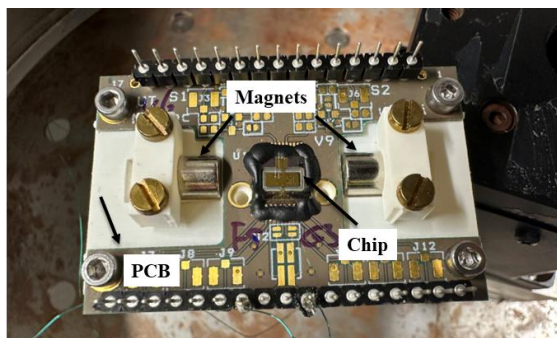


Figure 5. Photograph of the sensor chip mounted on PCB board.

For the pressure-dependent measurements, the PCB-mounted sensor was placed inside a vacuum chamber equipped with a pressure gauge. The external pressure surrounding the suspended channel was varied from approximately 10^{-4} to 10^2 mbar, and the twist-mode resonance response was measured at different pressure levels. The experiment was first performed with empty channels for both sensor geometries to characterize the impact of gas damping and determine the limited Q at reduced pressure.

For the liquid measurements, the sensor was connected to an external fluidic system consisting of liquid vessels, a degasser, and a flow controller. Deionized water, isopropyl alcohol (IPA), and acetone were introduced into the microchannel, and their twist-mode resonance responses were measured under ambient conditions without flow. In addition, a pressure-dependent measurement was performed with a liquid-filled channel and compared with the corresponding empty-channel response. This comparison was used to distinguish the effect of external air damping from additional damping introduced by the fluid inside the resonator.

RESULT AND DISCUSSION

Pressure-dependent damping of empty channel

Figure 6 shows the twist-mode quality factor of the two empty sensors as a function of surrounded pressure. As the pressure decreases from 10^{-4} to 10^2 mbar, Q increases by nearly two orders of magnitude due to the progressive reduction of gas damping. The measurements span the continuum, transition, and molecular flow regimes, as classified by the Knudsen number [7]. At pressures below approximately 10^{-2} mbar, Q approaches a plateau of approximately 11000 for Chip 1 and 8300 for Chip 2, indicating that gas damping is largely suppressed and pressure-independent loss mechanisms become dominant. The lower saturation Q of the smaller device further suggests geometry-dependent intrinsic losses. These results demonstrate that air damping dominates under ambient conditions and identify the pressure range in

which fluid-dependent damping effects can be investigated with enhanced sensitivity.

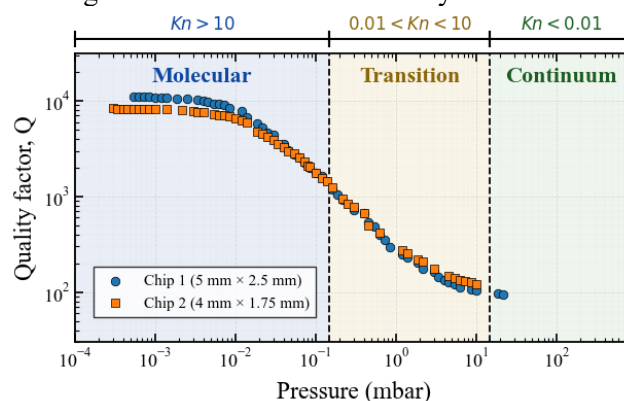


Figure 6. Twist-mode quality factor as a function of pressure for two micro Coriolis sensors. The shaded regions indicate the continuum, transition, and molecular flow regimes.

Liquid-filled channel under reduced pressure

To further distinguish external air damping from fluid-related damping, the pressure-dependent Q measurement was repeated with the microchannel filled with a water-acetone mixture. As shown in Figure 7, the liquid-filled channel exhibits a higher Q than the empty channel at relatively high pressure, where air damping is dominant and the additional liquid mass increases the effective resonator mass. However, under high vacuum, the liquid-filled channel shows a lower Q than the empty channel. Since external air damping is strongly suppressed in this regime, the reduced Q indicates additional energy dissipation associated with the liquid inside the channel. This result motivates the subsequent comparison of different liquids to investigate the contributions of density and viscosity to the measured Q .

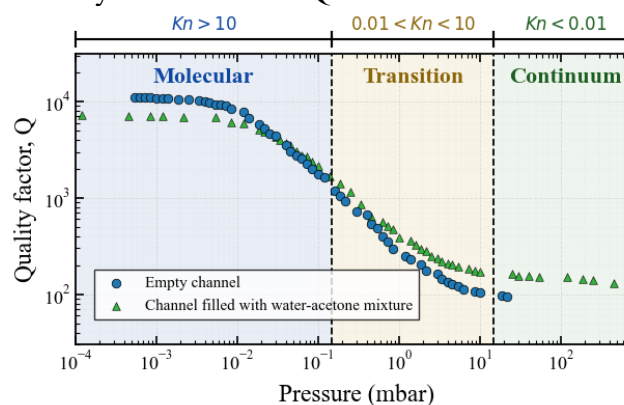


Figure 7. Pressure-dependent Q of the empty and liquid-filled channel, showing the influence of liquid loading as external air damping is progressively reduced.

Liquid-dependent Q and density effect

The influence of liquid properties on the resonator response was further investigated using DI water, IPA, and acetone at ambient pressure. As summarized in

Table 2, filling the channel with different liquids results in clear changes in both resonance frequency and Q. Water, with the highest density, produces the lowest resonance frequency due to the larger mass loading. The measured Q values are 96.1, 89.9, and 92.0 for water, IPA, and acetone, respectively.

In general, increased liquid viscosity is expected to introduce stronger fluid-related damping and consequently reduce Q. The measured results are consistent with this expected trend. Particularly, IPA and acetone have nearly identical densities (0.786 and 0.790 g/cm³), minimizing their difference in density-induced mass loading, while their viscosities differ considerably (2.381 and 0.331 mPa.s). The more viscous IPA exhibits the lower Q compared with which in case of less viscous acetone, supporting the presence of viscosity-dependent damping.

To consider the effect of density more quantitatively, a simplified mass-loading model assuming a constant damping coefficient was applied. Taking water as reference, the model predicts Q values of 90.9 for IPA and 91.0 for acetone, compared with the measured values of 89.9 and 92.0, respectively. Thus, density-induced mass loading explains a major part of the observed Q variation, while the remaining differences are consistent with additional fluid-dependent energy dissipation. Further measurements using calibrated viscosity standards are required to quantitatively establish the relationship between viscosity and Q.

Table 2. Physical properties of the tested liquids at 20 °C and corresponding resonance frequency and quality factor measured using the micro Coriolis sensor (*set as reference). ρ is density, μ is dynamic viscosity, f is resonance frequency.

Liquid	ρ (g/cm ³)	μ (mPa.s)	f (Hz)	Q test	Q model
Water	0.998	1.002	1868	96.1	96.1*
IPA	0.786	2.381	1975	89.9	90.9
Acetone	0.790	0.331	1951	92.0	91.0

CONCLUSION

This work investigates the feasibility of using the quality factor of a micro Coriolis mass flow sensor as an additional indicator of fluid viscosity. Pressure-dependent measurements show that air damping can be strongly reduced under vacuum, allowing intrinsic and fluid-related damping mechanisms to become more prominent. Measurements with a liquid-filled channel further demonstrate that internal fluid damping becomes distinguishable when external air damping is suppressed. At ambient pressure, measurements with water, IPA, and acetone follow the expected trend that

higher viscosity leads to stronger damping and lower Q.

These results provide a basis for extending the micro Coriolis sensor from simultaneous mass-flow and density measurement toward viscosity sensing using the same resonating channel. Future work will focus on measurements with calibrated viscosity standards under reduced pressure to establish a quantitative relationship between viscosity and Q and to separate viscosity-dependent damping from other loss mechanisms.

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3D-PRINTED DIFFERENTIAL PRESSURE MICRO FLOWRATE SENSOR WITH PIEZOELECTRIC RESONATOR

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Accurate flow monitoring remains a critical challenge in microfluidic systems, where conventional thermal, optical, and Coriolis flow sensors often suffer from complex integration, high power consumption and limited scalability [1, 2]. In this work, we present a piezoelectric-based differential pressure flow meter that determines flowrate from the pressure drop across a calibrated hydraulic resistance [3]. The pressure in each chamber is measured through resonance-frequency shifts of piezoelectric membrane resonators [4, 5]. Compared with existing flow-sensing approaches, the proposed architecture offers advantages in miniaturization, low system complexity and modular deployment, making it suited for next-generation microfluidic flow monitoring.

The sensing principle relies on the pressure-dependent resonance frequency of a clamped circular piezoelectric membrane. The resonance frequency f is influenced by pressure difference across the membrane ΔP [3]:

$$f = \frac{1}{2a} \sqrt{\frac{1}{\rho h} \left(\frac{\alpha_{ij}^2 h^3}{12\pi^2 a^2} E + \frac{\chi \beta_{mn}^2 a^2}{h} \Delta P \right)}, \quad (1)$$

where a is the diameter, h is the thickness, ρ is the mass density, E is the young's modulus of the membrane, $\chi = 0.1386$ is a geometric coefficient. α_{ij} and β_{mn} are dimensionless frequency parameters for the E and ΔP dominated terms. When the pressure is at a small scale, the resonance frequency shift Δf from the unloaded state (f_0) can be expressed as

$$\Delta f \approx \frac{\chi \beta_{mn}^2}{8\rho h^2 f_0} \Delta P = C \cdot \Delta P, \quad (2)$$

where C represents the responsivity of pressure difference. As shown in Fig. 1, because the employed resonators consist of a piezoelectric-brass bilayer membrane clamped by O-rings and directly exposed to liquid on brass side, their pressure responsivity deviates from that of an ideal membrane and is therefore determined experimentally.

As shown in Fig. 2, two identical pressure sensing units are positioned before and after a hydraulic resistance R_H , enabling flowrate Q determination from the measured differential pressure:

$$Q = \frac{P_1 - P_2}{R_H} = \frac{\Delta f_1 - \Delta f_2}{C R_H}. \quad (3)$$

As shown in Fig. 3, each pressure sensing unit consists of a 3D-printed microchamber with fluidic ports, O-rings, a commercial PZT-brass membrane resonator, and a threaded

clamping structure. The PZT and brass layers have diameters of 10 mm and 14 mm and thicknesses of 120 μm and 100 μm , respectively. During assembly, controlled O-ring compression is introduced through screw tightening, ensuring sealing and mechanical boundary conditions.

The repeatability and reproducibility of the pressure sensing units were evaluated using hydrostatic pressure loading. Repeatability tests were performed through multiple assembly and measurement cycles of the same device. As shown in Fig. 4, the result showed a linear relationship between resonance-frequency shift and applied pressure with a responsivity of $C = 4.03 \pm 0.36 \text{ Hz/mbar}$. Reproducibility tests conducted on three independently assembled devices showed comparable linear behavior, although with slightly larger variation, as shown in Fig. 5. The measurement instability was found to be below 9% for repeated measurements of the same device and approximately 11% across different devices. These variations are primarily attributed to manufacturing tolerances of the commercial piezoelectric resonators and assembly-dependent variations in O-ring compression.

To validate flow-sensing performance, five flow meters were assembled using pairs of pressure sensing units and calibrated hydraulic resistance $R_H = 6.7 \times 10^{11} \text{ Pa} \cdot \text{s/m}^3$. Water flow rates were generated using a pressure controller and measured with a commercial flow meter for reference. As shown in Fig. 6, the proposed device exhibited good linearity over the investigated flow range. The measured flowrates were 1.03 times the applied values, with a standard deviation of 9%. A slight overestimation was observed, likely due to additional hydraulic resistance introduced by the internal fluidic channels of the pressure sensing units.

In summary, we present a piezoelectric-based differential pressure flow meter for microfluidic applications with simple assembly in a compact format. The device demonstrates linear pressure and flow responses with good repeatability and reproducibility, achieving flow measurements within 3% of the reference value on average, which highlights its potential for next-generation microfluidic flow monitoring.

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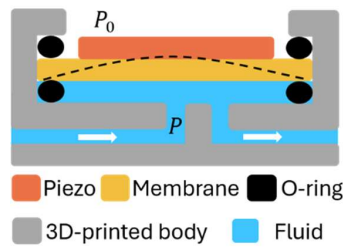


Figure 1: Schematic diagram of a clamped piezoelectric membrane as pressure sensing unit. The pressure difference $\Delta P = P - P_0$ induced in-plane tension will change membrane resonance frequency.

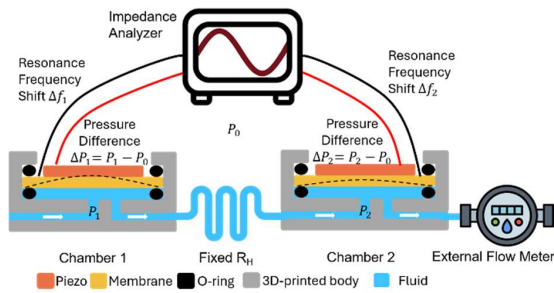


Figure 2: Schematic diagram of the working principle of piezoelectric based pressure difference flow meter.

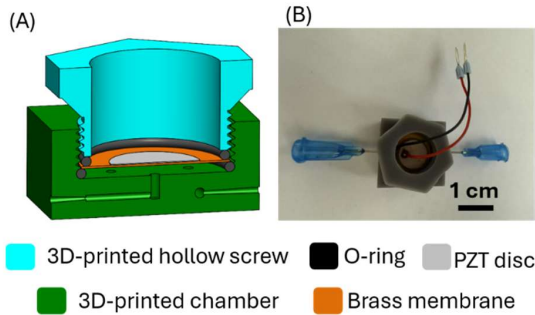


Figure 3: Design and fabrication results of a clamped piezoelectric membrane.

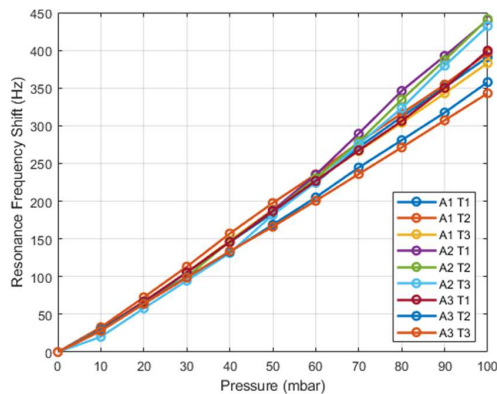


Figure 4: Repeatability of the pressure sensing unit. The legend of A and T means different assembling attempts and different tests after cleaning, respectively.

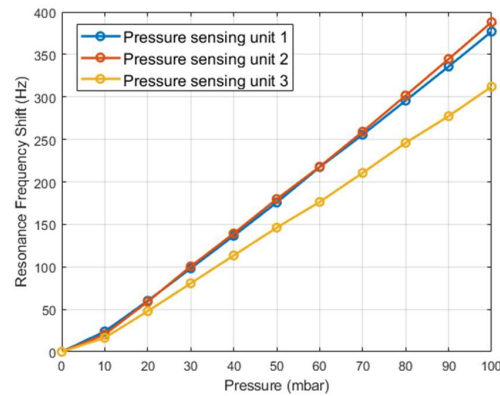


Figure 5: Reproducibility between different pressure sensing units.

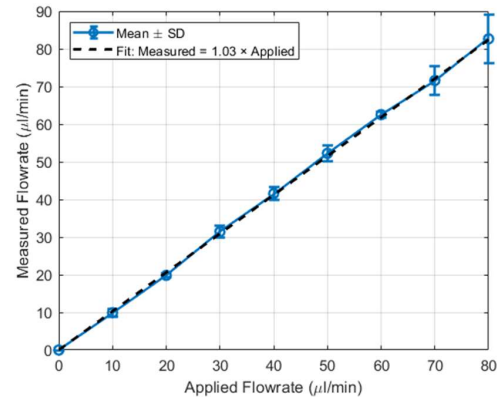


Figure 6: Flow meter measurement results of 5 different samples compared with the results of an external commercial flow meter.

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MODEL-ENHANCED THERMOFLUIDIC FLOW SENSING FOR NON-NEWTONIAN FLUIDS

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ABSTRACT

Thermal flow sensors commonly infer flow rates from heat-transfer measurements using calibrations established for Newtonian fluids. However, non-Newtonian rheology can alter both the flow field and the resulting heat transfer, potentially leading to biased flow-rate estimates. In this work, we develop a thermofluidic finite element framework to quantify these effects. Using a power-law fluid model, we systematically investigate the dependence of the heat-transfer coefficient on flow rate and rheological behavior. The results reveal substantial deviations from Newtonian calibration curves as the fluid departs from Newtonian behavior, giving rise to significant errors in the inferred flow rate. These findings highlight the importance of accounting for rheological effects when thermal flow sensing is applied to non-Newtonian fluids.

KEYWORDS

thermal flow sensing, non-Newtonian fluids, heat-transfer coefficient, finite element method

INTRODUCTION

Accurate flow sensing is essential for monitoring and controlling processes in application domains such as infusion systems, dosing and filtering systems, sequestration systems, organ-on-a-chip devices, and deposition processes [1]. In many of these applications the working fluid exhibits non-Newtonian rheology. Because most flow sensing technologies are developed and calibrated under Newtonian assumptions, their accuracy can deteriorate when applied to non-Newtonian fluids, resulting in biased flow-rate estimates [2, 3].

Owing to its simplicity and widespread use in industrial applications, hot-wire anemometry is among the most established thermal flow sensing technologies [4]. Its operating principle relies on measuring the power required to maintain a sensing element, in thermal contact with the fluid, at a prescribed temperature. Since the resulting heat transfer depends on the local fluid velocity near the heater, the measured power can be related to the flow rate through an appropriate cali-

bration [5].

Non-Newtonian fluids develop velocity profiles that differ from those of Newtonian fluids at the same flow rate [3]. In relation to this fluid flow behavior, thermal transport properties have also been reported to depend on the local shear rate [6], while heat-transfer characteristics vary with the rheological properties of the fluid [7]. These observations indicate that the thermal response of a flow sensor depends not only on the flow rate itself, but also on the rheological behavior of the fluid. Consequently, calibration procedures established under Newtonian assumptions may become unreliable when applied to non-Newtonian fluids, potentially leading to significant errors in the inferred flow rate.

In this work, we quantitatively investigate the impact of non-Newtonian rheology on thermal flow sensing. A high-fidelity finite element framework is developed to resolve the coupled flow and heat-transfer behavior of generalized Newtonian fluids in a thermofluidic sensing environment. Using this framework, we evaluate the sensitivity of the heat-transfer coefficient to rheological parameters and determine the errors introduced when conventional Newtonian calibration procedures are applied to non-Newtonian fluids.

THERMOFLUIDIC NON-NEWTONIAN CHANNEL FLOW

To investigate the influence of non-Newtonian rheology on heat transfer, we consider the steady thermofluidic behavior of a generalized Newtonian incompressible fluid flowing through a locally heated two-dimensional channel (Figure 1). The governing mass and momentum balance equations are given by

$$\nabla \cdot \mathbf{v} = 0, \quad (1a)$$

$$-\nabla \cdot (\eta(\dot{\gamma}) (\nabla \mathbf{v} + \nabla \mathbf{v}^T)) + \nabla p = \mathbf{0}, \quad (1b)$$

where $\mathbf{v}$ is the fluid velocity, p the pressure, $\eta(\dot{\gamma})$ the shear-rate-dependent viscosity, and $\dot{\gamma}$ the effective shear rate.

The fluid is modeled as a power-law fluid with

$$\eta(\dot{\gamma}) = m \dot{\gamma}^{n-1}, \quad (2)$$



Figure 1. Schematic of a locally heated channel with a non-Newtonian fluid flow.

where m is the consistency index and n the power-law index. Values $n < 1$ correspond to shear-thinning behavior, $n = 1$ recovers the Newtonian fluid, and $n > 1$ corresponds to shear-thickening behavior [3].

For a power-law fluid flowing at a constant rate between parallel plates, solving the momentum balance subject to no-slip boundary conditions yields the fully-developed analytical velocity profile

$$v(y) = \frac{2n+1}{n+1} \frac{\dot{V}}{H} \left[1 - \left| \frac{2(y - \frac{H}{2})}{H} \right|^{\frac{n+1}{n}} \right], \quad (3)$$

where $y \in [0, H]$ denotes the coordinate normal to the channel walls, and $\dot{V}$ the volumetric flow rate per unit out-of-plane depth of the two-dimensional channel. For $n = 1$, this reduces to the familiar parabolic Newtonian profile. For $n < 1$, the profile flattens into a more plug-like shape with steeper gradients near the walls, as shown schematically in Figure 1.

The temperature field is governed by the steady-state convection-diffusion equation

$$\rho C_p (\mathbf{v} \cdot \nabla T) - k \nabla^2 T = 0, \quad (4)$$

where ρ is the fluid density, C_p the specific heat capacity, and k the thermal conductivity. The heater section (Figure 1) is maintained at a prescribed temperature $T = T_h$. The inlet temperature is fixed at $T = T_c$, while all remaining boundaries are assumed adiabatic.

In hot-wire anemometry, the sensor response is commonly characterized through the heat-transfer coefficient, which relates the heat removed from the sensing element to the imposed temperature difference between the heater and the fluid, *i.e.*,

$$h = \frac{\dot{Q}_h}{T_h - T_c}, \quad (5)$$

where $\dot{Q}_h$ denotes the heat flux leaving the heater. This total heat flux is obtained by integrating the local conductive heat flux over the heating element Γ_h ,

$$\dot{Q}_h = \int_{\Gamma_h} \left(-k \frac{\partial T}{\partial n} \right) dx. \quad (6)$$

FINITE ELEMENT DISCRETIZATION

Since the velocity field is prescribed analytically through equation (3), we only solve the heat equation (4) numerically. We formulate the corresponding weak problem in the standard manner [8]. Since the parameter range considered includes convection-dominated transport regimes, we augment the weak formulation with a Streamline Upwind Petrov-Galerkin (SUPG) stabilization term to suppress spurious numerical oscillations [9].

We discretize the resulting Galerkin problem using bilinear Q_1 elements on a structured quadrilateral mesh (Figure 2), refined toward the channel walls to resolve the steep temperature gradients that develop near the heater. We solve the resulting linear system using a direct sparse solver and evaluate the heat-transfer rate $\dot{Q}_h$ as the sum of the nodal reaction fluxes at the prescribed-temperature nodes of the heating element. This yields a numerically consistent and locally conservative approximation of the boundary integral (6).

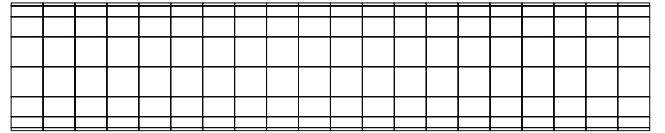


Figure 2. Structured quadrilateral mesh used for the thermal analysis.

Figure 3 shows representative temperature fields obtained for three values of the power-law index n at a fixed flow rate. As the fluid becomes increasingly shear-

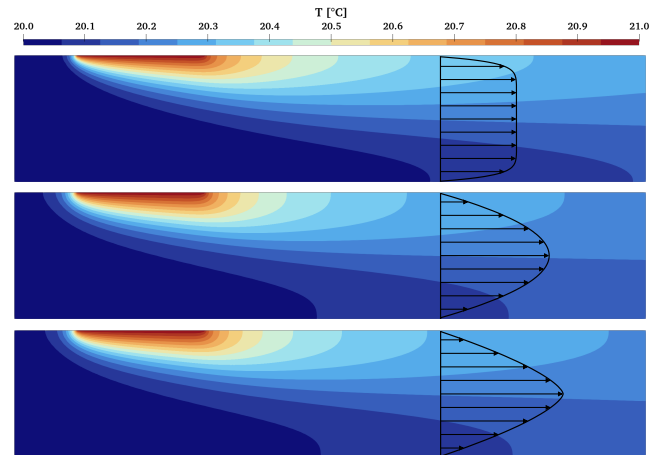


Figure 3. Temperature fields for three power-law indices ($n = 0.1, 1, 2$ [-], top to bottom) in a channel of unit height and at a fixed volumetric flow rate ($\dot{V} = 2.6$ [mm²/s]). The corresponding velocity profiles are overlaid as black arrows.

thickening, the velocity profile becomes more sharply peaked near the channel centerline and slower near the

walls, reducing convective heat removal at the heating element. Consequently, heat remains localized near the heater, resulting in a narrower and more intense thermal boundary layer. Conversely, shear-thinning behavior enhances near-wall transport, producing a broader temperature distribution.

To verify spatial discretization convergence, we perform a systematic mesh refinement study. Figure 4 shows the computed heat-transfer coefficient h as a function of the wall-normal resolution N_y for five fixed streamwise resolutions ($N_x = 10$ –640) at a representative power-law index of $n = 0.1$. The results exhibit clear convergence upon mesh refinement. Based on this study, we employ a mesh consisting of $N_x = 160$ and $N_y = 64$ elements for all subsequent simulations.

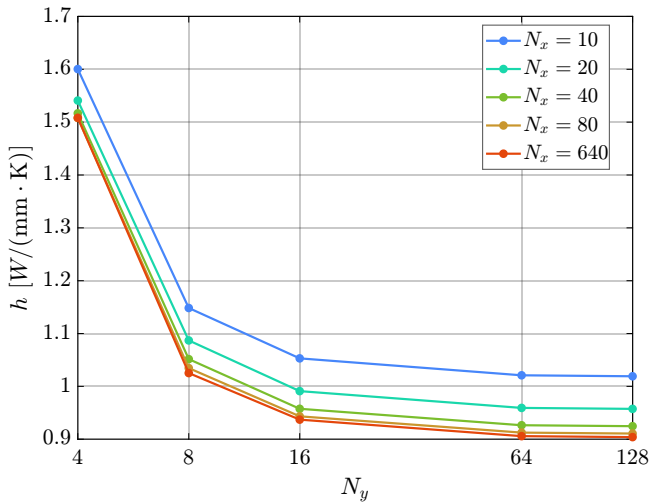


Figure 4. Computed heat-transfer coefficient h as a function of the wall-normal resolution N_y for five streamwise resolutions ($N_x = 10$ –640) at $n = 0.1$.

NUMERICAL EXPERIMENTS

To facilitate a dimensionless interpretation of the results, we characterize the thermofluidic response using the power-law index n and the Péclet number Pe . The power-law index quantifies the degree of non-Newtonian behavior, with increasing deviations from $n = 1$ corresponding to increasingly non-Newtonian rheology. The Péclet number is defined as

$$Pe = \frac{v_{\max} L_{\text{heater}}}{D}, \quad (7)$$

where $v_{\max}$ is the maximum horizontal fluid velocity, L_{heater} is the length of the heating segment, and $D = k/(\rho C_p)$ denotes the thermal diffusivity. Low values of Pe correspond to diffusion-dominated heat transport, resulting in temperature fields that extend nearly symmetrically around the heater. Conversely, high values

of Pe correspond to convection-dominated transport, for which heat is primarily advected downstream, producing the elongated thermal plume shown in Figure 3.

For all simulations, we consider a channel height of 1 mm and select the thermal properties such that the thermal diffusivity satisfies $D = 0.1 \text{ mm}^2/\text{s}$, which is representative of water-based fluids ($D \approx 0.1$ – $0.145 \text{ mm}^2/\text{s}$). The numerical experiments are therefore representative of dilute aqueous polymer solutions, whose thermal properties remain close to those of the solvent despite their non-Newtonian rheology.

Since the volumetric flow rate $\dot{V}$ is prescribed directly, the resulting velocity field is fully determined by the power-law index n and is independent of the consistency index m . Consequently, the temperature field depends only on n and $\dot{V}$. We vary $\dot{V}$ between 0.1 and 10.1 [mm^3/s] and n between 0.1 and 2.1 [–]. This range covers the shear-thinning behavior of common aqueous polymer solutions (e.g., xanthan gum, for which $n \approx 0.4$ – 0.7) and extends into the shear-thickening regime for completeness.

For the selected parameter ranges, the Péclet number spans approximately $1 \leq Pe \leq 170$, thereby covering both diffusion-dominated and convection-dominated heat-transfer regimes. Together with the considered range of power-law indices, this enables a systematic investigation of the sensitivity of the heat-transfer coefficient to non-Newtonian rheology.

RESULTS

Figure 5 shows the computed heat-transfer coefficient h as a function of the volumetric flow rate $\dot{V}$ and the power-law index n for a channel height of 1 mm. As expected, the results show that increasing the flow rate enhances convective heat transport and therefore increases h . More importantly, significant variations in h are observed as the power-law index departs from its Newtonian value $n = 1$, demonstrating that the thermal response is sensitive to non-Newtonian effects.

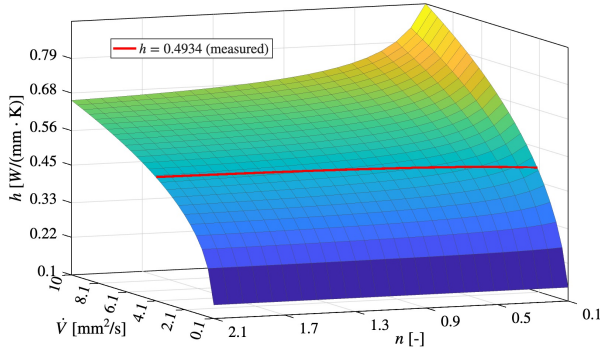


Figure 5. Dependence of the heat-transfer coefficient h on the power-law index n and volumetric flow rate $\dot{V}$.

From a flow-sensing perspective, the isoline shown in Figure 5 illustrates that a single measured value of the heat-transfer coefficient h can correspond to multiple combinations of flow rate and rheological properties. Consequently, applying a calibration obtained for a Newtonian fluid to a non-Newtonian fluid may lead to inaccurate flow-rate estimates. To quantify this effect, Figure 6 compares the true flow rate to the flow rate that would be inferred using a Newtonian calibration for the same measured value of h . The discrepancy increases as the power-law index deviates further from its Newtonian value ($n = 1$), indicating that non-Newtonian rheology can introduce significant systematic errors in thermal flow-rate measurements.

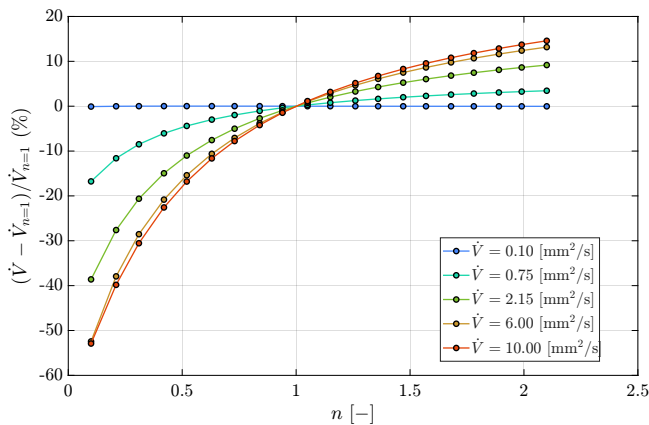


Figure 6. Relative error in the flow rate inferred using a Newtonian calibration, shown as a function of the power-law index n for a range of true volumetric flow rates $\dot{V}$ [mm²/s].

CONCLUDING REMARKS

We developed a thermofluidic finite element framework to quantify the influence of non-Newtonian rheology on thermal flow sensor measurements. Combining a power-law flow model with convective heat-transfer analysis, the framework enables a systematic investiga-

tion of the dependence of the heat-transfer coefficient on both the flow rate and the rheological properties of the fluid. The results show that non-Newtonian rheology can substantially alter the heat-transfer coefficient and thereby introduce significant errors when a Newtonian calibration is employed.

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TRANSCEIVER ASIC FOR ARRAY-BASED CLAMP-ON ULTRASONIC FLOW METERS

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Clamp-on ultrasonic flow meters are an essential industrial tool for monitoring critical infrastructure. Their main feature is the possibility of a non-invasive measurement; omitting risk to chemical exposure, custom pipe structures and interruption of the flow process. The research aims to solve their main disadvantage – installation and calibration complexity. The accuracy of the device is sensitive to positioning and requires preliminary information regarding the properties of the pipe and the contained liquid. By utilizing a matrix phased array, the ultrasonic beam can be electronically steered, making spatial analysis and autonomous calibration possible [1][2]. Our goal is the development and test of an application-specific integrated circuit (ASIC) which can drive the self-calibration and measurement techniques. While ultrasound matrix transceiver architectures have already been presented for imaging applications, e.g. in [3], no prior implementation has been established for clamp-on flow sensors.

The flow sensor consists of two identical arrays, placed side by side, on a steel pipe filled with water. The arrays are driven by a pair of ASICs, which in turn are programmed by a field-programmable gate array (FPGA). The chips are designed for a 16x6 transducer matrix, however, for the initial experiments presented in this paper, a linear 32-element array is used. A block diagram of the complete system is shown in Fig. 1. The experimental parameters are listed in Table 1, where D and t are the diameter and thickness of the pipe, d is the distance between the arrays, f_c is the modulation frequency of the excitation signals and p is the array pitch. Currently, the receiver is limited to time-multiplexing the matrix into 8x12 channels, where digitization is done externally with an ultrasound multi-channel system. The flow rate is measured by observing the phase/transit time difference between the signals propagating upstream and downstream with the flow.

To take an accurate flow measurement, multiple physical properties must be found: thickness and diameter of the pipe, and the bulk wave velocities in the fluid and the pipe wall. To perform the auto-calibration procedures and beamforming of the transmitted (TX) signals, the chips are equipped with

a pulse wave modulation (PWM) based arbitrary waveform generator and clocked time-delay circuits. Furthermore, to reduce the excitation of unwanted Lamb waves in the pipe wall, the signal amplitudes can be apodized [4]. A signal-flow diagram is shown in Fig. 2, where the binary TX waveforms are delayed and mixed according to the column-row settings. In Fig. 3, the last TX step is emphasized, where the differential PWM waveforms are combined and modulated by the element's apodization setting, and ultimately filtered by the bandpass behaviour of the transducer. The output amplitude of the class-A power amplifier is limited to 5V due to application safety requirements.

Table 1: Physical parameters used in the experimental setup.

Variable	Value	Unit
D	40	cm
d	80	cm
t	1	mm
f_c	1	MHz
p	0.72	mm

A micrograph of the ASIC is shown in Fig. 4. The apodization capability of the ASIC is demonstrated in Fig. 5, where the recorded amplitudes of the excitation signal differ per element. While the ASIC is designed to apply unique apodization values upon the supported 96 elements, for the linear array, only 16 unique window values can be utilized. Lastly, Fig. 6 shows the phase/transit time difference between the received upstream and downstream signals as a function of the flow speed. While the time uncertainty of ≈ 4 ns translates to a significant flow error of ≈ 0.08 m/s at zero flow, these initial measurements demonstrate the functionality of the prototype. Further characterisation is ongoing and the results will be presented at the conference.

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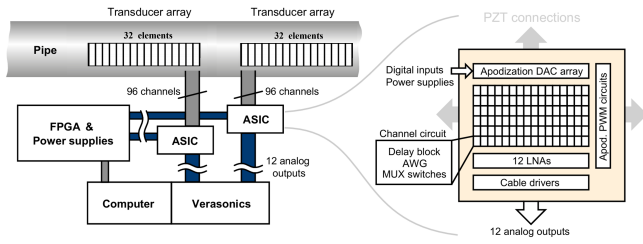


Figure 1: High level block diagram of the entire system.

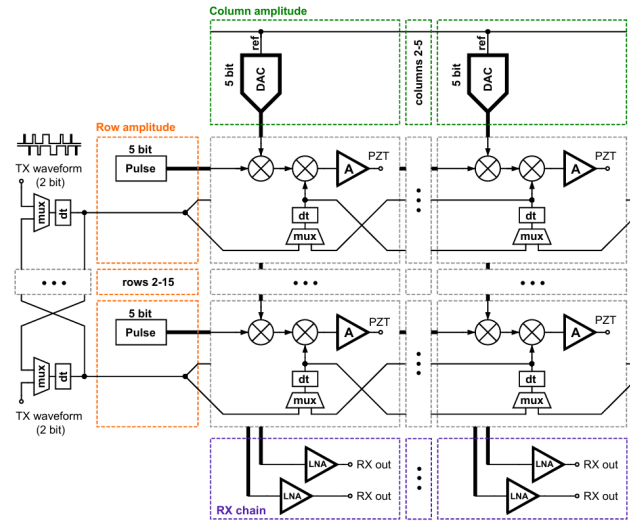


Figure 2: Block diagram of the ASIC signal path.

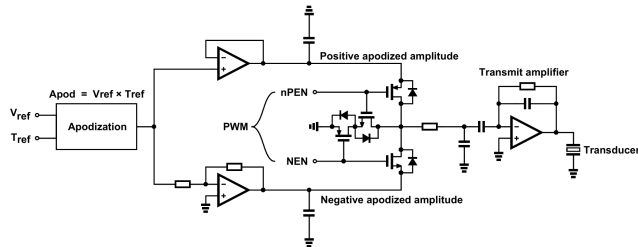


Figure 3: Circuit diagram of the final transmission stage for a single array element.

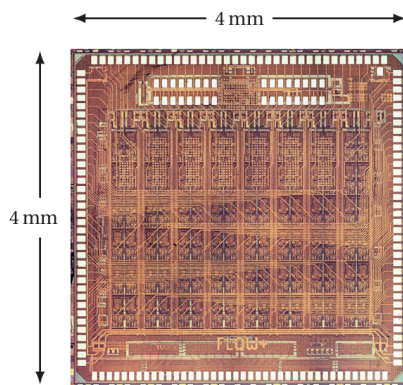


Figure 4: Micrograph of the ASIC as a part of the Flow+ project.

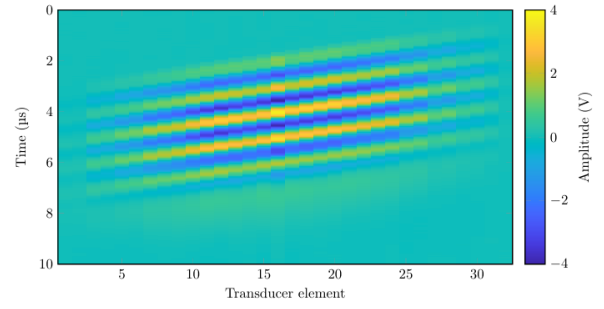


Figure 5: Output signals from the ASIC when driving a 32-element linear array with a Hanning window apodization.

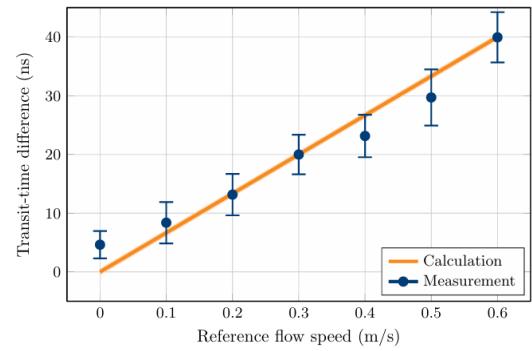


Figure 6: Transit-time difference as a function of the reference flow speed.

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EQUIVALENT-CIRCUIT ANALYSIS OF THERMAL AND ELECTRICAL IMPEDANCE IN A TEMPERATURE-CONTROLLED MICROFLUIDIC SETTING

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ABSTRACT

We report a combined electrical impedance spectroscopy (EIS) and thermal step-response measurement of the same liquid, in the same microfluidic channel, on a single time base. An integrated resistive element serves as both heater and thermometer, so that a calibrated power step can be applied between impedance sweeps while a PID loop holds the channel temperature. Both responses are reduced by the same means, a equivalent circuit fitted to the measured data, so each state is described by one set of parameters in a common form. Across 0–60 $\mu\text{L}/\text{min}$ and 23–31 $^{\circ}\text{C}$ the thermal network responds to flow alone, while the impedance parameters tracks the electrical properties of the sample and the influence of temperature.

KEYWORDS

Electrochemical impedance spectroscopy, thermal impedance, equivalent circuit analysis, microfluidics, biosensors

INTRODUCTION

Characterising a liquid inside a microfluidic channel usually means choosing a probe. Electrical impedance spectroscopy (EIS) reports on ion concentration, electrode condition and interfacial structure. Thermal methods report on heat transport and therefore on flow. Both are well established individually, and both are routinely integrated into microfluidic devices.

What is rarely available is both at once, on the same volume of liquid. When the two are performed on separate instruments, an observed change cannot be attributed unambiguously: a shift in impedance may reflect composition, or merely a difference in temperature or flow between the two measurements [1]. The problem is sharpest precisely where those variables are being manipulated, as they are here.

This paper describes a configuration in which the two modalities share a channel, a sample and a clock. One resistive element acts simultaneously as heater and resistance thermometer, so that a defined power step can be applied and its transient recorded on the same

element under closed-loop temperature control, with EIS sweeps interleaved between the steps. The heater thereby becomes an actuator as much as a regulator: a sample can be driven to a series of known temperatures and characterised at each within a single run. Because both modalities admit an equivalent-circuit description, each state of the sample can be reduced to a small set of lumped parameters in a common form, and the power required to hold each setpoint provides a further measurement at no extra cost.

DEVICE AND SETUP

The device is a flex-PCB substrate closed by a PMMA lid, with a channel of approximately 130 μm height defined by an acrylic-based adhesive layer laminated over the electrode layer. The stack-up comprises a 20 μm copper heater layer, isolated by a 25 μm PI core from a second 20 μm copper layer whose gold plating (0.025 μm) forms the interdigitated electrodes (IDE), the only layer exposed to the liquid on the channel floor. The heater covers 1.3 mm $\times$ 1.3 mm; the IDE fingers are 60 μm wide with 140 μm spacing.

The heater doubles as a resistance thermometer, with a temperature coefficient $\alpha = 3.87 \times 10^{-3} \text{ K}^{-1}$ and a resistance R_0 at the reference temperature $T_0 = 21^{\circ}\text{C}$ of $0.26 \pm 0.02 \Omega$ between devices. Its resistance and drive current are measured throughout, so the dissipated power and the element temperature follow directly as

$$P = I^2 R, \quad (1)$$

$$T = T_0 + \frac{R - R_0}{\alpha R_0}. \quad (2)$$

This readout closes a PID loop that regulates the heater power to hold a fixed setpoint.

A single liquid was used, a mixture of 0.5 mM NaCl and tap water. Flow was set with an Elveflow OB1 pressure controller, EIS performed with a PalmSens SensitBT potentiostat, and the heater driven and monitored with a Keysight B2901A source-measure unit in four-wire (Kelvin) configuration, so that lead and contact resistance do not enter the temperature readout. All three

instruments were controlled from a single Python program, giving the measurements a common time base.

MEASUREMENT PROTOCOL

The measurement run covered four temperature setpoints (23, 26, 29 and 31 °C) and, within each, seven flow rates stepped from 0 to 60 $\mu\text{L}/\text{min}$. In each of the 28 conditions the measurement sequence was repeated five times and averaged to one, giving 140 EIS sweeps and 140 thermal steps over 99 minutes. A single repeat consisted of an impedance sweep (41 frequencies, 20 Hz–195 kHz, 15 mV excitation amplitude, zero DC offset) immediately followed by a 3 s power step sampled every 2 ms, with repeats spaced approximately 40 s apart.

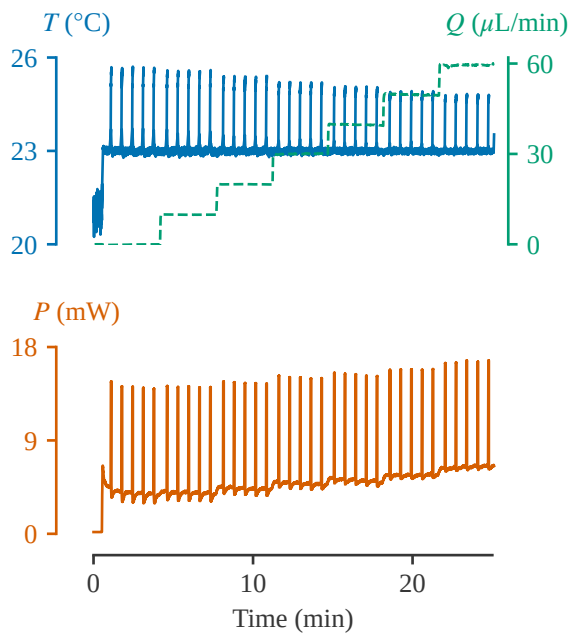


Figure 1: Measurement protocol, first flow ramp. Top: Heating element (RTD) temperature (solid) and flow rate (dashed). Bottom: heater power. Each spike is one 3 s thermal step; five repeats are taken at each of the seven flow rates.

Figure 1 shows the first flow ramp. The PID loop held the setpoint throughout: the measured temperature did not depart from it outside the noise band, and each thermal step appeared as a transient excursion that fully recovered before the next repeat. The heater power staircased upward with each flow step, since holding a fixed temperature against increasing convective loss costs more power. This steady-state power therefore serves as an additional flow-sensitive parameter alongside the impedance response.

STEADY-STATE HOLDING POWER

The resulting steady-state holding power rises from 3.60 mW at 0 $\mu\text{L}/\text{min}$ to 6.34 mW at 60 $\mu\text{L}/\text{min}$ for the 23 °C setpoint and from 19.58 to 38.24 mW at 31 °C. Each setpoint costs between 1.8 and 2.0 times more power at the highest flow rate than at rest, and the four curves remain fully separated over the whole range.

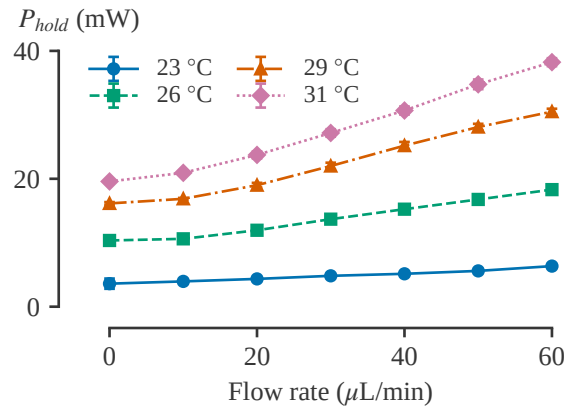


Figure 2: Steady-state power required to hold each temperature setpoint, against flow rate.

THERMAL STEP RESPONSE ANALYSIS

Each thermal step is a controlled excitation: its amplitude ΔP is the pulse power minus the steady-state holding power, measured in a settled, pulse-free window immediately before the step, and is recomputed from the measured resistance at the moment each step is triggered [1]. The absolute power during a pulse spans 14–49 mW across the protocol matrix, following the holding power it sits on, whereas the step itself is only 10.4 ± 0.4 mW and is therefore constant across conditions.

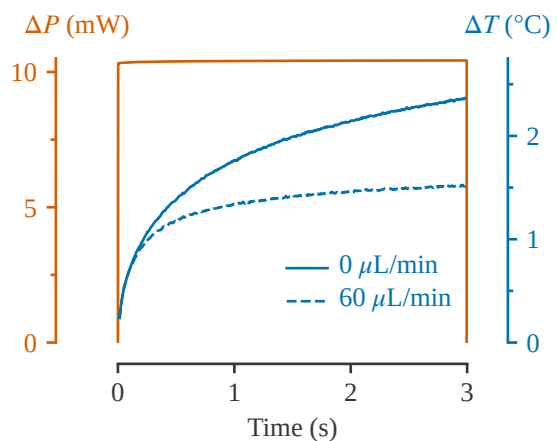


Figure 3: Applied power step (left axis) and the resulting temperature rise (right axis) at 0 and 60 $\mu\text{L}/\text{min}$, 23 °C. Each trace is the mean of five repeats at the given temperature and flow rate.

Figure 3 shows the drive and the response at the two extreme flow rates. The same power step produced

a 2.35 K rise at zero flow and only 1.52 K at 60 $\mu\text{L}/\text{min}$, and the high-flow transient had largely settled by 1.5 s where the zero-flow transient was still climbing at 3 s. Flow therefore changes both the magnitude and the time scale of the response.

To quantify this, the thermal impedance is defined as the temperature rise per unit applied power,

$$Z_{\text{th}}(t) = \frac{\Delta T(t)}{\Delta P} = \sum_{i=1}^3 R_i \left(1 - e^{-t/\tau_i}\right), \quad (3)$$

with $\tau_i = R_i C_i$ and stages numbered by increasing time constant, where ΔT is in K, R_i in K/W, C_i in J/K and τ_i in s. Equation (3) is a three-stage Foster network: it reproduces the measured thermal path as a whole, but its stages are a fitting basis rather than physical layers, and the individual R_i and τ_i cannot be directly assigned to particular materials in the stack [2].

Fitting Eq. (3) over 4 ms–3 s gave a median residual of 0.85 K/W, or 0.44% of Z_{th} . Three stages are necessary and sufficient: two leave a systematic residual three times larger, while a fourth improves the fit by under 3% with a time constant not identifiable in a 3 s window.

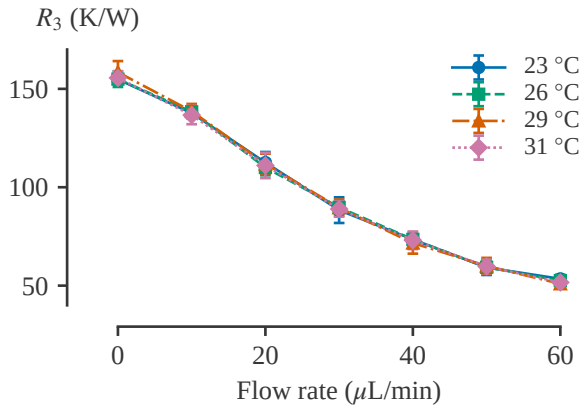


Figure 4: Slow-stage thermal resistance R_3 against flow rate at each temperature setpoint.

The stages separate by time scale and, more usefully, by what they respond to. Stage 1 ($R_1 = 33.6$ K/W, $\tau_1 = 21$ ms) and stage 2 ($R_2 = 66$ K/W, $\tau_2 = 190$ ms) are independent of both flow and temperature. Stage 3 carries the entire flow response: R_3 falls from 156 to 52 K/W as flow increases from 0 to 60 $\mu\text{L}/\text{min}$, with τ_3 falling from 1.55 to 1.03 s (Fig. 4).

Averaged over flow, R_1 , R_2 and R_3 are 34.3, 66.5 and 97.1 K/W at 23 °C against 33.3, 66.2 and 96.6 K/W at 31 °C, differences of order 1%. Within measurement protocol, the thermal network here therefore depends on flow alone.

ELECTRICAL IMPEDANCE ANALYSIS

The electrical impedance equivalent circuit used in this paper [3] is described by a solution resistance in series with a constant phase element (CPE), the pair shunted by the electrode capacitance:

$$Z(\omega) = \left[\left(R_s + \frac{1}{Q(j\omega)^n} \right)^{-1} + j\omega C_{\text{ide}} \right]^{-1}. \quad (4)$$

with Q and n the CPE magnitude and exponent, the latter dimensionless with $n = 1$ describing an ideal capacitor, where R_s is in Ω , Q in S s^n , C_{ide} in F and ω in rad/s. Equation (4) was fitted to each sweep by complex nonlinear least squares with modulus weighting, over 2–142 kHz. Over the 140 sweeps the median χ^2 was 9.4×10^{-3} and the median relative residual 2.28%, ranging only from 2.17 to 2.38% across sweeps. The residual is therefore systematic rather than random, and almost entirely common-mode, so comparisons between sweeps remain reliable even though absolute values carry a model-dependent bias.

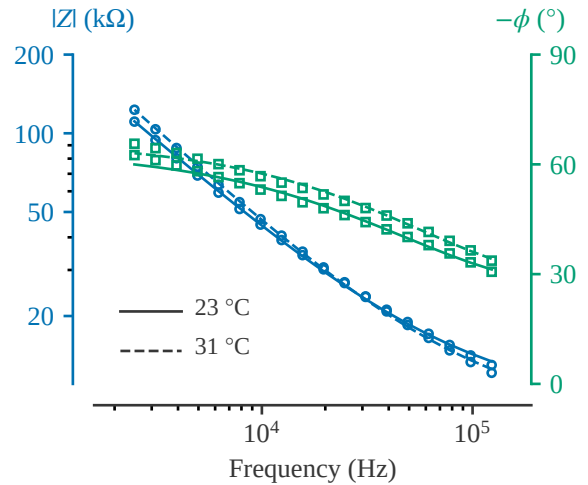


Figure 5: Impedance magnitude and phase at zero flow for the extreme temperature setpoints. Round markers are measured impedance magnitudes and square markers are measured phase, lines are fits of Eq. (4). Each trace is the mean of five repeats at the given temperature and flow rate.

All four circuit parameters varied monotonically with temperature (Fig. 6). Over 23–31 °C, R_s fell from 9.75 to 9.09 k Ω (−6.8%), Q fell by 22.6%, n rose by 2.6% toward ideal capacitive behaviour and C_{ide} rose by 13.4%.

The flow response for Q fell monotonically at every setpoint, the curves offset from one another by temperature. R_s was flat with flow at 23 °C but developed a

slope from 0 to 60 $\mu\text{L}/\text{min}$ at the higher setpoints. C_{ide} showed no consistent flow dependence.

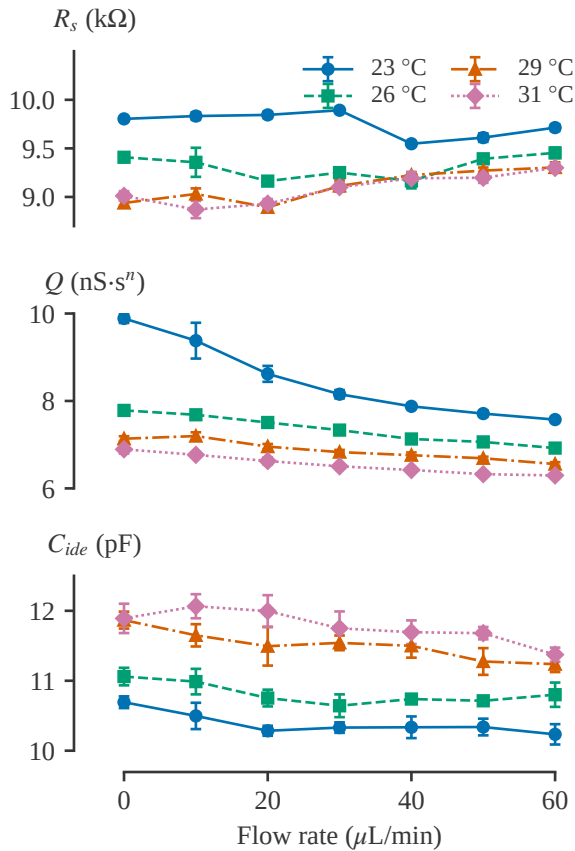


Figure 6: Solution resistance, CPE magnitude and electrode capacitance against flow rate, by temperature setpoint. Every 5 sweeps were averaged. The CPE exponent n is not shown.

DISCUSSION

With equivalent-circuit analysis applied to both, the two integrated modalities answer different questions at once: the thermal step response reports heat transport, responding to flow rate, while the impedance sweep reports the electrical properties of the liquid and the electrode interface, responding to the imposed temperature. The heater makes temperature an actuator as well as a measurand, so the sample can be driven to a series of known states and measured at each. Because that effect on the circuit parameters is now known, temperature can be compensated for, leaving composition as the variable of interest.

Three directions follow. The monotonic flow ramp confounds flow rate with elapsed time, and an interleaved order would separate a genuine flow response from slow drift at no cost in measurement time. A circuit capturing the missing physics would lower χ^2 and open the full 20 Hz–195 kHz band to analysis. Lastly, the analysis can be advanced from lumped parameters

to intrinsic material properties: R_s converts to electrical conductivity through the cell constant of the IDE, while thermal conductivity would require a Cauer-type transformation or a calibrated model of the stack [2]. Being intrinsic to the liquid rather than the device, such features are transferable, so combining both parameter sets across a range of compositions would give a physically interpretable classifier.

CONCLUSION

Electrical and thermal impedance were measured on the same liquid, in the same microfluidic channel, under closed-loop temperature control, with a single element acting as both heater and thermometer. Reducing both responses to lumped equivalent-circuit parameters shows that they probe almost disjoint physics: only the slowest Foster stage responds to flow, by a factor of three and independently of temperature, while the impedance parameters track the imposed temperature. The combination offers a route to separating flow from compositional effects in a single device, still to be tested across liquids.

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OPTIMIZATION OF MEMS THERMAL FLOWMETER SIMULATION MODELS

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ABSTRACT

This paper presents a finite-element model of a MEMS thermal flow sensor based on a Coriolis microfluidic structure. The model was simplified to reduce computational cost while preserving the relevant thermal behavior. Experimental data were used for parameter estimation with the derivative-free BOBYQA algorithm. The optimized model showed good agreement with measurements within the considered flow range. At higher flow rates, gas heat transport increasingly affected the temperature field and limited the validity of the simplified model.

KEYWORDS

COMSOL Multiphysics, data-based model optimization, MEMS flowmeter, thermal flowmeter.

INTRODUCTION

Finite element method (FEM) simulations provide an effective approach to accelerating and improving the development of MEMS flow sensors for both gasses and liquids. Simulations make it possible to evaluate basic operating principles and estimate important sensor parameters such as operating temperatures, power losses, sensitivity, natural frequencies, and other relevant characteristics.

In this work, the thermal flow sensing properties of a microfabricated sensor has been investigated by simulation. The sensor consists of a suspended straight tube that could also be used for Coriolis mass flow sensing; see figure 1. The microfluidic design is based on previous work presented in [1, 2]. The integrated resistors on the Coriolis tube were used for flow measurement in a constant power thermal anemometric mode. The cavity surrounding the flow channel was advantageously utilized as thermal insulation for the heated part of the sensor. The chip is covered at the top by silica glass. Combining multiple measurement principles on a single chip can extend the operating range of the sensor and improve its measurement performance under different operating and environmental conditions.

The simulated data were subsequently compared

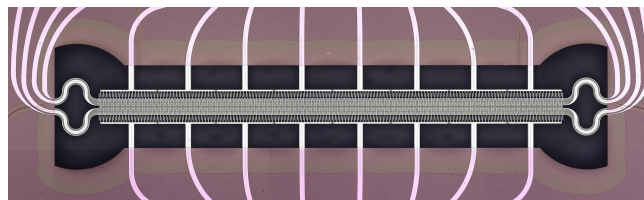


Figure 1: A photograph of a flow meter taken with a microscope. The cavity is approximately 5.2 mm long and 0.7 mm in diameter.

with the experimental measurements. The discrepancy between the simulation and measurement results was reduced using optimization methods implemented in COMSOL Multiphysics. This paper presents the procedure used to develop the numerical model of the flow sensor, defines the parameter optimization problem, and discusses the obtained optimization results.

COMSOL MODEL STRUCTURE

Sensor segment

The approximately 4 mm long sensor was divided into 0.5 mm segments corresponding to the length of the electrode comb, see Figure 2. Preliminary results were obtained using a single segment, and the model was subsequently refined. Simulating a single segment of the sensor significantly reduces the computational requirements. However, particular attention must be paid to the boundary conditions of the model.

The silicon wafer acts as a heat sink. As a first approximation, the wafer boundaries in the model can be considered as surfaces with constant ambient temperature, T_a . To obtain more realistic simulation results while maintaining relatively low computational requirements, the bottom surface of the wafer can be modeled using the External Natural Convection boundary condition [3]. The External Natural Convection boundary condition can also be applied to the upper surface of the glass protection layer on top of the chip. In the actual device, the wafer extends several millimeters on both sides of the modeled segment. From the perspective of the small, thermally isolated heater, these regions therefore behave approximately as an ideal heat sink, and a constant-temperature boundary condition can be ap-

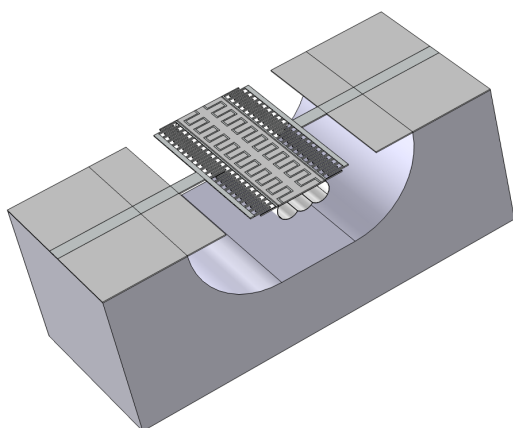


Figure 2: Geometric model of a single segment of the sensor.

plied to the lateral sides of the wafer.

At the outlet side of the modeled sensor segment, the structure can be assumed to continue into the next segment. The temperature gradient at this boundary is minimal; therefore, the entire outlet-side boundary can be modeled as Thermal Insulation.

The only problematic boundary condition is located at the inlet side, where the previously described boundary conditions cannot be applied satisfactorily. The active part of the sensor (heater) is located directly adjacent to the boundary of the simulation domain, so there is a relatively steep temperature gradient expected. Therefore, the simulated domain must be extended. This can be achieved in two ways: by explicitly simulating an additional segment representing the actual connection of the tube to the rest of the sensor chip, or by using the computationally less demanding Thin Layer boundary condition [4].

Full sensor approximation

To obtain more representative data, the model was extended to the full sensor length by creating an array of eight segments based on Figure 2. Due to the computational demands of the full model, only a single simulation was performed to determine the overall shape of the temperature field. The temperature distribution was found to be nearly identical from the second to the penultimate segment in the range of fluid flows from 0.1 to 10 l/min, which correspond to Reynold's numbers from 0 to 100. Therefore, these middle segments were represented by a single equivalent segment in subsequent simulations.

The simplified sensor model therefore consists of three segments: an inlet segment, a representative middle segment corresponding to six identical segments, and an outlet segment. Additional segments represent-

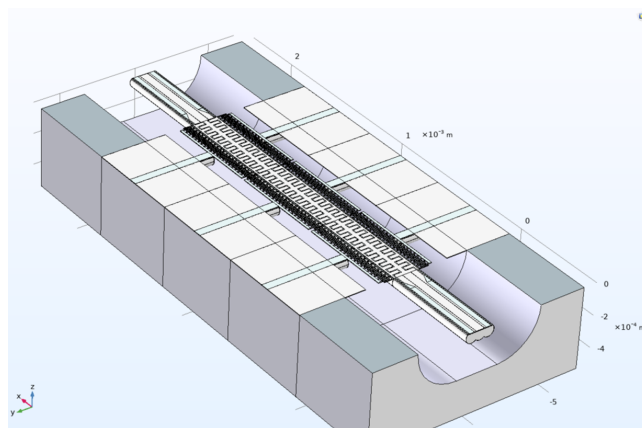


Figure 3: Geometric model of three segments of the sensor.

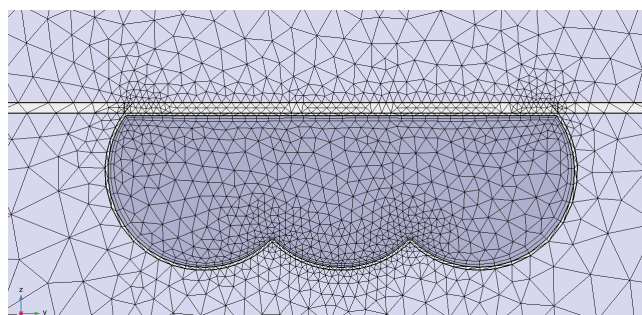


Figure 4: Minimum recommended mesh size for a flow channel with a heating element.

ing the beginning and the end of the cavity were also included in the model, as shown in Figure 3. Because the surrounding silicon acts as a heat sink, the boundary conditions on the inlet and outlet sides of these additional segments can be simplified by assuming a constant temperature.

It should be noted that, for flow rates between 10 and 50 ml/min, the gas does not reach the tube temperature within the first sensor segment. At these flow rates, heat dissipation in the gas becomes also significant. The expected viscous dissipation is approximately 1 mW per sensor segment, which can noticeably affect the gas temperature. Consequently, heat transfer between the gas and the tube influences the temperature field in the following segments. Therefore, for flow rates greater than 10 ml/min, the sensor tube cannot be shortened in the simulation. This effect is discussed in more detail in the Results section.

Used materials

The materials used in the model are listed in Table 1. Most of them were taken from the standard COMSOL material library. Some materials, specifically silicon nitride, air, and nitrogen, were modified during the parameter estimation process.

*Table 1: COMSOL Simulation Material Properties. Materials that have been modified during parameter estimation process are marked with *.*

Material	Applied to the domain	Thermal conductivity
Silicon (single-crystal)	sensor substrate	130 [$\text{Wm}^{-1}\text{K}^{-1}$] (constant)
Air (gas)*	the working medium	Standard COMSOL function (polynomial)
Nitrogen (gas)*	cavity surrounding flow pipe	Standard COMSOL function (polynomial)
Silica Glass	chip cover from the top	1.38 [$\text{Wm}^{-1}\text{K}^{-1}$] (constant)
Silicon nitride*	pipe, combs and silicon surface	Standard COMSOL function (polynomial)
Platinum	RDT's wire	Standard COMSOL function

Mesh options

The sensor model contains strongly different geometric scales; e.g., the heater dimensions and tube-wall thickness are orders of magnitude smaller than the tube length and wafer thickness. Therefore, the mesh should be switched to user-controlled and the model needs to be divided into several regions.

The mesh can be separated into the fluid-flow domain and the remaining solid parts of the model. It is advisable to define a separate mesh region for the heater and its surroundings, where a significantly finer mesh is used. As a practical minimum, at least five mesh elements should be used between two relevant surfaces or points. Figure 4 shows the minimal recommendation for the size of the mesh in the area of interest.

MODEL PARAMETER ESTIMATION

The model includes simplifications and uncertainties in geometry and material properties, which cause differences between simulated and measured data. The input of the model is the gas flow rate and the heater power, while the main output is the heater temperature. Since only steady-state conditions are considered, heat capacities can be neglected, and the optimization can focus on thermal conductivities. Where possible, dimensional uncertainties are represented by changes in effective thermal conductivity to avoid remeshing at ev-

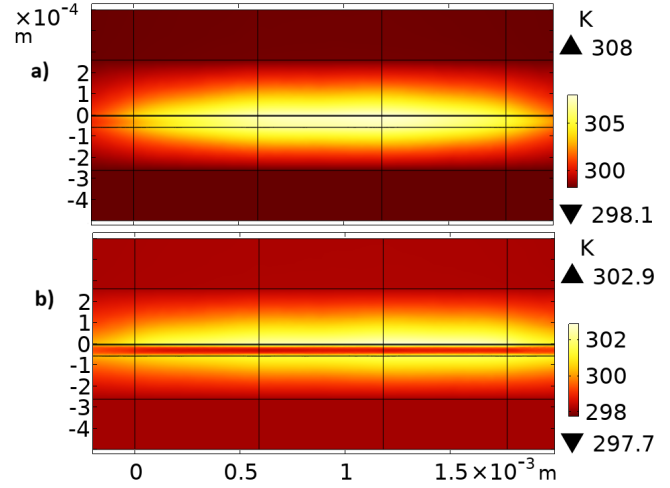


Figure 5: Simulated temperature field in the three-segment model, shown in an XY cross-section through the tube for gas flow rates of a) 1 ml/min and b) 50 ml/min.

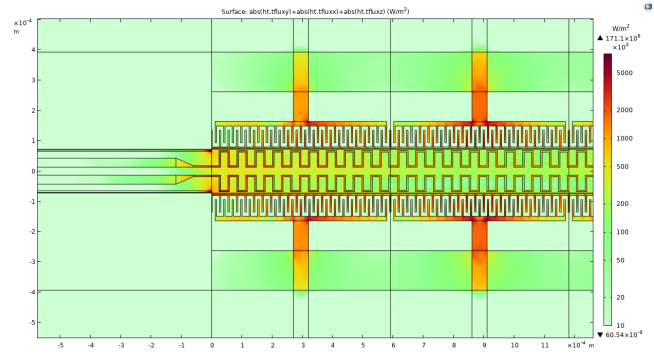


Figure 6: Absolute heat flux in the three-segment sensor model. The main heat losses occur through the electrode combs.

ery optimization iteration.

Parameter estimation was performed using one-parameter and three-parameter approaches. The thermal conductivity of the silicon nitride sensor tube, which has the dominant influence on heat transfer, was used as the optimization parameter in both cases. Approximately 80% to 90% of the heat leaves the modeled region through the silicon nitride electrode, see Figure 6. In the three-parameter estimation, the thermal conductivity of air was additionally used to represent uncertainty in the gap between the tube and electrodes, while the third parameter was the thermal conductivity of the working fluid, nitrogen.

Parameter estimation method

The model parameters were estimated using the derivative-free BOBYQA algorithm[5], which constructs a quadratic approximation of the objective function within a trust region. The method was selected because it requires only objective-function evaluations

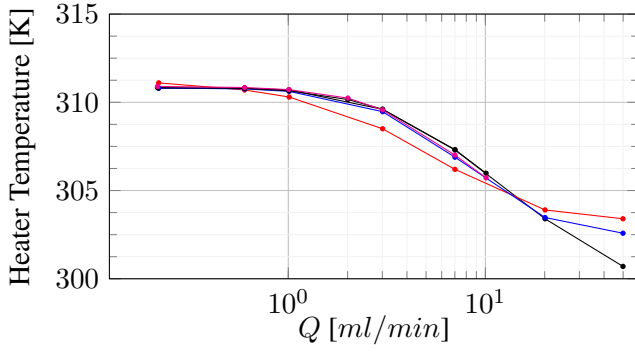


Figure 7: Measured heater temperatures (●), simulated one parameter (●) and three parameters (●) optimized heater temperatures for flow range (0.1; 50) ml/min. One parameter and three parameters (●) optimized heater temperatures for flow range (0.1; 10) ml/min.

and is therefore suitable for computationally expensive FEM models.

SIMULATION RESULTS

A MEMS thermal flowmeter model was successfully developed and properly parameterized. The model is valid only within the flow-rate range of up to 10 ml/min. After parameter optimization, the model error is below 4% of the difference temperature, see Table 2. When the flow range is extended to 50 ml/min, the model is no longer able to reproduce the measured data accurately, as shown in Figure 7 and 8. The possible reason for the error is shown in Figure 5. At high fluid velocity cool gas significantly influence the thermal field in the sensor middle segment. Therefore, the assumed simplification of the model no longer holds.

The thermal conductivity values obtained from optimization differ considerably from the theoretical values (see Table 2). This could be caused by material inhomogeneities that affect heat transfer and structural deformations, such as tube bulging. This deformation increases the distance between the tube and the electrodes, thereby reducing heat transfer through the electrode structures.

CONCLUSION

The sensor model and parameter estimation process are still evolving and the results of this study are preliminary. The sensor model precision with maximum error 3.5% of different temperature has been achieved in the 10 ml/min range. The optimization method and simulation results will be used in future sensor development and dynamic behavioral testing.

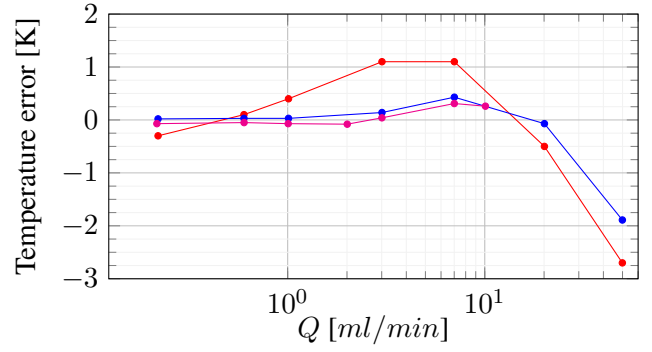


Figure 8: One parameter model (●) and three parameters model (●) temperature error for flow range (0.1; 50) ml/min. One parameter and three parameters model (●) temperature error for flow range (0.1; 10) ml/min.

Table 2: The materials thermal conductivity parameter relative changes for different optimization models. Error [K] refers to the maximum heater temperature deviation from the data, Error [%] refers to maximal heater temperature deviation in percent of different temperature against ambient temperature $T_a = 293.15[K]$.

Optimization model	Silicon nitride	Nitro-gen	Air	Error [K]	Error [%]
One parameter (10 ml/min)	0.42	-	-	0.3	3.3
Three parameters (10 ml/min)	0.42	1.03	0.50	0.3	3.4
One parameter (50 ml/min)	0.1	-	-	2.7	107.8
Three parameters (50 ml/min)	0.44	1.50	0.48	1.9	42.7

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A COMPACT, NMR RELAXOMETRY-BASED MEASURING SYSTEM FOR INLINE FLOW AND FLUID COMPOSITION ANALYSIS

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ABSTRACT

Nuclear magnetic resonance (NMR) is a versatile technology that allows for the measurement of both transport and sample properties in liquids. An NMR relaxometry-based measuring system was developed to support process monitoring and process control applications that require inline fluid flow and/or fluid composition analysis capabilities in a compact, remotely controllable apparatus. A suite of signal processing algorithms is available to support a wide range of sample analysis requirements. Application examples in NMR relaxometry, diffusometry, and velocimetry are presented to show how a single inline NMR measuring system can serve widely different processes and sample analysis requirements.

KEYWORDS

Inline NMR, Compact Magnet Design, CPMG, Relaxometry, Diffusometry, Velocimetry.

INTRODUCTION

Nuclear magnetic resonance (NMR) is a versatile measurement technology with the potential to help resolve the long-standing challenge of robust and accurate inline analysis of moving samples under industrial process conditions [1]. These challenges, occur in product quality assurance, for instance, of foods, chemicals, and pharmaceutical products, and in flow measurement applications for process control.

NMR allows both transport properties [2] and sample properties [3,4] to be measured using a single technology. Due to its contactless and non-destructive measurement principle, NMR measurements do not affect product quality and do not disturb sample transport, and the NMR equipment requires little to no maintenance. In addition, NMR measurements can be designed to be intrinsically safe to humans. Despite these positive attributes, the large size and high cost of NMR hardware often limit the technology's applicability to industrial processes.

In a collaboration between the University of Twente (magnet design) [5], Delft University of Technology (electronics design) [6], and KROHNE (system integration), a compact NMR system has been developed with the aim to lift these limitations for a wide range of different process monitoring and process control application that require inline fluid flow and fluid composition analysis.

In this article the design of the compact NMR

system is discussed and the wide variety of NMR analysis applications that are supported by the system will be illustrated. For static samples, an NMR relaxometry and diffusometry example is given, and NMR velocimetry is presented on flowing samples.

NMR SYSTEM DESIGN

The compact, inline NMR analyzer system embeds all components in a sleek and rugged anodized aluminum housing (35 x 23 x 7 cm), as shown in Figure 1 together with a glass of water and a 60 ml syringe as scale reference. The power and data cable connections are located at the back of the housing, while the process connections that support inline installation of the system are located on the front panel.

Two Luer lock connectors on the NMR analyzer system front panel allow for connection of syringes and/or flexible tubing for feeding samples into the ROI. The tubing inside the system can be modified to support applications in different flow rate operating ranges.

The compact NMR analyzer system combines the 8.0 x 3.5 x 3.5 cm, 0.5 T yoke-based permanent magnet shown in Figure 2 that is fitted with two steel inserts for magnetic field shimming purposes, with compact analog and digital electronics. The magnetic field distribution simulation results presented in the right side of Figure 2 show that the magnet has a limited stray field, despite the compact and open design.

Figure 3 shows how the magnet, electronics, and process connectors are all mounted on a single base plate to ensure rigid and stable connections between



Figure 1: The compact NMR system shown together with a glass of water and a 60 ml syringe as scale reference.

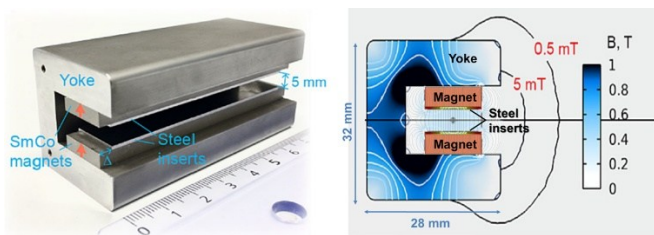


Figure 2: Despite its compact size and open design, the yoke-based permanent magnet design has a limited stray field [5].

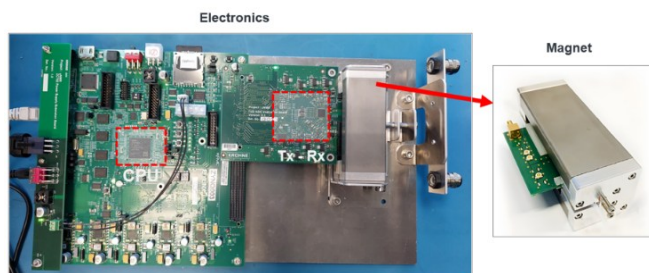


Figure 3: The NMR analyzer system without the housing cover shows the power and data connections (left), compact electronics and magnet (center) and process connectors (right) mounted on a single base plate.

all components to make the system resilient against shocks and vibrations.

Magnetic field mapping measurement results for the yoke-based permanent magnet are shown in Figure 4 as a set of 2D slices along the center axis (top) and for three cross sections (bottom). These representations illustrate that this design offers better than 200 ppm field homogeneity in a 20 mm long and 1 mm diameter region-of-interest (ROI) that is positioned at roughly $\frac{3}{4}$ of the magnet length. This off-center positioning of the ROI maximizes fluid polarization time for flowing samples without affecting measurement performance on static samples.

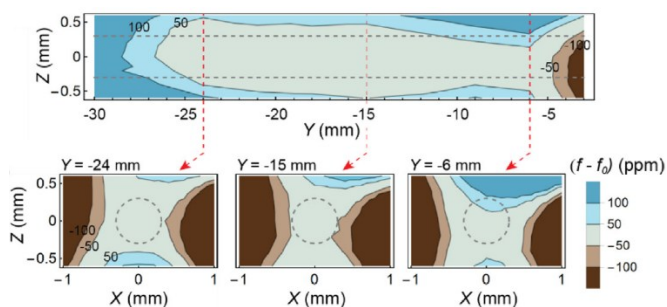


Figure 4: A set of 2D representations of the measured magnetic field distribution within the permanent magnet system in which the 20 mm long, 1 mm diameter ROI is indicated by dashed lines [5].

MEASUREMENT SOFTWARE DESIGN

The NMR analyzer can be remotely controlled via Ethernet communication by any PC or server that runs proprietary NMR measurement control software. This

software architecture allows control from outside specialized process environments, such as (bio)chemical laboratories and clean rooms. In addition, this architecture supports for a single PC or server to operate multiple NMR analyzers at the same time, providing enhanced automation and integration possibilities in process control systems, for instance, in pharmaceutical and biotech production facilities.

The NMR analyzer system's software currently supports transverse relaxation-based relaxometry analysis using the CPMG pulse sequence, but the hardware can support longitudinal relaxation-based relaxometry analysis as well. The number of acquired echoes in the CPMG can be varied from 1-16,000, and CPMG echo spacings from 186 μ s to 17 s are supported, which allows CPMG-based diffusion measurements to be performed as well. Figure 5 shows the first three echoes in a CPMG measurement on water in which a 4 ms echo spacing was used.

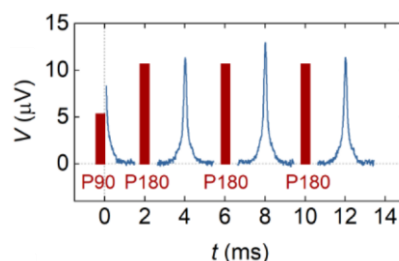


Figure 5: The first three echoes in a CPMG measurement with 4 ms echo spacing measured on water with the position of the RF pulses illustrated as vertical bars [5].

A variety of signal processing algorithms are implemented in the software that support both single and multiexponential relaxation time distribution analysis. Both discrete and continuous T_2 distribution or Inverse Laplace Transform (ILT) analysis is available, thus providing signal analysis optimization flexibility to each specific sample and/or application.

APPLICATION EXAMPLES

To illustrate the capabilities of the compact NMR analyzer several examples of NMR relaxometry and diffusometry analysis for static samples, and NMR velocimetry analysis in fluid flow are presented below.

CPMG diffusometry

As discussed in the preceding section, the compact NMR analyzer system supports a wide range of echo spacings in CPMG pulse sequences. To illustrate this capability, Figure 6 shows the T_2 measurements results for a CPMG diffusometry experiment. The NMR analyzer system was fitted with a 1 mm internal diameter flow tube to hold the water sample, and the CPMG echo spacing varied logarithmically between

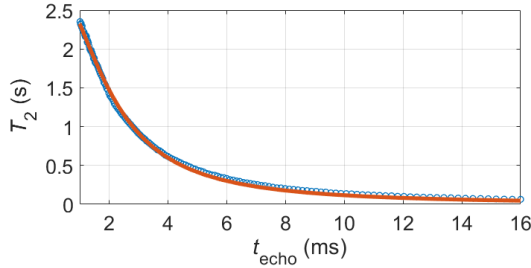


Figure 6: Measured T_2 of water as a function of CPMG echo spacing between 1-16 ms (markers) together with a fit of the theoretical T_2 variation (Eq. 1) expected due to diffusion in a constant background gradient (solid line).

1-16 ms for this experiment.

The 200 ppm magnetic field inhomogeneity in a flow tube of 1 mm diameter corresponds to an effective constant background field gradient of 100 mT/m or 10 G/cm. The random, diffusive translational motion of water molecules during the time between refocusing pulses results in an additional signal dephasing that increases with increasing t_{echo} . The resulting reduction of the measured, effective T_2 is given by [7]:

$$1/T_{2,\text{eff}} = 1/T_2 + \gamma^2 G^2 t_{\text{echo}}^2 D/12. \quad (1)$$

The solid line in Figure 6 shows a fit of Eq. (1) to the measured T_2 of water as a function of CPMG echo spacing. The good correspondence between data and fit illustrates how such an experiment can be used to measure the diffusion coefficient of the sample.

T_2 distribution-based composition analysis

The signal processing methods implemented in the compact NMR analyzer system control software are well-suited to study simple mono-exponential T_2 decays, like observed for water in the diffusometry experiment presented above, but are also capable of doing more advanced multi-exponential T_2 relaxation-based signal analysis.

Figure 7 shows the CPMG signals measured for a set oil-water emulsions in which the mass fraction of oil varied from 0% to 50% in steps of 10%. To stabilize the oil emulsions, 1-2% of soy lecithin was used as an emulsifier. For consistency, this emulsifier was also added to the sample that contained 0% oil, hence it is labelled as “W+L”. The initial part of the CPMG signals shows a progressively steeper decay as the oil content increases. This can be explained by the much shorter T_2 times of oil as compared to water, and its increasing contribution to the total signal with increasing oil mass fraction.

The Inverse Laplace Transform (ILT) analysis results for two samples are highlighted in the inset of Figure 7. These T_2 distributions were derived from the CPMG signals of the 0% and 40% oil mass fraction

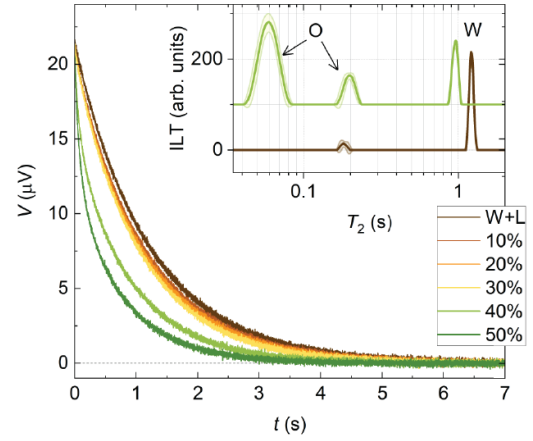


Figure 7: The measured CPMG signals of static oil-water emulsions with varying mass fractions of oil. The inset shows the continuous T_2 distributions derived from the CPMG signals of the 0% (W+L) and 40% oil mass fraction samples.

samples and show the clear separation in oil relaxation times (< 0.5 s) and water relaxation times (> 0.5 s) for the 40% oils sample. The small relaxation time contribution around 0.2 s in the water sample, can be attributed to the presence of soy lecithin emulsifier in this sample.

CPMG velocimetry

In static samples as discussed above, T_2 relaxation, including its diffusion dependence, is the only effect to be considered. In the presence of coherent translational motion, such as fluid flow, the time-evolution of CPMG echo amplitudes will additionally be modified by the flow of spins in and out of the ROI. As such, the time evolution of the CPMG echo amplitudes can be utilized for NMR velocimetry.

Let u be a uniform flow velocity in the sample and let L_1 be the effective length of the ROI along the flow direction. The volume excited by the P90 pulse of the CPMG pulse sequence will then flow out of the ROI within a time $t_0 = L_1/u$. Since the fresh spins that flow into the ROI did not experience the P90 pulse, these spins do not contribute to the CPMG echo amplitudes. The uniform outflow of the excited volume consequently results in a linear decay of the CPMG echo amplitude towards zero over the time t_0 . Note that T_2 relaxation is always present in the sample as well and, as a result, the resulting time-evolution of the CPMG echo amplitudes is given by [2],

$$S(t) = (1 - L_1/t_0) \exp(-t/T_2). \quad (2)$$

Since the CPMG echo amplitude represents the volume integral of the NMR signal inside the ROI, in the presence of a general time-dependent and spatially non-uniform flow velocity profile,

$$u(r, t) = u_0 + u_1(r, t), \quad (3)$$

the time t_0 at which the linear decay reaches zero amplitude is related to the average flow velocity u_0 as

$$t_0 = L_1/u_0. \quad (4)$$

Figure 8 shows the CPMG echo amplitude as function of time as measured (left) and after correcting for T_2 relaxation (right) for a static water sample (0.0 ml/min) and eight different water flow rates in the range 0.1-20.0 ml/min. The linear decay of the CPMG echo amplitude due the mean flow velocity is observed in the T_2 relaxation corrected signals. The extrapolated time t_0 is indicated for the CPMG signals at flow rates of 0.5, 1.0, and 2.0 ml/min. It can be seen that the time t_0 is indeed halved with each consecutive factor 2 increase in u_0 . The T_2 relaxation corrected CPMG signals at these flow rates show a linear decay up to approximately $t = t_0/2$, and after that a rounded tail is visible in the CPMG signal.

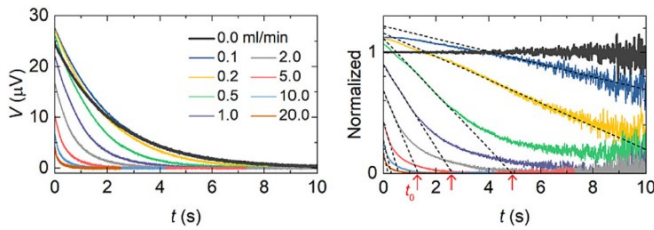


Figure 8: (left) CPMG signals for a static water sample and eight different water flow rates. (right) After correcting for T_2 relaxation, the initial part of the CPMG signal follows a linear decay that crosses the x-axis at a time t_0 , which is a measure for the sample's average flow velocity [5].

In these experiments the flow velocity profile was laminar, and thus $\max\{u\} = 2u_0$. The time $t = t_0/2$ thus corresponds with the time at which the flow streamlines with the maximum flow velocity have just left the ROI and do not contribute to the CPMG signal anymore. As time goes on, progressively more flow velocity components disappear from the ROI and the average flow velocity $\langle u \rangle$ of the spins contributing to the NMR signal decreases accordingly, such that

$$\begin{cases} \langle u \rangle(t) = u_0 & (t < t_0/2) \\ \langle u \rangle(t) < u_0 & (t > t_0/2) \end{cases} \quad (4)$$

A progressively lower value for $\langle u \rangle(t)$ corresponds with a progressively weaker linear decay in the T_2 relaxation corrected CPMG signal, which results in the rounded tail observed in Figure 8.

In general, $\langle u \rangle(t)$ and the time $t_0(t)$ at which the tangent of the T_2 relaxation corrected CPMG signal intercepts the x-axis can be related as

$$\begin{aligned} \langle u \rangle(t) &= u_0 + \langle u_1 \rangle(t) \\ &= L_1/(t_0(t) - t), \end{aligned} \quad (5)$$

with

$$u_0 = \langle u \rangle(0) \quad (6)$$

and

$$\langle u_1 \rangle(t) = \langle u \rangle(t) - u_0. \quad (7)$$

When considering time-independent or time-averaged velocity profiles, $u(r, t) = u(r)$, the spatial dependence of the flow profile is encoded in $t_0(t)$ and rheological sample information can be inferred from the (time-averaged) flow induced CPMG signal decay.

CONCLUSION

The NMR analyzer system design and application examples presented here show that the compact, NMR relaxometry-based measuring system developed in a collaboration between the University of Twente, Delft University of Technology, and KROHNE is capable of performing NMR relaxometry-based analysis on both static and flowing samples using a single, compact system. The hose connectors on the housing's front panel, the flexible internal tubing size, and the variety of signal processing algorithms available support inline flow and fluid composition analysis for a variety of different fluids, flow rates, and process applications.

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TOWARDS A COMPACT MULTIDIRECTIONAL HOT-WIRE ANEMOMETER FOR AIRFLOW SENSING IN GREENHOUSE CANOPIES

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ABSTRACT

Airflow in dense greenhouse canopies is difficult to measure with conventional anemometers, limiting spatially resolved microclimate assessment. This work develops and characterizes the Localized Environmental AirFlow (LEAF) sensor, a compact hot-wire anemometer with four Pt100 elements for multidirectional sensing. A digital proportional-integral controller uses pulse-width-modulated heating to maintain near-constant element temperature. Wind-tunnel tests with one element at a 2048-count setpoint showed stable operation under airflow. Between 0 m s^{-1} and 1 m s^{-1} , sensitivity reached $9.23 \text{ \%}/(\text{m/s})$ to $10.21 \text{ \%}/(\text{m/s})$. Between 1 m s^{-1} and 5 m s^{-1} , sensitivity was $2.17 \text{ \%}/(\text{m/s})$. These results support directional sensing development and greenhouse validation.

KEYWORDS

Thermal flow sensor, hot-wire anemometry, constant-temperature anemometry, multidirectional airflow sensing, greenhouse microclimate, horticulture.

INTRODUCTION

Controlled-environment agriculture increasingly relies on distributed measurements of temperature, relative humidity (RH), CO_2 concentration, and light for climate and crop management [1, 2]. Airflow is similarly important because it governs heat, water-vapor, and CO_2 transport, yet is rarely measured in or around crop canopies. Dense foliage can create stagnant, spatially varying microclimates with local humidity and temperature differences, CO_2 depletion, and conditions favorable to fungi and crop disease [3, 4]. Distributed airflow sensing combined with feedback-controlled ventilation could promote more homogeneous growing conditions and thereby improve yield.

Commercial anemometers are primarily intended for single-point outdoor, room-scale, or duct measurements. Their size, cost, and geometry hinder dense deployment within crop canopies. Although miniaturized hot-wire and calorimetric flow sensors have shown potential for horticultural microclimate measurements [5, 6], practical in-canopy sensing also requires adjustable sensitivity, directional information, local processing, and replication at multiple canopy heights.

We present the Localized Environmental AirFlow (LEAF) sensor, an initial anemometer design addressing these requirements. Four platinum resistance temperature detectors (Pt100 RTDs) positioned around a narrow printed-circuit-board (PCB) section serve as combined heating and sensing elements. Constant-temperature operation of one element was achieved using a proportional-integral (PI) controller, which regulates its heating power through the PWM duty cycle to maintain a fixed temperature setpoint as airflow changes. Wind-tunnel experiments then characterized the duty-cycle response over a range of airflow velocities and compared measurements at four sensor orientations to investigate the sensor's angular response.

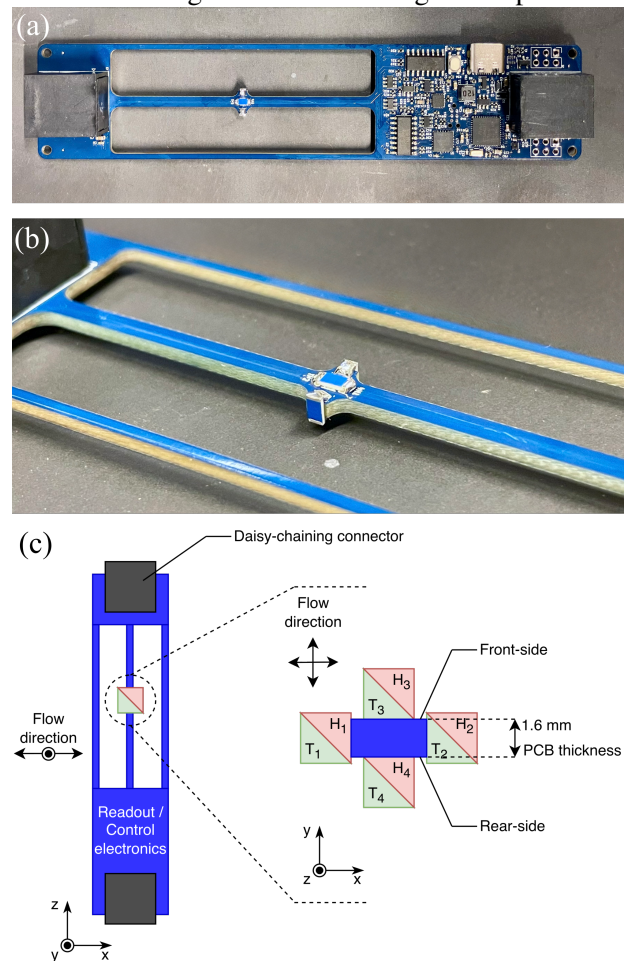


Figure 1: (a) Assembled LEAF sensor PCB. (b) Closeup of the four Pt100 heating/sensing elements. (c) Positioning of the four sensing elements relative to the direction of airflow.

SENSOR DESIGN

The LEAF sensor PCB measures approximately 30 mm by 140 mm and has a narrow central region designed to minimize disturbance of the local airflow. Four surface-mount Pt100 elements are positioned on the front, rear, and sides of this region (Figure 1b and Figure 1c). Each element acts as a self-heated resistance thermometer. In hot-wire operation, convective cooling increases the electrical power required to maintain the setpoint temperature, with a PWM duty-cycle serving as a measure of the applied heating power and therefore as the flow-dependent output. Comparing the responses of the four elements is intended to enable two-dimensional directional sensing, while combined four-element and calorimetric operation remain subjects of future characterization.

Each Pt100 is incorporated into a Wheatstone bridge whose balance point is adjusted using a digital potentiometer. The amplified bridge output is sampled by the microcontroller's 12-bit analog-to-digital converter. Analog multiplexers allow the digital potentiometer and instrumentation amplifier to be shared between the four sensing channels, reducing component count and PCB area. An on-board Sensirion SHT41 measures ambient temperature and RH for future environmental compensation.

For vertically distributed measurements, multiple LEAF sensors can be daisy-chained using selectable-length cables. The resulting sensor string can be suspended within a crop canopy to measure spatial airflow gradients at multiple heights.

MATERIALS AND METHODS

Constant-temperature control

The Wheatstone bridge containing the selected Pt100 is powered by a 12 V supply and switched by a MOSFET driven by a 1 kHz pulse-width-modulated (PWM) signal (Figure 2). Varying the PWM duty cycle controls the average electrical power applied to the Pt100 and therefore its heating. The amplified bridge output is sampled during the high phase of the PWM waveform, when the element is actively heated. Samples near the PWM edges are excluded in firmware to reject switching artifacts caused by the instrumentation amplifier's transient response. Hardware averaging over 16 ADC samples and a 64-sample moving-average filter further reduce high-frequency fluctuations before controller input (Figure 2).

The operating temperature of the Pt100 element was set to a nominal value of 60 °C by adjusting the digital potentiometer in the reference branch of the Wheatstone bridge. At bridge balance, the amplified output is approximately 1.65 V, corresponding to the 12-bit ADC midpoint of 2048 counts, which was used as the controller setpoint throughout the experiments. The PI controller adjusts the PWM duty cycle to minimize the ADC error and maintain a near-constant element temperature under changing airflow. Empirical tuning resulted in gains of $K_p = 0.213$ and $K_i = 0.24$. Because of the sensing element's thermal inertia and the comparatively slow airflow variations expected within greenhouse canopies, derivative action was not considered necessary.

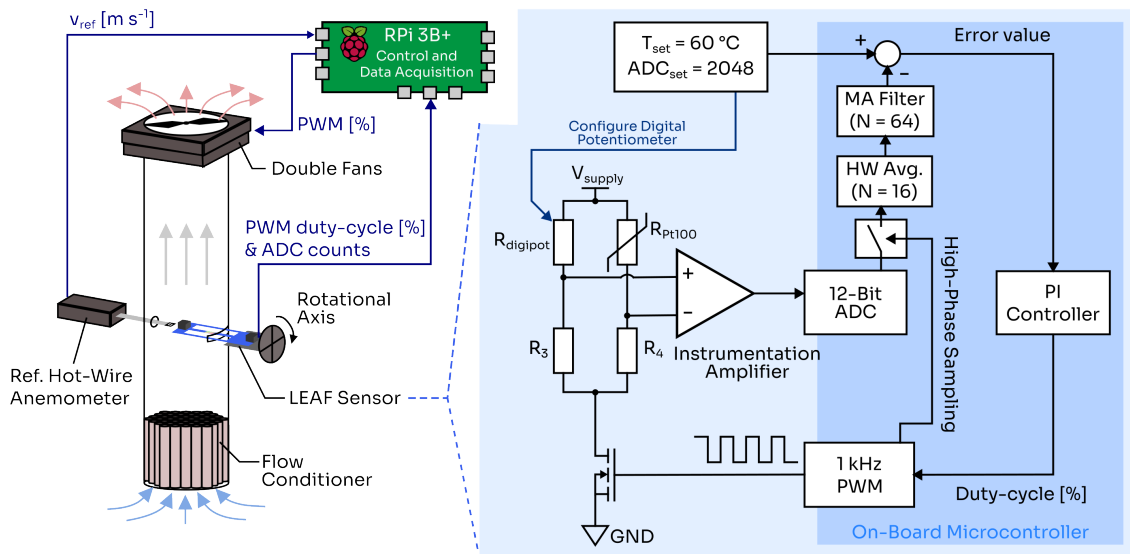


Figure 2: The sensor characterization setup showing the custom-built wind tunnel with reference sensor, controller, and data acquisition is shown on the left. A representation of the LEAF's PI-controlled readout circuitry is shown on the right.

Wind-tunnel characterization

The LEAF sensor was tested in a custom-built wind tunnel containing a flow conditioner and separately controlled fans for lower and higher velocities (Figure 2). A Delta Ohm HD29V3 TO3 hot-wire anemometer was used as the reference sensor. The LEAF sensor was mounted on a rotational stage, while a Raspberry Pi logged the LEAF ADC value, PWM duty-cycle, reference velocity, and controlled fan speeds. Fan speed was increased in 1 % increments at 30 s intervals, producing 30 samples per setting at a reporting rate of 1 Hz. The samples at each setting were averaged.

Initial characterization used one Pt100 element in hot-wire mode. Measurements below 1 m s^{-1} were performed at sensor rotations of 0° (facing upstream), 90° , 180° , and 270° to examine whether the board orientation influenced the response. A separate characterization at 0° covered a higher velocity range of 1 m s^{-1} to 5 m s^{-1} . Below approximately 0.5 m s^{-1} , changes in apparent sensitivity were observed. Their origin remains unresolved and may involve the flow field, the wind-tunnel openings, or the reference measurement. Further experiments are needed before drawing conclusions in this range.

RESULTS AND DISCUSSION

PI controller performance

The PI controller maintained the filtered ADC signal within approximately ± 1 count of the 2048-count setpoint during steady airflow. Following abrupt changes in wind-tunnel velocity, the signal returned to the setpoint within 0.1 s to 0.5 s, depending on the magnitude of the change. This indicates that the controller can maintain near-constant-temperature operation under varying airflow conditions.

With the ADC signal maintained near the setpoint, the PWM duty cycle serves as the flow-dependent output. As airflow increases, greater convective heat loss causes the controller to increase the duty cycle and restore the bridge balance. This behavior was observed at all four tested sensor orientations (Figure 3).

Low-flow and orientation response

Figure 3a shows the PWM duty-cycle response of a single Pt100 between 0 m s^{-1} and 1 m s^{-1} at sensor orientations of 0° , 90° , 180° , and 270° . At each orientation, the duty cycle increased with airflow velocity as the controller compensated for greater convective heat loss. Linear fits yielded an average sensitivity of $9.23 \text{ \%}/(\text{m/s})$ for the 0° and 180° measurements and

$10.21 \text{ \%}/(\text{m/s})$ for the 90° and 270° measurements. The Root Mean Square Errors (RMSEs) of the four linear fits ranged from 0.183 % to 0.308 %, indicating limited output variability around the fitted responses.

The absolute duty cycle depended on sensor orientation. At 180° , the sensing element was shielded from the incoming airflow by the PCB and therefore required a lower duty cycle to maintain the temperature setpoint than at 0° , where it was directly exposed. After normalization, the responses at 0° and 180° were nearly identical, as were those at 90° and 270° (Figure 3b). This pairwise behavior demonstrates a repeatable influence of sensor orientation on the response and supports the potential of the four-element arrangement for directional sensing. Measurements from a single element are, however, insufficient to determine a unique airflow direction.

Changes in apparent sensitivity remain visible at orientations of 90° and 270° , and require further investigation. The reported sensitivities should therefore be interpreted as average responses over the complete 0 m s^{-1} to 1 m s^{-1} range.

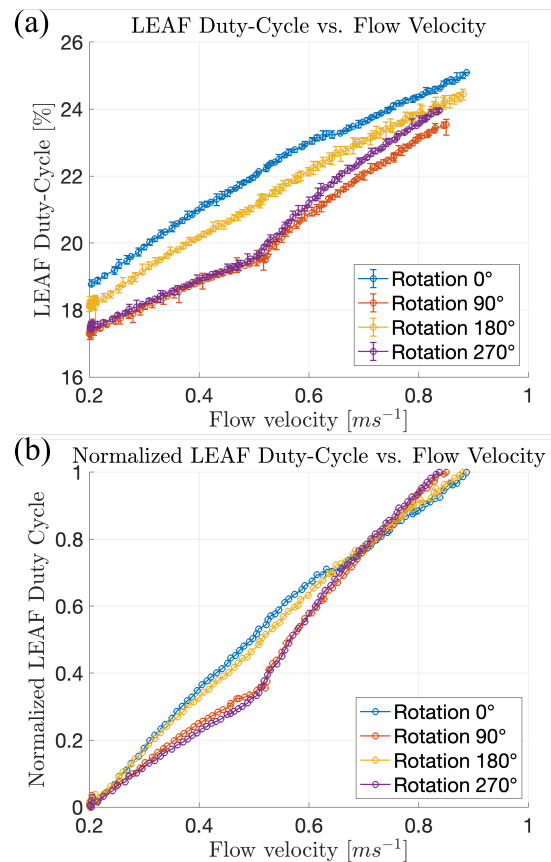


Figure 3: Initial characterization results at a range of 0 m s^{-1} to 1 m s^{-1} , showing (a) duty-cycle curves for four orientations, and (b) normalized versions of the curves.

Higher-flow response

The response at higher airflow velocities was characterized between 1 m s^{-1} and 5 m s^{-1} at an orientation of 0° (Figure 4). The duty cycle increased consistently with airflow velocity, and a linear fit yielded a sensitivity of $2.17 \text{ \%}/(\text{m/s})$. This lower value compared with the low-flow sensitivities indicates that the sensor is more sensitive to velocity changes in the low-flow range. The reduction in sensitivity at higher velocities is consistent with the nonlinear relationship between convective heat transfer and airflow velocity in hot-wire anemometry. Nevertheless, the consistent increase in duty cycle demonstrates that the sensor remained responsive throughout the tested 1 m s^{-1} to 5 m s^{-1} range.

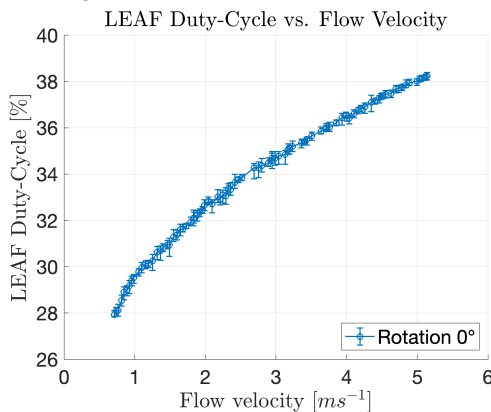


Figure 4: Initial characterization results at a range of 1 m s^{-1} to 5 m s^{-1} , showing duty-cycle versus flow velocity.

Relevance and limitations

The sensor's higher sensitivity between 0 m s^{-1} and 1 m s^{-1} shows that the sensor is particularly responsive in the low-flow range relevant to in-canopy measurements. The RMSEs of $0.183 \text{ \%}$ to $0.308 \text{ \%}$ indicate limited output variability around the low-flow linear fits, but do not represent the sensor's absolute measurement accuracy. Changes in apparent sensitivity at orientations of 90° and 270° remain unexplained and require repeated measurements with improved low-speed flow control and reference instrumentation.

The four-orientation measurements demonstrate that the response is influenced by the sensing element's exposure to the airflow and by the PCB geometry. The similar normalized responses within the $0^\circ/180^\circ$ and $90^\circ/270^\circ$ pairs provide initial support for the intended directional sensing principle. However, measurements from one element at four sensor orientations cannot determine a unique airflow direction. Directional measurement will require characterization of all four Pt100 elements over a larger number of airflow angles. The

effects of ambient temperature, relative humidity, foliage, and greenhouse airflow conditions also remain to be evaluated.

CONCLUSION

This work demonstrates PI-controlled constant-temperature operation of one Pt100 element on the LEAF sensor, with the controller maintaining the 2048-count setpoint under changing airflow. Between 0 m s^{-1} and 1 m s^{-1} , the pair-averaged sensitivities were $9.23 \text{ \%}/(\text{m/s})$ at $0^\circ/180^\circ$ and $10.21 \text{ \%}/(\text{m/s})$ at $90^\circ/270^\circ$, with linear-fit RMSEs of $0.183 \text{ \%}$ to $0.308 \text{ \%}$. Between 1 m s^{-1} and 5 m s^{-1} , the sensitivity decreased to $2.168 \text{ \%}/(\text{m s}^{-1})$, demonstrating greater sensitivity in the low-flow range. Normalized responses within each orientation pair indicate orientation dependence, although one element cannot uniquely determine airflow direction. Future work will address the lowest-velocity behavior, characterize all four elements, compensate for ambient conditions, and validate the sensor in greenhouse canopies.

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Design and FEM Validation of a Perforated MEMS Paddle for Viscosity-Dependent Gas Flow Sensing

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Abstract—This paper presents a MEMS gas sensor based on viscous drag generated by flow through a suspended perforated silicon paddle. The proposed architecture distributes the gas flow over thousands of parallel micro-openings, combining a small hydraulic diameter and large total flow area to obtain substantial viscous interaction without concentrating the pressure drop in a single narrow channel. A $2 \times 2 \text{ mm}^2$ paddle containing thousands of parallel rectangular microchannels formed by the perforations was designed. The selected $3.5 \times 11.5 \text{ }\mu\text{m}^2$ pores have a hydraulic diameter of $5.3 \text{ }\mu\text{m}$ and give ≈ 2 times the calculated viscous force of a circular-pore design with the same paddle footprint. The paddle is suspended by four folded-beam springs and read out using capacitive comb transduction. Finite-element analysis predicts an out-of-plane stiffness of 10 N/m , a first resonance at 1048.7 Hz , and a maximum stress of approximately 40 MPa at $300 \text{ }\mu\text{N}$ loading. Fluidic FEM predicts a pressure drop of 65.7 Pa through a single pore, in close agreement with the analytical value of 65.9 Pa . These results demonstrate the feasibility of a perforated MEMS structure for viscosity-dependent gas sensing.

Index Terms—MEMS, drag force, gas sensing, viscosity, gas mixture, gas identification, microfluidics

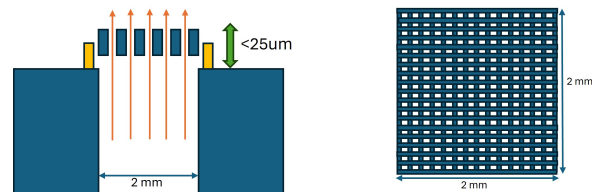
I. INTRODUCTION

Gas-flow sensors are widely used in industrial process control, environmental monitoring, biomedical systems, and gas analysis [1], [2]. Besides flow rate, gas properties such as density and viscosity contain information about gas species and composition. Conventional MEMS flow sensors are predominantly thermal [1], [3]. Although thermal sensors can be highly sensitive, they require continuous power dissipation and are affected by gas-dependent thermal properties and temperature variations [4].

Mechanical drag-force sensing offers an alternative approach in which the momentum and viscous interaction between a flowing gas and a compliant microstructure are converted into mechanical displacement [5]. At very low Reynolds numbers ($Re \ll 1$), viscous effects dominate and the resulting force is strongly dependent on dynamic viscosity [6], [7].

Conventional viscosity sensors based on hydraulic resistance face an important design trade-off. Increasing sensitivity generally requires smaller flow channels and higher hydraulic resistance, which simultaneously increases the pressure drop across the sensor. This can limit their use in low-pressure gas-flow systems due to the associated pressure losses.

This work addresses this trade-off using a suspended perforated MEMS paddle. Instead of routing the complete flow through one high-resistance channel, the flow is distributed



(a) Device concept and flow path. (b) Perforated sensing paddle.

Fig. 1: Concept of the perforated MEMS viscosity sensor. Gas flows through the perforated sensing paddle, generating a viscous drag force that causes out-of-plane deflection. The resulting displacement is used for capacitive readout. The maximum deflection is below $25 \text{ }\mu\text{m}$, limited by the device-layer thickness.

through more than 30,000 parallel micro-openings. The architecture combines a small hydraulic diameter with a large total flow area, allowing substantial cumulative viscous drag while keeping the pressure drop across the parallel pore array relatively small. The objective of this work is to develop and validate the analytical and numerical design of a MEMS viscosity sensor operating in the creeping-flow regime. The design includes optimization of the perforation geometry, mechanical suspension, fluidic response, and capacitive transduction.

II. OPERATING PRINCIPLE AND PADDLE DESIGN

The device consists of a suspended sensing paddle, folded-beam suspension, flow-guiding trench, and capacitive readout. It is intended for fabrication in a silicon-on-insulator (SOI) process. The $25 \text{ }\mu\text{m}$ silicon device layer defines the paddle and suspension, while the handle layer forms the flow-guiding structure.

Fig. 1 illustrates the operating principle. Gas enters the flow-guiding trench and passes through the perforations. Viscous shear at the pore walls generates a drag force on the paddle. The viscous force can be derived starting from the Hagen-Poiseuille relation for fully developed laminar flow in a microchannel, where the pressure drop scales as [8], [9]:

$$\Delta p \sim \frac{\mu L Q}{D_h^4}, \quad (1)$$

where μ is dynamic viscosity, L is pore length, Q is volumetric flow rate, and D_h is hydraulic diameter.

For one pore, the viscous force can be written as

$$F_{\text{pore}} = C_{\text{visc}} \frac{\mu L v_{\text{pore}} A_{\text{pore}}}{D_h^2}, \quad (2)$$

where C_{visc} accounts for non-ideal geometry, A_{pore} is the pore cross-sectional area of a single channel, and v_{pore} is the mean velocity inside the channel. For N identical pores,

$$F_{\text{total}} = N C_{\text{visc}} \frac{\mu L}{D_h^2} v_{\text{pore}} A_{\text{pore}}. \quad (3)$$

The total open area of the perforated paddle is related to the porosity ϕ ,

$$N A_{\text{pore}} = \phi A_{\text{total}}, \quad v_{\text{pore}} = \frac{v}{\phi}. \quad (4)$$

Thus,

$$F_{\text{total}} = C_{\text{visc}} \frac{\mu L v A_{\text{total}}}{D_h^2} \quad (5)$$

This result provides an important design insight for the perforated paddle. For a given inlet velocity, paddle area, channel length and fluid viscosity, the total viscous force is independent of the porosity explicitly. Instead, the force is strongly governed by the hydraulic diameter through the $1/D_h^2$ dependence. Consequently, reducing the hydraulic diameter increases the viscous force generated by the perforated structure.

III. PADDLE GEOMETRY AND GAS RESPONSE

The hydraulic diameter is defined by

$$D_h = \frac{4A}{P_{\text{wetted}}}, \quad (6)$$

where A is flow area and P_{wetted} is wetted perimeter [6]. Increasing wetted perimeter at fixed flow area reduces D_h and enhances viscous interaction.

The sensing area was selected as $2 \times 2 \text{ mm}^2$ and the pore length as $25 \text{ }\mu\text{m}$. Circular, square, and rectangular perforations were compared. The results are summarized in Table I.

TABLE I: Comparison of perforation geometries for the $2 \times 2 \text{ mm}^2$ paddle. Calculations use air, $\mu = 1.8 \times 10^{-5} \text{ Pa s}$, $p = 101325 \text{ Pa}$, and $T = 298 \text{ K}$.

Shape	Short side (μm)	Long side (μm)	Pitch (μm)	Porosity	D_h (μm)	F_{total} (nN)
Circle	7.5	7.5	11.0	0.365	7.500	3125
Square	6.5	6.5	10.0	0.422	6.500	4155
Rectangular	3.5	11.5	15×7	0.383	5.367	6089

The selected rectangular geometry gives the smallest hydraulic diameter and the highest calculated viscous force. At the same footprint, it provides approximately $1.95\times$ the force of the circular design and $1.47\times$ that of the square design. The final paddle contains 37905 rectangular pores.

For a fixed mass flow rate, $\dot{m} = \rho v A_{\text{total}}$, Eq. (5) becomes

$$F_{\text{total}} = C_{\text{visc}} \frac{\mu L}{D_h^2} \frac{\dot{m}}{\rho}. \quad (7)$$

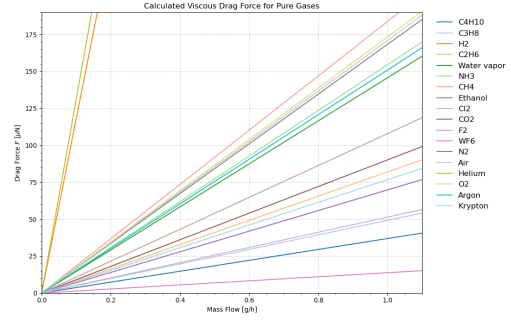


Fig. 2: Calculated viscous force versus mass flow rate for selected pure gases at $p = 101325 \text{ Pa}$ and $T = 298 \text{ K}$.

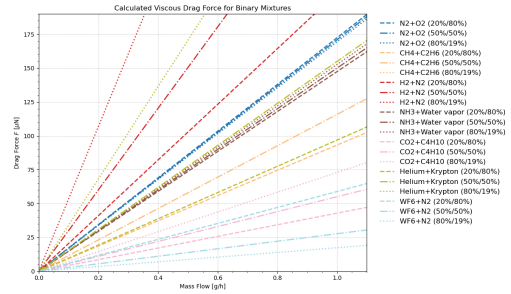


Fig. 3: Calculated viscous force versus mass flow rate for selected binary gas mixtures. The slope changes with mixture composition through $\mu_{\text{mix}}/M_{\text{mix}}$.

Using $\rho = pM/(RT)$ for an ideal gas gives

$$F_{\text{total}} = C_{\text{visc}} \frac{\mu}{M} \frac{RT}{p} \frac{L}{D_h^2} \dot{m} \quad (8)$$

where M is molar mass. Thus, for fixed geometry, pressure, temperature, and mass flow, the gas response is governed primarily by μ/M .

The calculated response for selected pure gases is linear with mass flow rate, while its slope varies with μ/M . Light gases such as H_2 and He therefore give relatively high force per unit mass flow, whereas heavier gases such as Kr , Cl_2 , and WF_6 give lower responses. At a maximum mass flow of 1.2 g/h , most investigated gases remain within approximately $0\text{--}160 \text{ }\mu\text{N}$.

For binary mixtures, Wilke's mixing rule is used to obtain the effective viscosity [10], while molar mass is obtained from the mole-fraction-weighted component values. The resulting response is governed by the effective $\mu_{\text{mix}}/M_{\text{mix}}$ ratio.

Mixture responses remain approximately linear over the investigated range. However, mixtures having similar $\mu_{\text{mix}}/M_{\text{mix}}$ ratios can produce force differences below the target resolution of $5 \text{ }\mu\text{N}$. This limits discrimination of closely related compositions and defines an important requirement for the readout.

IV. MECHANICAL SUSPENSION AND CAPACITIVE READOUT

The paddle is suspended by four folded-beam springs arranged symmetrically around the sensing area (Fig. 4). The

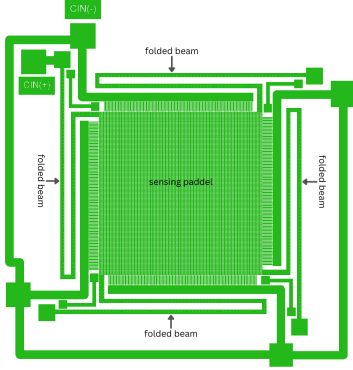


Fig. 4: Four folded-beam springs supporting the sensing paddle.

suspension targets an out-of-plane stiffness of approximately 10 N/m while suppressing parasitic in-plane and rotational motion [11], [12].

For small deflections, each beam segment is approximated using Euler–Bernoulli theory [12]:

$$k_i = \frac{Ewt^3}{L_i^3}. \quad (9)$$

The four segments of one folded spring act approximately in series, while the four folded springs are connected in parallel:

$$\frac{1}{k_{\text{single}}} = \sum_{i=1}^4 \frac{1}{k_i}, \quad k_{\text{total}} = 4k_{\text{single}}. \quad (10)$$

For a beam width of $w = 31 \mu\text{m}$ and thickness of $t = 25 \mu\text{m}$, the analytical model yields a stiffness of $k_{\text{single}} = 3.06 \text{ N/m}$ for each folded-beam suspension, resulting in a total stiffness of $k_{\text{total}} = 12.24 \text{ N/m}$. The longest beam segments dominate the overall compliance due to the cubic dependence of beam stiffness on length.

The capacitive readout uses 1040 interdigitated comb fingers with an overlap length of $110 \mu\text{m}$, thickness of $25 \mu\text{m}$, and effective gap of $3.5 \mu\text{m}$. The resulting parameters are listed in Table II.

TABLE II: Capacitive transduction parameters for 1040 comb fingers.

Parameter	Unit	Value
Comb fingers	–	1040
Overlap length	μm	110
Finger thickness	μm	25
Effective gap	μm	3.5
Displacement range	μm	1–25
Baseline capacitance	pF	7.23
Capacitance range	fF	6945.58
dC/dx	fF/ μm	289.40
dC/dF	fF/ μN	28.94

Using the target stiffness of 10 N/m, a $200 \mu\text{N}$ force corresponds to a displacement of

$$x_{\text{max}} = \frac{F_{\text{max}}}{k_{\text{total}}} = 20 \mu\text{m}. \quad (11)$$

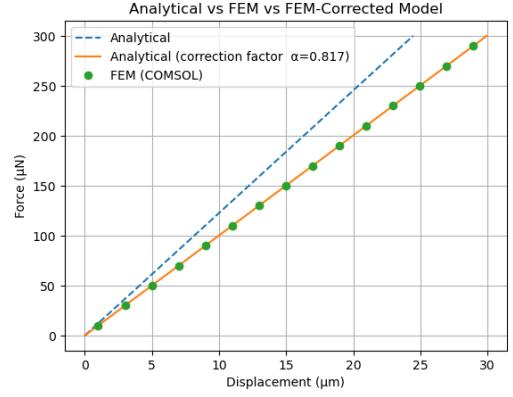


Fig. 5: Analytical and FEM force–displacement responses. FEM predicts an effective stiffness of approximately 10.0 N/m.

This displacement remains within the specified transduction range, providing a practical mechanical operating range for the intended force levels.

V. FINITE-ELEMENT VALIDATION

The mechanical and fluidic designs were evaluated using COMSOL Multiphysics 6.2. The simulations were used to verify suspension stiffness and linearity, determine resonance frequency and stress, and validate the analytical pore-flow model.

A. Mechanical and Modal Analysis

A stationary analysis was performed for applied forces from 0 to $300 \mu\text{N}$. The force–displacement response was approximately linear, and the FEM stiffness was extracted from

$$k_{\text{FEM}} = \frac{F}{x}. \quad (12)$$

The resulting stiffness is $\approx 10 \text{ N/m}$, compared with the analytical prediction of 12.2 N/m , corresponding to an 18.34% difference.

The lower FEM stiffness is attributed to additional compliance at the folded-beam joints, short beam segments, and three-dimensional deformation not captured by the simplified Euler–Bernoulli model [12], [13]. A correction factor can consequently be defined as

$$\alpha = \frac{k_{\text{analytical}}}{k_{\text{FEM}}} \approx 1.22. \quad (13)$$

At $300 \mu\text{N}$, the maximum von Mises stress is approximately 40 MPa and occurs near the inner folded corners. This is well below the assumed polysilicon critical stress of 300 MPa, indicating elastic operation under the designed loading condition.

Eigenfrequency analysis gives a first mode at 1048.7 Hz, corresponding to the intended out-of-plane translation of the paddle. Higher modes occur above 2 kHz, satisfying the design target of a first resonance above 1 kHz.

B. Fluidic FEM Validation

Flow through one $3.5 \times 11.5 \mu\text{m}^2$ rectangular pore with a length of $25 \mu\text{m}$ was simulated. The analytical model uses the Shah–London Poiseuille formulation for non-circular ducts [8]:

$$\Delta P = \text{Po} \frac{\mu L}{D_h^2} v_{\text{pore}}, \quad (14)$$

where Po is the Poiseuille number, D_h is the hydraulic diameter, and v_{pore} is the *mean* velocity through the pore.

A mean inlet velocity of $v_{\text{pore}} = 90 \text{ mm/s}$ was applied at the pore entrance. The analytical model predicts a pressure drop of 65.9 Pa , in close agreement with the FEM result of 65.7 Pa . The FEM solution gives a maximum local velocity of approximately 242 mm/s within the rectangular pore, as expected for the developed velocity profile. The comparison is summarized in Table III.

For $N = 37,905$ pores, the total flow rate is

$$Q = N A_{\text{pore}} v_{\text{pore}} = 1.375 \times 10^{-7} \text{ m}^3/\text{s}. \quad (15)$$

For air at the simulated conditions, this corresponds to $\dot{m} \approx 0.59 \text{ g/h}$.

TABLE III: Analytical and FEM results for a single rectangular pore.

Parameter	Analytical	FEM
Aspect ratio, β	0.304	–
Poiseuille number, Po	17.458	–
Mean inlet velocity, v_{pore}	–	90 mm/s
Maximum pore velocity, v_{max}	–	242 mm/s
Pressure drop, ΔP	65.9 Pa	65.7 Pa

The close agreement in pressure drop between the analytical model and FEM validates the non-circular Poiseuille formulation for the selected rectangular pore. The small discrepancy is mainly attributed to entrance and contraction effects captured by the FEM model but neglected in the fully developed analytical formulation.

VI. CONCLUSION

This work presented a MEMS viscosity sensor based on direct measurement of viscous drag force on a perforated sensing paddle. Unlike hydraulic-resistance-based viscosity sensors, in which increased sensitivity is inherently accompanied by increased pressure loss, the proposed architecture distributes the flow across more than 30,000 parallel rectangular micro-holes. This enables a small hydraulic diameter of $D_h = 5.37 \mu\text{m}$ and strong viscous interaction while avoiding the large localized pressure drop associated with a single high-resistance microchannel.

The analytical model shows that, at low Reynolds numbers ($Re \ll 1$), the measured force is proportional to the dynamic viscosity and, for a fixed mass flow rate, is governed primarily by the ratio μ/M . This provides sensitivity to gas composition while maintaining a linear force–mass-flow relationship. The selected $3.5 \times 11.5 \mu\text{m}^2$ rectangular perforations provide $\approx 2\times$ higher calculated viscous force than the circular design and $\approx 1.5\times$ higher force than the square design.

The mechanical suspension combines four folded-beam springs with capacitive comb-drive transduction. Finite-element analysis predicts an effective out-of-plane stiffness of approximately 10 N/m , a first resonance frequency of 1048.7 Hz , and a maximum stress of approximately 40 MPa under the investigated loading conditions. The fluidic FEM results also show close agreement with the analytical model, with a predicted single-pore velocity of approximately 242 mm/s and a pressure drop of approximately 66 Pa .

The proposed perforated-paddle architecture therefore provides a compact and mechanically simple approach for gas-viscosity sensing, combining distributed viscous-force generation, low-Reynolds-number operation, and capacitive readout. The comparison with conventional hydraulic-resistance-based sensing indicates that the architecture can generate a measurable viscous force without requiring a large global pressure drop. Future work should focus on experimental fabrication and characterization of the sensor, including calibration of the force-to-capacitance response and experimental discrimination of gas mixtures with closely spaced μ/M ratios.

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ELECTRICALLY-ACTUATED ACTIVE MICROVALVE ARRAYS

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INTRODUCTION:

In microfluidic systems microvalves are essential components that enable fluid handling operations like routing, pumping, dosing, and mixing [1]. Yet microvalve solutions oftentimes suffer from requiring: bulky peripheral equipment [2], large footprints (>0.1 mm), and low deflections for the relatively large microchannels that are found in applications like Organ-on-Chip (OoC). Consequently, integration of large active microvalve arrays on-chip remains a challenge. We overcome these issues by building electrically-actuated microvalves. Our most promising candidates are electrothermal and electroosmotic flow microvalves. These can be driven by a single PCB and meet the deflection, force and footprint requirements. In this abstract we present our current work on the fabrication and performance of electrothermal and electroosmotic microvalve arrays.

ELECTROTHERMAL MICROVALVES

Electrothermal microvalves make use of the thermal expansion of an encapsulated working medium (gas, liquid, or solid) [3]. We fabricated on-chip arrays of 16 electrothermal microvalves by common micromachining processes (Fig.1). As working medium we use a solid silicone elastomer, which, unlike fluid working media, cannot leak or evaporate and shows no degradation in our initial testing. Open, semi-circular microchannels were rapid-prototyped by micro-milling into Polymethylmethacrylate (PMMA) plates. These are simply clamped onto the microvalve array chips, allowing reuse, cleaning and exchange of the channel layout for different applications (Fig. 2).

Our microvalves can be operated with just one PCB. They reach enough deflection to close off microchannels of the dimensions ($w=120\text{ }\mu\text{m} \times h=70\text{ }\mu\text{m}$, or $w=250\text{ }\mu\text{m} \times h=75\text{ }\mu\text{m}$). Figure 3 shows a microscope image of a valve closing such a channel. Closed valves and clamped channels withstand inlet pressures of >2 bars. They open or close within <400 ms and can be proportionally actuated to throttle flow (Fig. 4). And we saw no reduction of performance after >1000 cycles.

Peristaltic pumping seems possible with these microvalves, but was not quantified yet. In the near future we will test the microvalve arrays in two applications that require routing, peristaltic pumping, mixing and metering: A biological sampling device running a glucose assay on-chip, and an active ring mixer.

ELECTROOSMOTIC FLOW MICROVALVES

The second microvalve design bases on recent work of

Shultz et al. [4,5] and Srirathan et al. [6,7] who build actuators employing electroosmotic flow (EOF) pumps: A thin ($\sim 180\text{ }\mu\text{m}$) porous membrane (filter paper) is placed between two perforated electrodes. Applying an electric field pumps liquid via electroosmosis from a common reservoir through the membrane into a top chamber. The increasing pressure moves a compliant membrane upwards. Their actuators ($\varnothing 2\text{-}10$ mm footprint) have shown to reach deflections of $400\text{ }\mu\text{m}$ - 5 mm (scaling with actuator diameter) and lifting loads of up to 140 g, at for EOF untypically low, driving voltages of 250 V. Both groups used salt-free propylene carbonate as the working fluid instead of water, which inhibits electrochemical reactions at the electrodes even at kilovolts [6].

As EOF benefits from miniaturization, we plan to develop a scaled-down version of this technology and incorporate it as microvalve into microchannels. We are confident that we can reach valve diameters of $\sim 400\text{ }\mu\text{m}$ and a small enough valve pitch to realize over 1000 valves on a $15\text{ mm} \times 30\text{ mm}$ device. We plan to fabricate a micromachined version that uses a thin, porous silicon nitride membrane, which should reduce the required driving voltage below <200 V (Fig. 5). For initial testing, and the convenience of not requiring cleanroom facilities, we want to fabricate a rapid-prototyped version as well.

We believe these two microvalve technologies have great potential to automatize fluid handling for various microfluidic applications in a miniaturized manner.

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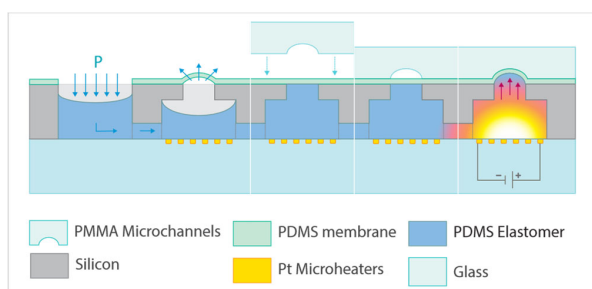


Figure 1: Concept and materials of the electrothermal microvalves. From left to right: the filling, clamping PMMA microchannels, microvalves in off and on state.

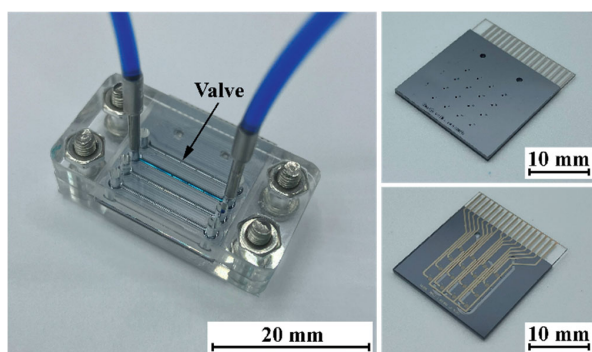


Figure 2: Photograph of the electrothermal microvalve array with (left) and without (right) PMMA channels on top.

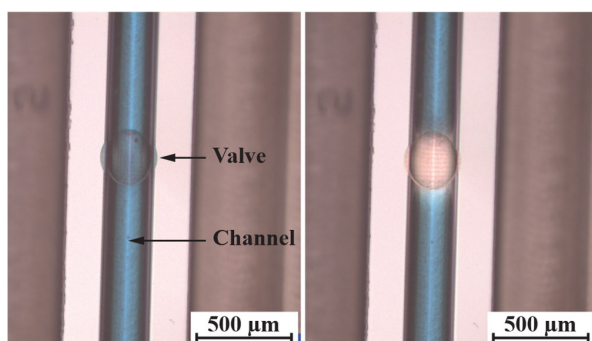


Figure 3: Microscope images of an open (left) and closed (right) electrothermal microvalve in a channel with blue food dye.

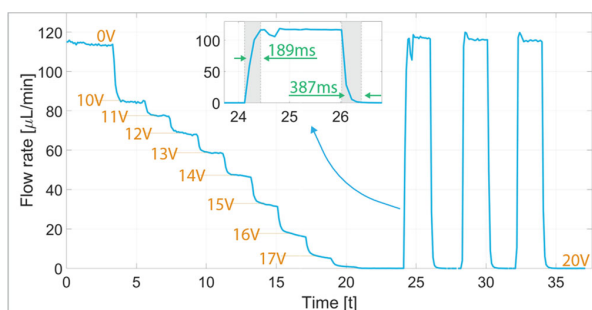


Figure 4: Flow plot showing flow rate of water at 160mbar inlet pressure: Proportional flow control and full opening

and closing of the electrothermal microvalve. Insert shows a close up of opening and closing time.

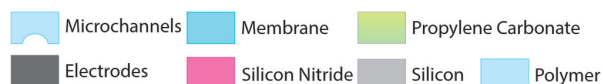
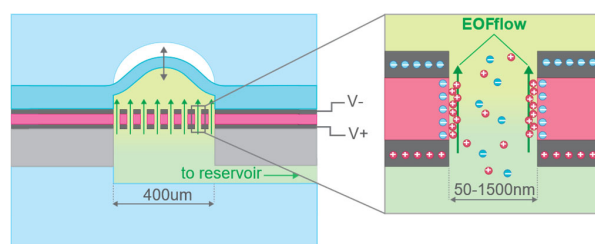


Figure 5: Cross-section, our concept of a microfabricated electroosmotic valve.

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SILICON CHANNELS WITH SMOOTHER SURFACE BY ALTERING SLIT GEOMETRY

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ABSTRACT

Microfluidic channels can be made in silicon and used for flow sensors. After patterning slits in a hard mask, holes are etched with inductively-coupled plasma. These holes slowly fuse together to form a channel, which leaves scallops and thereby channel roughness. This study investigates if different slit patterns can reduce this roughness. Preliminary results suggest narrow slits with a circle or diamond shape should be etched at high power and high SF₆ flow to obtain smoother channels. A mean-deviation roughness between 0.10 and 0.30 µm is achievable. The slit separation width seems irrelevant for roughness.

KEYWORDS

surface channel technology, microfluidics, channel smoothness, channel roughness, channel scallops, flow sensor, micro coriolis mass flow sensor

INTRODUCTION

Microfluidic channels can be made in silicon. They are used for flow sensors, including thermal [1], differential pressure and mass flow sensors [2, 3]. Microfluidic handling systems benefit from their small feature size and chemical inertness [4]. Such channels are made through the surface channel method [4]. However, this method leaves periodic scallops shown in Figure 1. The effective roughness of these scallops may have undesirable effects.

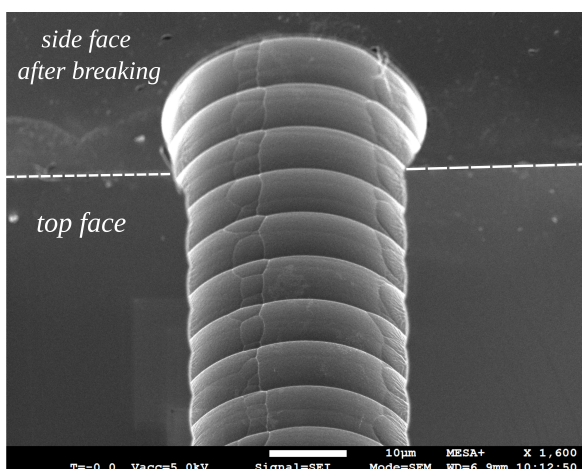


Figure 1: A scanning electron microscope picture of a channel, taken at a 45° angle to highlight the scallops.

Fabrication (Figure 2) starts with low pressure chemical vapour deposition (LPCVD) of a Si_xN_y layer on the silicon substrate. An aluminium-oxide hard-mask is then deposited by electron beam evaporation. Afterwards, etching windows called slits are patterned atop this hard-mask using direct-write photolithography. Inductively-coupled plasma (ICP) etching then opens the hard-mask below the slits, exposing the substrate. Through reactive-ion-etching with SF₆, spherical cavities form in the substrate that grow during etching. The separation between slits causes scallops when these cavities join to form a connected channel. Although not done in this study, another LPCVD of Si_xN_y forms a fully closing channel wall (Figure 3). Instead, the Si_xN_y was removed through HF wet-etching to make the scallops visible from the top.

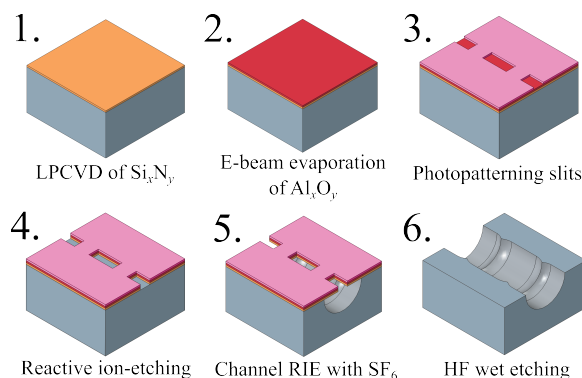


Figure 2: The fabrication procedure for this study.

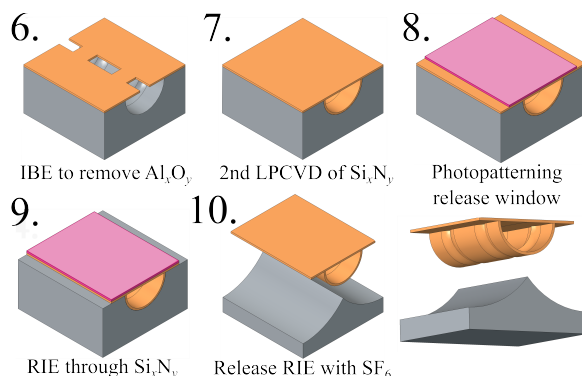


Figure 3: The remaining fabrication steps in the surface channel technology process not performed in this study.

However, separations remain necessary to prevent bending from stress accumulation [3], keep channels uniform and minimise unpredictable etch-rate varia-

tions [5]. Different slit geometries lead to different channel geometries. Hence, this study investigates the relation between slit patterns and channel roughness.

Channel wall roughness can affect friction between the fluid and the channel. This friction may induce a pressure drop. The Darcy-Weissbach friction factor (f) models this pressure drop (Δp). The friction factor has been approximated using the Churchill approximation [6]. Figure 4 shows a theoretical comparison between a flow with a wall roughness found in currently used sensors ($R_a = 0.71 \mu\text{m}$); and a perfectly smooth channel. The modelled channel is 10 mm long, $32 \mu\text{m}$ high and $40 \mu\text{m}$ wide. Although the computed pressure drop probably deviates from reality, the relative difference may still be instructive. For laminar flows ($Re < 2500$), roughness is not expected to increase pressure drop. However, for very high mass flows (10 g/h), smooth channels could reduce the pressure drop by 55.4 %. This gives room for improvement.

$$\Delta p = \frac{8 f \dot{V}^2}{\pi^2 g r_H^5} \cdot \quad (1)$$

$$f_{\text{Churchill}} = 8 \left(\frac{1}{(a+b)^{\frac{3}{2}}} + \left(\frac{8}{Re} \right)^{12} \right)^{\frac{1}{12}}; \quad (2)$$

$$a = \left(-2.457 \ln \left(\frac{0.27 R_z}{2 r_H} + \left(\frac{7}{Re} \right)^{\frac{9}{10}} \right) \right)^{16};$$

$$b = \left(\frac{37530}{Re} \right)^{16}.$$

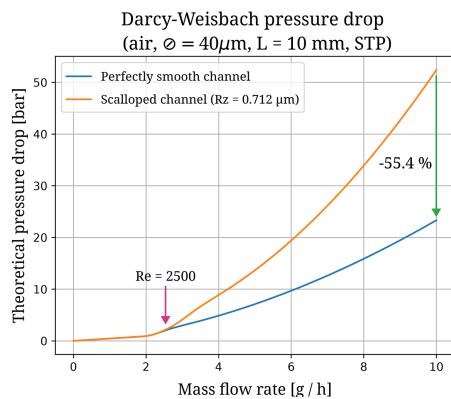


Figure 4: A theoretical approximation of the pressure loss for smooth and scalloped channels at very high flow rates.

Furthermore, reducing the width of the slits requires less Si_xN_y to close the channel, leading to thinner channel walls [2]. This would increase the ratio of the flowing mass to the empty channel mass. Thinner walls also make released channels more compliant. Both effects could cause more deflection in micro Coriolis mass flow sensors [3] and with it improve resolution. Therefore,

if thinner slits also lead to smoother channels, it would be doubly advantageous.

METHODS

Rows of slits have been patterned with direct-write photolithography. A prior fabrication run showed that $1.0 \mu\text{m}$ was the minimal feature size. The rows are $150 \mu\text{m}$ long to display tapering effects but also fit in one microscope view. Figure 5a and Table 1 show how slit dimensions have been varied.

- Reducing the width of the slits may reduce the bottom roughness as it limits the channel width and etching plasma directly reaching the bottom of the channel.
- Increasing the slit length may reduce the amount of scallops by unit length, but may also increase tapering.
- According to Groenesteijn et al. [2], the scallop height is proportional to the separation distance, because the channel forms from joining spheres.
- A lane offset will change where the etched spheres join and with it change scallop formation.
- Different shapes may alter scallop formation.

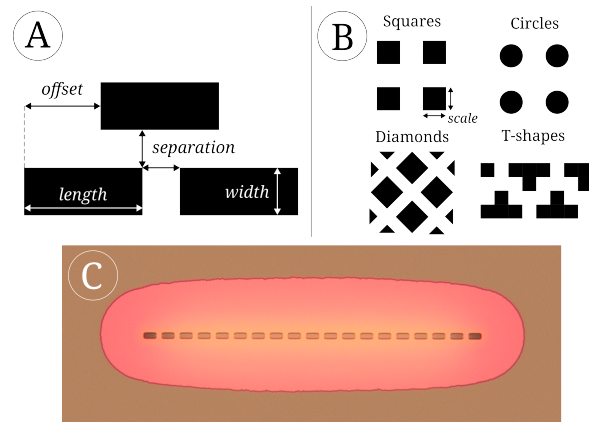


Figure 5: (a) The definition of the geometric parameters that have been varied. (b) The different slit shapes tested separately. (c) Before HF-etching, the slits are still visible.

Table 1: Studied slit geometry parameters compared to the previous study by Groenesteijn.

Parameter	Previous [2]	This study	Step size	Unit
slit width	2	2 - 10	(1)	μm
slit length	5	2 - 10	(1)	μm
separation	3.0	0.8 - 4.0	(0.4)	μm
offset	0 %	0 % - 50 %	(5 %)	-
shape scale	-	1.0 - 3.0	(0.2)	μm

Removing the hard mask makes the channels visible from the top. This enables optical profilometry measurements using the *Keyence VK-X3000* (Figure 6a). A cross-sectional scan (Figure 6b) yields the channel depth and channel width from the top, although the channel is actually wider due to slightly anisotropic etching. Therefore, the channel radius was inferred from a round arc made of three points on the bottom of the channel. A scan over the bottom (Figure 6c) measures the channel roughness. Roughness may be defined in different metrics. The mean-deviation roughness (R_a) has been chosen for comparisons because the peak-to-valley roughness (R_z) over the whole measurement may instead measure the taper of the channel. The scallop height has not been measured directly, only the roughness.

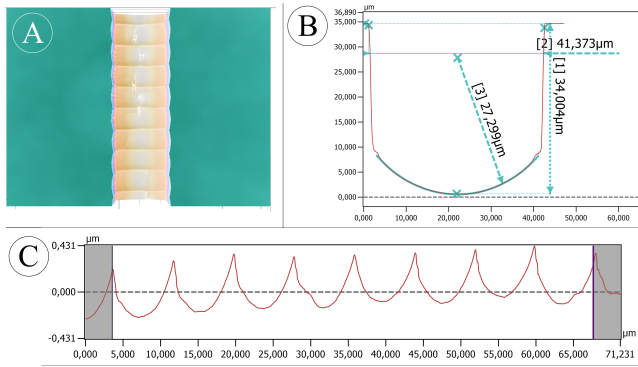


Figure 6: (a) A typical height map of a channel retrieved from the optical profilometer. (b) A scan of the cross-section with inferred values. (c) A scan over the bottom of the channel. Note that in some channels, the scallops remain unidentifiable over the roughness.

Two different ICP etching machines have been used to assess if etching settings influence roughness:

- the *SPTS LPX Pegasus* (at 3000 W ICP; 600 SCCM SF_6 for 20, 30, and 40 minutes);
- and the *Oxford Instruments PlasmaPro 100 Estrelas* (at 5000 W ICP; 800 SCCM SF_6 for 10, 15, and 20 minutes).

These etching settings have been used previously to make 40 μm wide channels (at 30 and 15 minutes respectively) [2, 3, 4] using the slits from the second column in Table 1. The *Estrelas* etch step was changed from 4000 W to 5000 W to increase anisotropy as recommended by previous operators.

RESULTS

In Figure 7, increasing the slit width appears to broadly

increase the roughness. Increasing the slit length however, appears irrelevant. This finding means that scallops alone do not determine the roughness, as more separations per unit length would increase the number of scallops and with it the mean-deviation roughness. Thus, there is no trade-off between the advantages of many separations (minimal taper and stress), and a low channel roughness.

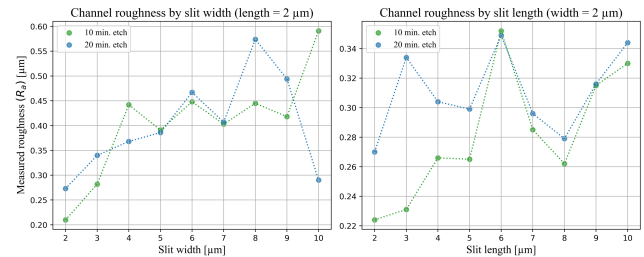


Figure 7: The channel roughness for different slit widths (left) and lengths (right).

There seems to be no correlation between the separation and the measured roughness (Figure 8). This contradicts the hypothesis that the separation determines the scallop height. A pattern offset from lane to lane does not seem to benefit the roughness in any way, although it shows the difference in etch time.

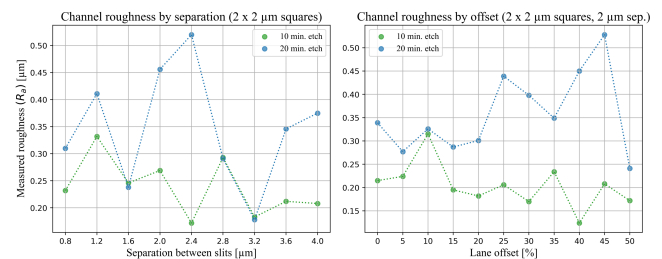


Figure 8: The effect of the separation (left) and the offset (right) on the channel roughness.

However, the shape of the slits appears to impact the channel roughness (Figure 9). Within the limited sample size, the round and diamond-shaped slits leave smoother channels than the squares or T-shaped slits.

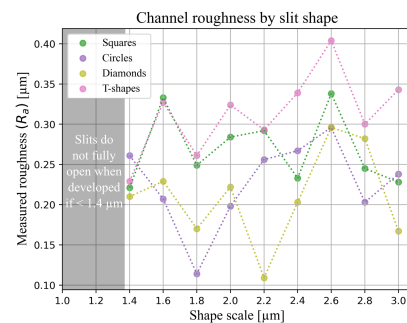


Figure 9: How different slit shapes produce different channel roughnesses. Slits do not fully open when they are developed if the scale is below 1.4 μm.

The most consistent method of reducing roughness appears not to lay in redesigning the slits, but in the ICP etch. Figure 10 shows that the channel roughness consistently remains lower for the higher power and higher flow setting. The channel width from the top remains within 7 μm of each other. The cause behind the different etcher performance could either be the power difference, the SF_6 flow, or the vessel geometry.

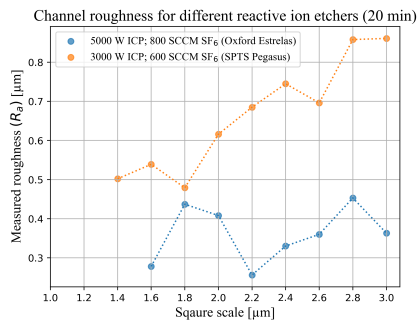


Figure 10: The roughness inside channels patterned with the Oxford Instruments Cobra compared to the SPTS Pegasus.

The variations in slit patterns and shapes have not significantly reduced the channel roughness compared to the recommended pattern from previous studies [2], including when compared to the diamond-shaped slits as shown in Figure 11.

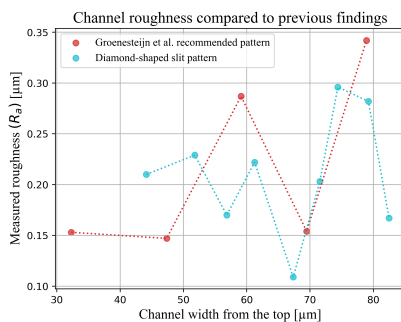


Figure 11: The roughness of the best slit pattern from this study compared to the pattern from Groenesteijn [2].

DISCUSSION

Only the shape and the slit width seem to affect channel roughness. The former may have to do with edges in the slit pattern that are perpendicular with respect to the channel direction. Minimising perpendicular edges may reduce the scalloping or roughness in the direction of the channel, as the circles and diamonds have minimal perpendicular edges, unlike the squares and T-shapes. Wider slits may allow for more etchant gases to escape directly below the slit, leading to locally deeper valleys in the channels.

In Groenesteijn et al. [2], a claim was made that scallop size is proportional to the separation. This study does not find such a correlation. It hints at the plasma still being subject to forces pushing it away from its original trajectory after entering the channel through the slits. Considering the most important factors for channel roughness are the etching settings, The momentum and current that the plasma enters the slits with, appear more important than the shape of the slits themselves.

CONCLUSION AND OUTLOOK

To reduce the channel roughness, the findings suggest that slits should be narrow, have a circle or diamond-shape, and be etched at high power with high SF_6 flow. The mean-deviation roughness can be kept within 0.10 μm to 0.30 μm . Since the sample size is limited, these conclusions are not definitive. Therefore, the continuation of this study will measure more channels, measure the height of individual scallops, and investigate different etching settings to make the smoothest channels possible.

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MAGNETIC POLYMER MICROFLUIDIC ACTUATORS FOR FLEXIBLE AND WEARABLE MICROFLUIDIC FLOW CONTROL

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ABSTRACT

Hard-magnetic soft polymer composites enable remotely controlled actuation for microfluidic flow control. This paper describes lessons learned in the development, characterization, and application of permanently magnetized rare-earth polymer composites actuators, including bi-directional artificial cilia, cantilevers, and membrane actuators. Representative example applications are discussed, highlighting the importance of magnetic and mechanical materials characterization for the continued development and design optimization of hard-magnetic polymer composite microfluidic actuators.

KEYWORDS

hard-magnetic polymers, magnetic composites, microactuators, magnetic actuation, valve arrays, magnetic cilia

INTRODUCTION

Magnetic polymer actuators have become an increasingly important class of smart materials for microfluidic flow control. Over the past two decades, research has progressed from ferrite-filled elastomers and magnetorheological composites toward high-performance hard-magnetic polymer composites capable of large deformation, programmable shape change, wireless actuation, and multifunctional operation [1-4]. The resulting materials combine the compliance and manufacturability of polymers with the remote actuation and force-generation capabilities of permanent magnetic materials.

Early magnetic polymer systems were primarily based on soft-magnetic fillers such as ferrites and carbonyl iron particles that were embedded in a polymer matrix. These materials enabled microfluidic valves, micropumps, and tunable stiffness structures, but typically produced relatively small actuation forces that could only be actuated in one direction (attracted) by external magnetic fields [1,2]. The introduction of hard-magnetic rare-earth particles such as NdFeB into elastomeric matrices enabled a new generation of magnetic polymer actuators possessing significant remanent magnetization and bidirectional (attraction, repulsion) actuation capability [3-5]. These developments laid the foundation for hard-magnetic soft materials, which have since become a major area of research in soft robotics, programmable

matter, medical microrobotics, and wearable systems [3-6].

In microfluidics, however, actuator requirements differ from those encountered in other systems. Actuators must operate within confined geometries, generate useful displacement and force over sub-millimetre dimensions, overcome fluidic pressure, and remain compatible with microfabrication. Remanent magnetization and coercivity must be considered together with mechanical properties such as modulus of elasticity, actuator geometry, magnetic field strength and orientation, and the pressure or flow requirements of the intended microfluidic system. These coupled requirements make both quantitative materials characterization and actuator-level design optimization particularly important. This paper examines these important considerations with representative examples from the author's and other research groups.

HARD MAGNETIC SOFT POLYMER COMPOSITES

Hard magnetic composites are formed by embedding hard magnetic nano- or micro-particles into a polymer matrix which may then be permanently magnetized using a large (e.g., 2 - 3T) magnetic field [7]. The amount of particles in the polymer base is often given as a weight-% (wt-%), which can range from zero (polymer base with no particles) up to, e.g., 80 wt-%, at which point the polymer and particles may no longer integrate properly [8].

Our research has concentrated on the development of permanently magnetized polymer composites specifically optimized for microfluidic flow control and biomedical MEMS applications [9-16]. Beginning with rare-earth magnetic powder embedded in polydimethylsiloxane (PDMS) and SU-8 photopolymer, we demonstrated some of the earliest hard-magnetic polymer composites designed for integrated microfluidic systems [11,12]. A central aspect of this work has been quantitative characterization of the composites as engineering materials. Magnetic properties including remanence, coercivity, and generated permanent magnetic fields have been measured together with mechanical properties such as modulus of elasticity. This characterization is important because magnetic particle concentration alone is insufficient to predict actuator performance. Increasing the concentration of

magnetic particles can increase the potential for higher magnetic force, but can also change the stiffness and processing characteristics of the composite [17].

In terms of magnetic characterization, permanent micromagnets fabricated from our materials have achieved remanent magnetizations of approximately 60–63 emu/g and coercivities exceeding 5200 G. The modulus of elasticity of our materials increases with increasing wt-% of particles, e.g., for NdFeB particles in PDMS, from 0.52 MPa at 0 wt-% to 1.62 MPa at 80 wt-% [8]. This combined magnetic and mechanical characterization provides a foundation for a family of bidirectional microfluidic actuators including artificial cilia, flap valves, and membrane actuators [11–16].

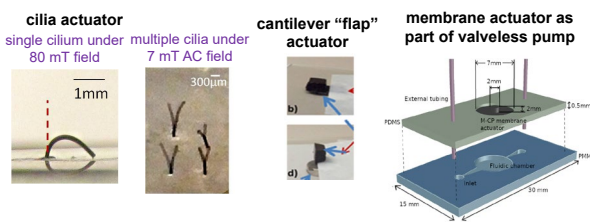


Fig. 1: Representative hard-magnetic soft polymer composite microfluidic actuators [13,15,16].

MICROFLUIDIC ACTUATORS

As shown in Fig. 1, rare-earth magnetic composite polymers have been incorporated into a range of microfluidic actuator types.

High-aspect-ratio artificial cilia provide one example of the ability of permanently magnetized polymer structures to generate substantial deformation at the microscale. Individual cilia and cilia arrays were fabricated from rare-earth magnetic polymer composites and actuated using external magnetic fields as low as approximately 1–7 mT [13,14]. Arrays of magnetic cilia provide opportunities for localized fluid manipulation and mixing under low-Reynolds-number conditions. Permanent magnetization is crucial for these structures and indicative of why hard magnetic particles must be used; the amount of actuation drops significantly if the structures are left unmagnetized [18].

We have also developed actuators for microfluidic valving and flow switching. All-polymer magnetic flap valves were integrated directly into microfluidic channels and demonstrated the ability to block pressures approaching 10 kPa [15]. Magnetic actuation enables these valves to be controlled remotely while maintaining the advantages of polymer microfluidic fabrication. Integration of multiple magnetic valves also provides a route toward reconfigurable flow networks in which fluid paths can be selected without conventional electrically

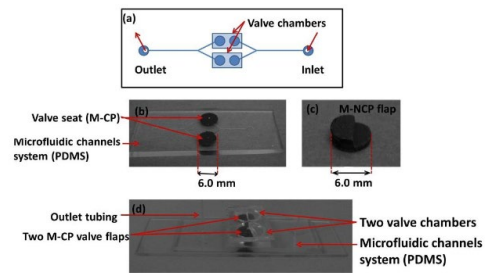


Fig. 2: Two flap-valve array for flow switching (figures reprinted with permissions [8,15].

connected valve actuators. Fig. 2 shows an example of a two-valve array for flow switching.

Membrane structures extend the approach from cantilever- or flap-like motion to displacement of a larger fluid-contacting area. Such membrane motion can be used to displace fluid, generate pressure, or form the basis of pumping and other active microfluidic functions [16]. The ability to actuate the membrane in both directions is an important advantage of using a permanently magnetized material.

We have developed criteria and metrics for optimizing the design of microfluidic actuators based of hard magnetic soft polymer materials [8,18]. For example, fabricating thicker “boss” structures in an actuator from high particle wt-% magnetic polymer composite, combined with 0 wt-% features where high compliancy is needed (e.g., a flap type actuator hinge) can be used to optimize both actuator force and displacement under an external magnetic field.

SCALING MANUFACTURING AND SYSTEMS

Compatibility with large-scale integration and polymer microfabrication are also important considerations. Developed and characterized actuators provide building blocks for applications including reconfigurable valve arrays, micropumps, fluid manipulation, and mechanobiology platforms [11–16, 19]. Fig. 3a shows a conceptual multi-valve array for a complex microfluidic analysis instrument. While we have not yet realized this entire system, we have made headway towards development of the external magnetic field control for the hard magnetic polymer flap valves and cilia mixers [20]. Fig. 3b shows a mechanobiology platform used for the controlled stretching and compressions of biological cells [19]. The device in Fig. 3b is based on a doubly-supported cantilever beam actuator rather than a singly-supported flap-type or membrane actuator.

More recent work has extended hard-magnetic polymer materials toward fabrication processes suitable for larger-scale manufacturing and new classes of devices. Magnetic off-stoichiometric thiol-

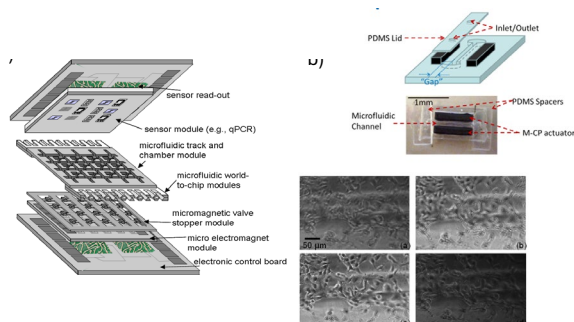


Fig. 3: Example applications of hard magnetic polymer composite actuators: a) reconfigurable microfluidic system; b) mechanobiology for stretching/compressing arterial endothelial cells [19, 22].

ene epoxy (OSTE+)-based composites containing approximately 25 wt-% rare-earth magnetic particles were developed with permanent magnetic fields of up to 3 mT retained for more than 15 months [21]. In addition to their magnetic properties, these composites are compatible with reaction-injection molding and thermoplastic-compatible fabrication, providing a route beyond conventional soft-lithographic processing.

This manufacturing direction has subsequently been extended to textile-printable magnetic composite inks for wearable actuators [23] (Fig. 4). NdFeB particle concentrations ranging from approximately 29.8 to 69.9 wt-% produced retentivities of 15.3–53.5 emu/cm³ and coercivities of 4128–6457 Oe, with measured permanent magnetic fields of approximately 0.066–0.496 mT. Printable hard-magnetic materials



Fig. 4: Magnetic polymer patterned on textile [23].

create opportunities for integrating remotely actuated structures directly onto textiles and other flexible substrates, potentially extending magnetic microactuation concepts into wearable biomedical and wearable microfluidic systems.

DISCUSSION AND CONTEXT

While most applications of hard magnetic polymers have been in the areas of soft robotics and tuneable structures [3-6], there has also been work by other research groups in using hard magnetic polymers for microfluidic flow control (e.g., [24-29]). While non-exhaustive, Table 1 shows a summary of a few representative hard magnetic soft polymer materials for microfluidic actuators developed by both our group and other researchers.

Table 1 highlights the considerable diversity of hard-magnetic polymer materials and actuators already demonstrated for microfluidic systems and the roles they have played in advancing polymer microfluidics and lab-on-chip technologies. NdFeB-polymer composites have been used for pressure-sensitive and actively controlled microfluidic valves

Table 1. A Sample of Representative Magnetic Material Platforms for Microfluidic Actuation and Flow Handling

Materials Platform	Ref's, Year	Key Materials/Magnetic Characteristics
NdFeB-PDMS valve composites	[24], 2012	NdFeB:PDMS ratios of 1:1 to 3:1; generated field ~40 mT at composite surface
NdFeB-paper/polymer valve composites	[25], 2018	NdFeB powder combined with polymer and paper; generated stray field $\sim 3.0 \pm 0.2$ mT at 1.5 mm; bidirectional attraction/repulsion
NdFeB-PDMS artificial cilia composites	[26], 2017	1:4 NdFeB:PDMS; cilia permanently magnetized after fabrication; demonstrated for microfluidic pumping and mixing
NdFeB-PDMS composite-membrane	[27], 2005	40 vol-% NdFeB; NdFeB powder Br ~0.75 T and estimated saturated composite Br ~0.30 T
NdFeB-PDMS compsite membrane	[28], 2016	2–30 vol-% NdFeB particles
Matrix-patterned NdFeB-PDMS membrane	[29], 2018	6% NdFeB-PDMS composite, remanence Br ~37.64 mT and coercivity Hc ~2720 G
NdFeB magnetic polymer composites for flaps, cilia, and membranes	[7-19], 2010-2020	Mr ~ 60–63 emu/g; Hc ~ 5260–5290 G; permanently magnetizable rare-earth composites compatible with soft lithography and polymer MEMS fabrication; generated fields 1 – 9 mT
Magnetic NdFeB OSTE+ composites (membrane)	[21], 2021	25 wt-% rare-earth magnetic particles; up to 3mT permanent magnetization generate fields retained >15 months; reaction-injection-moldable and thermoplastic-compatible
Textile ink-based magnetic composite inks	[23], 2025	29.8–69.9 wt-% NdFeB particles; retentivity 15.3–53.5 emu/cm ³ ; coercivity 4128–6457 Oe; generated fields 0.066–0.496 mT

[24,25], hard-magnetic artificial cilia have been demonstrated for pumping and mixing [26], and NdFeB-PDMS composite membranes have been developed for intended use in electromagnetic micropumps [27–29]. These studies demonstrate the versatility of permanently magnetized polymer composites for manipulating and controlling fluids at small scales.

At the same time, comparison among reported actuator systems remains difficult because the underlying materials are not characterized consistently. Particle composition and magnetic loading are commonly reported, but quantitative values for remanent magnetization, coercivity, elastic modulus, generated magnetic field, and these metrics' dependence on particle loading are less consistently available. Table 1 also thus highlights the need for additional research to systematically characterize hard magnetic polymers (including obtaining magnetic and mechanical materials property constants) to develop robust design criteria for microfluidic actuators that use them.

CONCLUSIONS

Hard-magnetic polymer composites have evolved into a versatile materials platform. The combination of permanent magnetization, polymer mechanical compliance, and compatibility with microfabrication has enabled actuator architectures ranging from artificial cilia and flap valves to bidirectional membranes and integrated biomedical systems. More recent developments in reaction-injection-moldable composites and textile-printable magnetic inks further demonstrate opportunities for scalable manufacturing and wearable applications.

Continued progress, however, would benefit from additional materials characterization specific to predictive actuator design and the development of robust simulation. Magnetic properties such as remanence and coercivity must be considered together with elastic modulus, particle loading, actuator geometry, applied-field conditions, actuator generated fields, and the resulting fluidic performance.

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CONTROLLING ANISOTROPIC DEPOSITION ONTO HARD SURFACES THROUGH THE IMPACT DYNAMICS OF TRANSIENT NON-CIRCULAR MICROJETS

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ABSTRACT

Transient microjets generated from a rectangular microchannel were investigated to determine how jet velocity and stand-off distance control deposited pattern morphology. Experiments covered Weber numbers of 180–810 and impact distances of 0.3–4.5 mm, with orthogonal high-speed imaging used to characterise the jet before impact. Distinct anisotropic patterns were obtained by varying these two parameters, while increasing stand-off distance progressively reduced the deformation and led to more axisymmetric deposits. Time-resolved imaging showed that the preferred spreading direction develops during the transient impact stage. The results demonstrate controllable microscale deposition through coordinated adjustment of jet velocity and stand-off distance.

KEYWORDS

transient microjets; liquid deposition; anisotropic spreading; pattern control

INTRODUCTION

Liquid microjets are used in processes where small liquid volumes must be delivered or deposited with high spatial control, including printing and needle-free injection [1][2]. In these applications, the final outcome depends not only on the delivered volume and jet velocity, but also on the jet shape at impact. This becomes particularly relevant for non-circular jets, whose cross-section evolves during free-flight propagation rather than retaining the geometry imposed at the source. Surface tension and inertia drive this deformation, which can lead to alternating transverse shapes during propagation [3].

Most previous studies of non-circular jets have focused on continuous or quasi-steady conditions, where the influence of nozzle geometry and Weber number on free-flight deformation has been extensively characterised [4][5][6][7]. Separately, jet-impact studies have shown that incident geometry can affect impact pressure, liquid-film development, and heat transfer [8][9]. However, the direct relationship between the evolving jet state before impact, the

transient spreading dynamics, and the final deposited pattern remains insufficiently understood.

This relationship is particularly important for impulsively generated microjets. In laser-induced systems, the jet is produced by a short pressure pulse, and its velocity, width, and transverse deformation evolve along the liquid column [10][11]. Consequently, the stand-off distance between the source and substrate determines which deformation state reaches the surface. Together with jet velocity, it can therefore act as a control parameter for the morphology of the deposited liquid.

Here, we investigate laser-induced microjets emerging from a rectangular microchannel and impacting a glass substrate. By varying the Weber number over $We = 180$ –810 and the stand-off distance over 0.3–4.5 mm, we obtain distinct deposited patterns ranging from strongly anisotropic to nearly axisymmetric. Orthogonal high-speed imaging is used to characterise the evolving jet cross-section before impact and relate it to the orientation and elongation of the deposited patterns. The results show that jet velocity and stand-off distance provide complementary means of controlling anisotropic liquid deposition without modifying the microchannel geometry.

METHODS

Laser-induced transient microjets were generated in a glass microfluidic chip using a 4 ns, 532 nm laser pulse focused on an aqueous Allura Red solution with properties close to those of water. The liquid chamber had an obround cross-section of 700 x 400 μm with rounded ends and a length of 1.8 mm. Laser-induced cavitation accelerated the confined liquid and produced a high-speed jet through the channel outlet (see Figure 1a).

The jet dynamics were recorded simultaneously from two orthogonal directions (XZ and YZ) using two high-speed cameras at 40 000–100 000 fps (Figure 1b). The filling level and laser focal position were kept constant, while the laser energy was varied to control the jet velocity. Multiple experiments were performed for each condition to ensure

reproducibility.

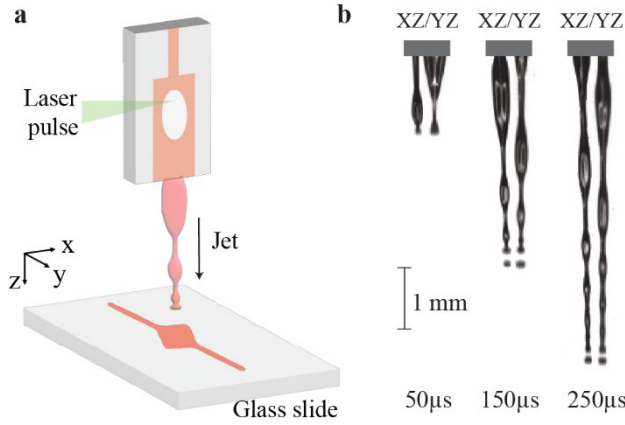


Figure 1: (a) Schematic of the laser-induced jetting setup. (b) Free-flight evolution of a microjet observed from the orthogonal XZ and YZ planes at three different times. The images in (b) are displayed with a 20 % horizontal enlargement for improved visualization of the jet deformation.

The recorded images were processed in MATLAB to extract the projected jet widths, D_x and D_y , along the propagation direction. The instantaneous cross-sectional deformation was characterised by

$$AS = \ln \left(\frac{D_x}{D_y} \right) \quad (1)$$

where positive and negative values indicate preferential jet elongation along the X and Y directions, respectively.

We calculate the Weber jet number at the exit of the microfluidic channel using the effective diameters $D_{x,0}$ and $D_{y,0}$, representing the initial balance between inertial and capillary forces during jet formation $We_{jet,0} = \frac{\rho V^2 D_{eq0}}{\sigma}$, with $D_{eq0} = \sqrt{D_{x0} D_{y0}}$, where ρ is the liquid density, V the measured jet velocity, σ the surface tension, and $D_{eq,0}$ the equivalent diameter using the geometric mean of $D_{x,0}$ and $D_{y,0}$.

Jet impacts were performed on smooth glass microscope slides positioned normal to the jet axis. The stand-off distance was varied from 0.3 to 4.5 mm, and each impact was performed on a fresh area of the substrate. The final deposited patterns were imaged with a stereomicroscope.

Pattern anisotropy was quantified from the maximum deposited lengths l_x and l_y using

$$PA = \ln \left(\frac{l_y}{l_x} \right) \quad (2)$$

where the sign indicates the preferred elongation direction and $PA = 0$ corresponds to equal maximum extents along both axes. Pattern circularity was additionally calculated from the deposited area and perimeter. Time-resolved images of selected impacts were used to track the spreading front and determine

when the directional preference developed during impact.

We also calculated the circularity index as $C = \frac{4\pi A}{P^2}$, where A and P are the area and perimeter of the pattern, respectively. By definition, $C = 1$ for a perfect circle and decreases as the contour deviates from circularity.

RESULTS AND DISCUSSION

Figure 2 summarizes the free-flight evolution of the jet cross-sectional deformation for the investigated Weber numbers.

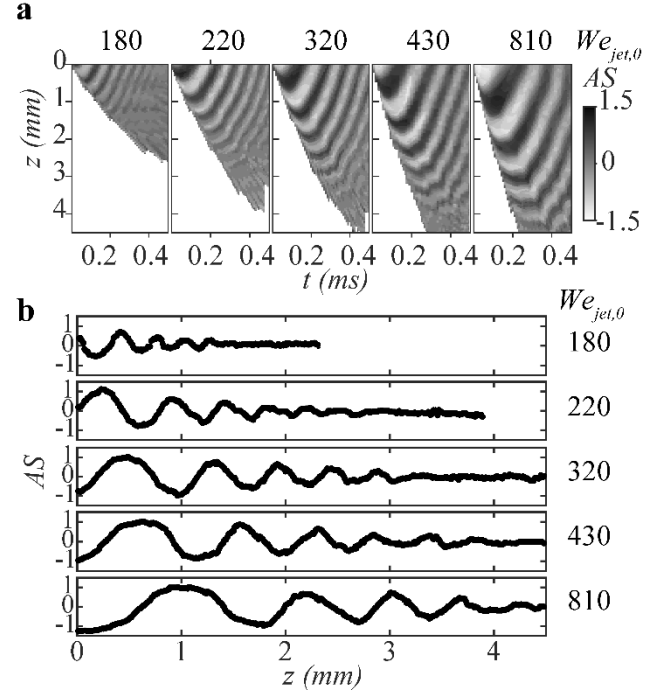


Figure 2: Weber dependence of the free-flight jet dynamics. (a) STDs of $AS(t, z)$ for jets at $We_{jet,0} = 180, 220, 320, 430$ and 810 , respectively. (b) Corresponding experimental impact-state profiles $AS(z)$.

The spatiotemporal diagrams of AS (Figure 2a) show alternating positive and negative regions, corresponding to preferential elongation along the two orthogonal directions. This deformation progressively weakens with propagation distance, but its persistence and spatial evolution depend strongly on We . Higher We jets retain a pronounced non-circular deformation over longer distances, whereas at lower We the jet approaches an axisymmetric state more rapidly.

The corresponding spatial profiles (Figure 2b) further illustrate that both the magnitude and orientation of the jet deformation vary with propagation distance and We . Consequently, a given stand-off distance does not correspond to a unique jet geometry at impact: depending on We , the substrate can be reached by jets with different degrees and directions of deformation. This combined dependence

on We and stand-off distance provides the basis for the different deposited patterns discussed below.

To examine how these differences in jet state are transferred to the deposited pattern, the impact dynamics were recorded from a near-top view for selected stand-off distances at the highest Weber number. Figure 3 shows that the characteristic pattern shape is established during the early stages of spreading. At $z = 1.9$ mm, the lamella rapidly develops a strong preferential direction, producing elongated arms that persist in the final pattern. At $z = 3.3$ mm, the spreading remains anisotropic but the directional contrast is weaker, resulting in a more compact deposit. At $z = 3.9$ mm, the spreading front is nearly axisymmetric and evolves towards an almost circular pattern. These observations show that the deformation state of the incoming jet is transferred to the initial spreading dynamics and ultimately determines the morphology of the deposited liquid.

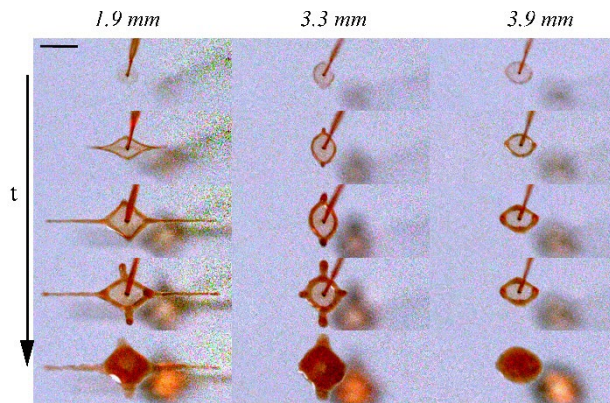


Figure 3: Time-resolved spreading on glass at $We=810$ for stand-off distances $z=1.9$, 3.3 , and 3.9 mm. Successive snapshots show the spreading evolution from top to bottom, as indicated by the time arrow. Scale bar: 0.5 mm.

The effect of We and stand-off distance on the final deposited morphology is summarized in Figure 4. At low We , the patterns remain predominantly compact and nearly axisymmetric over most of the investigated range. As We increases, anisotropic patterns persist over longer propagation distances and their preferred orientation changes with stand-off distance. At the highest We , alternating elongations along the two substrate directions, together with intermediate diamond-like and nearly circular shapes, are obtained as the substrate position is varied. At larger stand-off distances, the patterns progressively approach axisymmetry. These results demonstrate that We and stand-off distance can be combined to select markedly different deposition morphologies without changing the microchannel geometry.

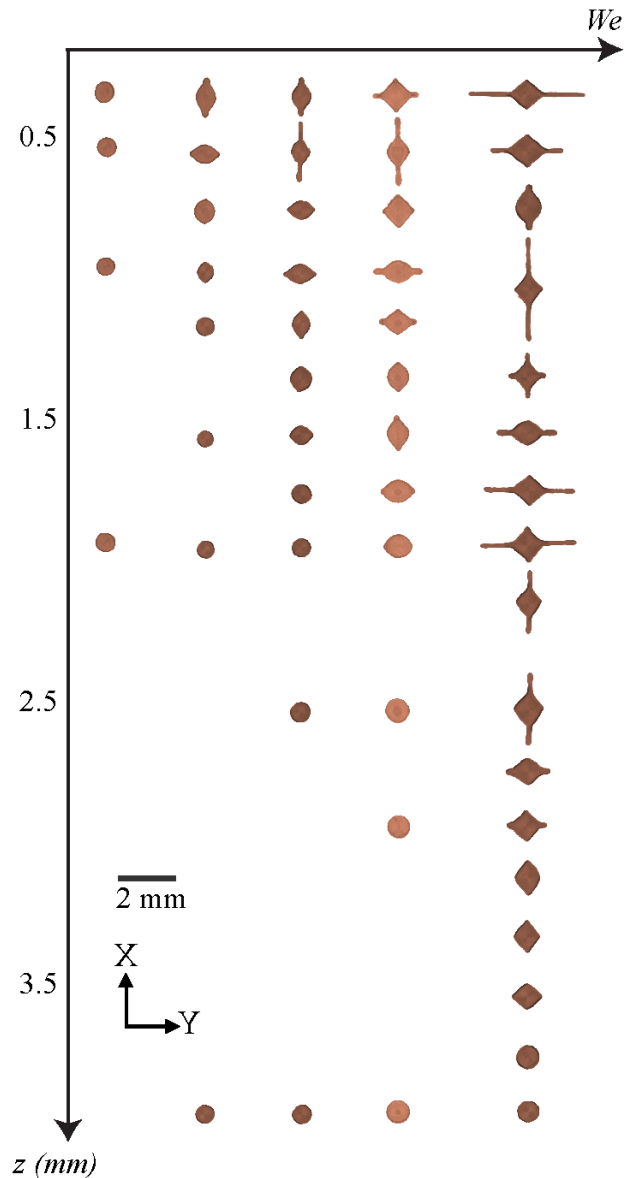


Figure 4: Final deposited patterns as a function of stand-off distance and Weber number. Increasing We extends the range over which anisotropic patterns are observed, while variation of the stand-off distance produces different pattern orientations and morphologies.

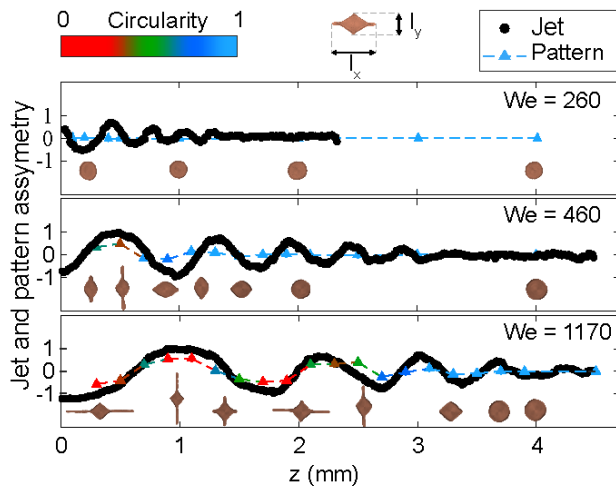


Figure 5: Relationship between jet deformation and deposited pattern morphology for three representative Weber numbers. *AS* describes the incoming jet deformation, *PA* the anisotropy of the deposited pattern, and the colour scale indicates pattern circularity. Selected final patterns are shown for comparison.

The relationship between the incoming jet deformation and the deposited morphology is summarized in Figure 5 for three representative Weber numbers. The jet deformation, quantified by *AS*, is compared with the pattern anisotropy, *PA*, while the pattern circularity is indicated by colour. The changes in pattern orientation broadly follow the oscillatory evolution of *AS* with stand-off distance. In particular, pronounced jet deformation is associated with strongly anisotropic deposits, with the dominant elongation of the pattern generally oriented approximately perpendicular to that of the incoming jet. As *AS* decays with propagation distance, *PA* approaches zero and the deposited patterns become progressively more symmetric. This correspondence establishes the link between the free-flight jet state and the final pattern morphology, while also showing that the subsequent impact and spreading dynamics contribute to the final deposited shape.

CONCLUSIONS

Transient non-circular microjets can produce a wide range of deposited morphologies depending on jet velocity and stand-off distance. The jet cross-section evolves continuously during free flight, so that changes in either parameter modify the deformation state reaching the substrate. This state is transferred to the early spreading dynamics and ultimately to the final pattern, producing alternating anisotropic orientations as well as nearly axisymmetric patterns. The results show that Weber number and stand-off distance provide complementary control parameters for tuning microscale liquid deposition without

modifying the microchannel geometry.

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LAMINAR FLOW ELEMENT BASED CALIBRATION PLATFORM FOR GASSES

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ABSTRACT

A flexible platform for gas-flow calibration has been developed with an overall uncertainty of 0.3%, based on measurement of the differential pressure and temperature of laminar flow through an annular duct. The system incorporates three interchangeable modules that can be selected to cover flow ranges up to 300 mln/min, 3ln/min, and 30 ln/min.

Temperature and pressure dependencies due to varying operating conditions are compensated based on a model based approach making the devices flexible and straightforward to calibrate and adjust against a primary flow standard.

KEYWORDS

Gas flow, differential pressure, laminar flow, gas mass flow calibrator.

INTRODUCTION

Calibration equipment that is used as a working standard should not only be accurate and traceable, but when used in the field should also be compact, robust and stable over time.

Differential pressure based flow meters can fulfill these functions and have been successfully demonstrated in the field as secondary flow standard [1]. Their working principle is based on the flow of gas through a Laminar Flow Element (LFE) and temperature and differential pressure sensors.

Typically for high accuracy LFE based flow standards calibration is performed at different temperatures to compensate for temperature effects or care is taken to make sure the devices operate at constant temperature. Here we made use of a model-based approach to compensate for temperature effects of medium properties i.e. viscosity and density, furthermore the LFE geometry is chosen to ensure that temperature effects have a minimum impact on the flow characteristics.

Design

Each module consists of a cylindrical and a matching spline insert, manufactured with high-precision tolerances to create annular slits of 25 μm , 55 μm , and 80 μm , respectively, details of the system are shown in Fig.1. The benefit of this type of annular LFE is the large surface to volume area to

maintain low Reynolds numbers and thus laminar flow, while at the same time increasing cross section area to increase the flow rate with a large coupling of the gas to the body, assuring a stable temperature of the medium. The geometries were designed such that each laminar flow element (LFE) produces a pressure drop of approximately 1 bar(a) at full-scale flow under atmospheric downstream conditions. Differential pressure is measured using two TERPS DPS8000 absolute pressure sensors with a 2-bar(a) full-scale range, while gas temperature is monitored using SMT172 temperature sensors. Measurements are performed at 2 locations to be able to compensate for possible gradients.

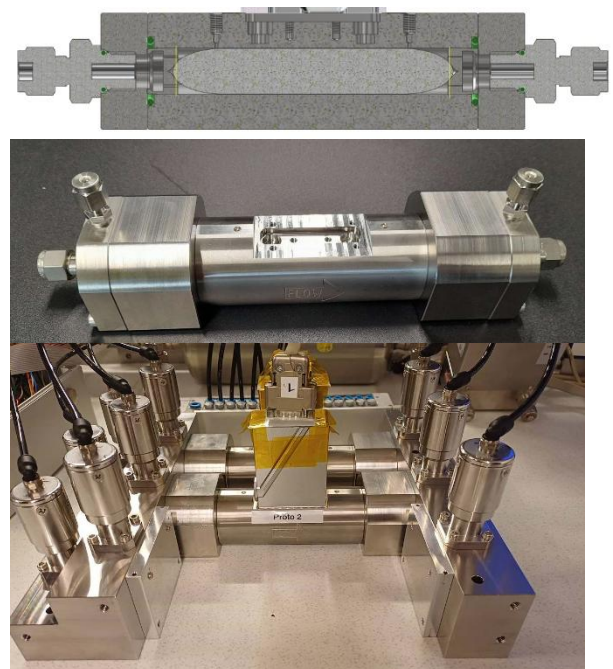


Figure 1. Sketch of an LFE calibration module depicted at the top showing a central spline in a cylinder. Middle: assembled module with adapters for pressure sensors and flow. Bottom assembled system with 2 modules.

Modeling

The pressure drop over an annular slit with laminar developed flow is given by the formula below (1). With V_{act} the actual flow, dP/dx the pressure gradient, η the viscosity and r_{in} and r_{out} respectively the annular slit inner and outer radius.

$$V_{act} = \frac{dP}{dx} \frac{\pi}{8\eta} \left(r_{out}^4 - r_{in}^4 - \frac{(r_{out}^2 - r_{in}^2)^2}{\ln\left(\frac{r_{out}}{r_{in}}\right)} \right) \quad (1)$$

Deviations from the linear Hagen-Poiseuille flow can occur due to several effects, for instance, gas expansion, kinetic effects due to entrance or exit effects, and impact of temperature gradients due to Joule Thomson effects [2].

Here we characterize the manufactured devices with an in-house high-accuracy flow standard with uncertainty of approximately 0.06 % R.D. [3]. The output of each module is computed using a first-order analytical model based on Hagen-Poiseuille laminar-flow theory. Deviations from ideal behavior are corrected using a Reynolds-number-dependent compensation term that accounts for non-ideal effects mentioned previously.

Conversion from actual to normal flow is based on the average temperature and pressure readings. The thermal entrance length is characterized by the Reynolds and Prandtl number, the system is designed such that Reynolds number is small. i.e. less than 300 for the largest flow range and less than 20 for the smallest range with a Prandtl number of 0.7 for Nitrogen gas the thermal entrance length is appropriately 0.25% of the total channel length. It can thus be assumed that the gas temperature is in equilibrium with the wall temperature. This way the temperature sensors inserted in the body close to the slit are representative of the gas temperature. Furthermore, the inlet and outlet pressure are measured at locations close to the annular slit such that entrance effects are minimized and included in the measurement.

The average pressure P_{av} is determined with Eq. 2, accounting for expansion effects. with P_{in} and P_{out} the in- and outlet pressure, respectively.

$$P_{av} = \frac{2(P_{in}^3 - P_{out}^3)}{3(P_{in}^2 - P_{out}^2)} \quad (2)$$

Results

A concern when fabricating an annular slit is that the spline should be placed centrally in the cylinder to form a uniform circular slit. Figure 2 sketches a situation where a spline (dark blue) touches the wall (grey) at opposite sides of the cylinder leading to a nonuniform slit (light blue) over the LFE length, in this case the larger gap will dominate the flow resistance as can be seen from formula 1.

A test structure was filled with epoxy and cut through

to be able to visually inspect the slit geometry resulting from the assembly method. The bottom part of figure 2 shows a uniform annular profile with only moderate deviation over the geometry.

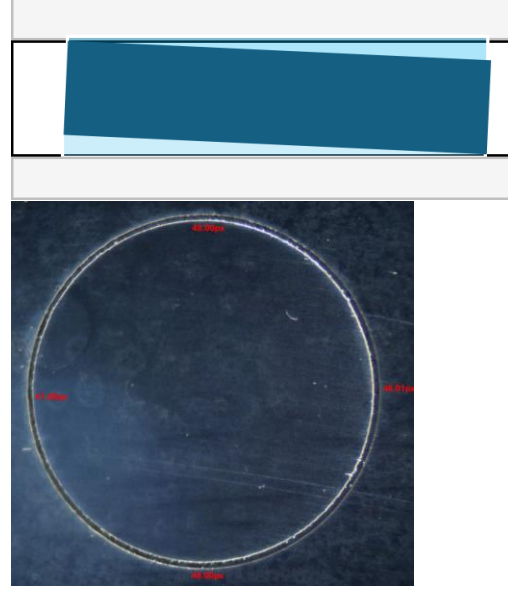


Figure 2.top; Sketch of a nonuniform slit due to tilt of the spline in the cylinder. Bottom; measured circular slit geometry.

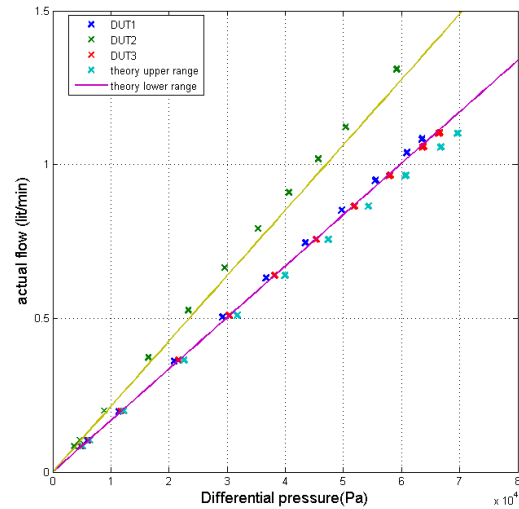


Figure 3. Flow characteristics for 4 fabricated devices for the mid flow range with the upper and lower range according to theory.

The relation between differential pressure and the actual flow was measured and compared to the theory based on formula 1. In the figure above results are shown for the mid flow range. Spline and cylinder geometries were measured and the resulting slit size was used as input. The LFE geometries are in the order of 55 μm and tolerances on the measurements can impact the resulting outcome, here we show the theory based on the upper and lower range for the resulting slits respectively of 54 and 58.5 μm .

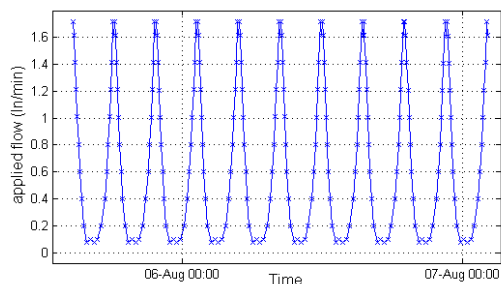


Figure 4. Applied flow steps during testing.

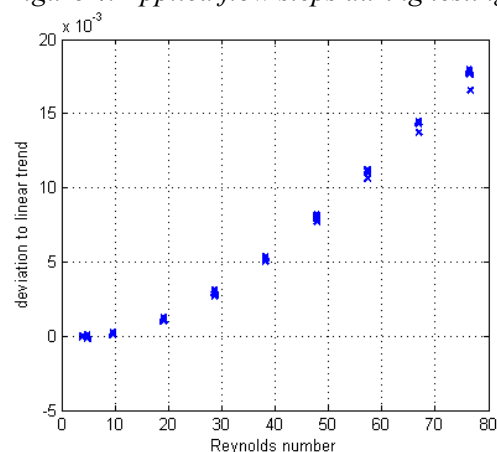


Figure 5. deviation to linear trend for LFE of DUT 1 as a function of Reynolds number

The assembled devices were calibrated against the reference primary flow standard and adjusted. Subsequently, the resulting stability was tested, with the test profile shown in figure 4. Here we show results for the mid flow range for nitrogen. Adjustment was performed based on a Reynolds correction curve. Deviation with respect to the theoretical linear Hagen-Poiseuille relationship was determined as a function of the Reynolds number, viscosity and density as a function of the local pressure and temperature was calculated based on the Fluidat database [4]. Velocity data was calculated based on the measured device geometry.

After initial adjustment, flow calculations were performed based on the measured pressures and temperatures and an iterative calculation procedure. Initially flow was determined based on linear relations, after this the value was updated based on the resulting Reynolds number, using the newly calculated flow value. This procedure is repeated until a stable value is determined.

Figure 6 gives the results after adjusting the devices and measuring their stability against the reference at room temperature over a period of 30 hours.

The measurements show good agreement with a deviation generally within 0.2 % reading with a

turndown of 1:10. For all devices some outliers were observed where an increased deviation is seen in all cases during the first measurement cycle. This is likely caused by residual air, or humidity traces in the piping. Resulting in a different viscosity and/or density as assumed.

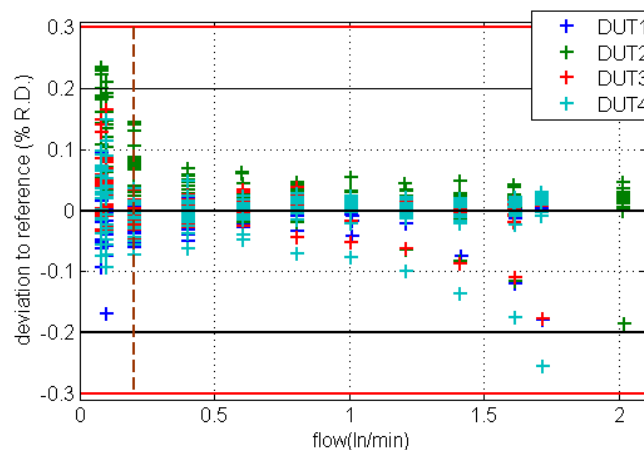


Figure 6. agreement between flow measurement of the manufactured and adjusted devices and the reference.

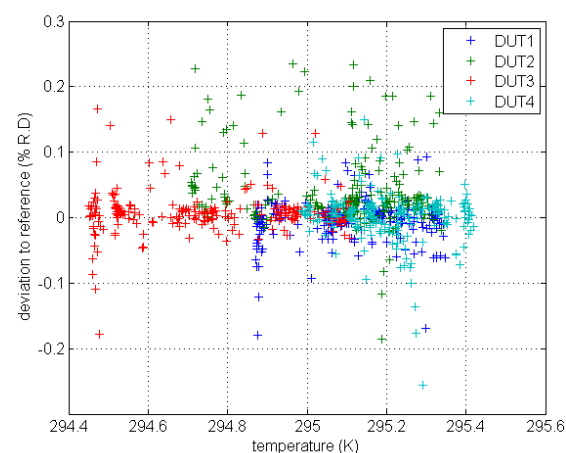


Figure 7. deviation as a function of room temperature.

CONCLUSIONS

Laminar flow based devices have been fabricated in the range of 30 mln/min up to 30 litn/min, here we present results for the mid flow range. Device flow characteristics show good agreement between measurements and theory indicating a robust fabrication and assembly process leading to predictable laminar flow elements. After adjustment, devices show accurate and repeatable behavior at room condition compared to a primary flow standard with agreement within 0.2 % reading at a turndown of 1:10.

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NANOSPRESSO-NL: Local preparation of high quality, personalised nucleic acid nanomedicines using a microfluidic platform

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Abstract: Orphan diseases affect approximately 8% of the world's population, which is 400 million people (Ruseckaite et al., 2023). The majority of these diseases decrease life expectancy and lead to physical, emotional and/or psychosocial limitations with a wide range of disabilities when left untreated (Rajmil et al., 2010). Unfortunately, there is a lack of effective personalized treatment options for many patients with orphan diseases (Ruseckaite et al., 2023). 72% of orphan diseases are genetic and mostly affect the enzymes involved in the metabolic pathways within the liver, influencing the physiology of many organs (Rare Disease Day, n.d.). The cause can be relatively easily treated by administering mRNA encapsulated in lipid nanoparticles (= nucleic acid nanomedicine) (Damase et al., 2021). For this, a microfluidic platform needs to be designed to produce monodisperse (pDI < 0.20) lipid nanoparticles with a size smaller than 100 nm, which enables the release of mRNA within the cytoplasm of liver cells.

For the microfluidic chip fabrication, the split-and-recombine design (containing 5 rings) is fabricated in polymethyl methacrylate using micromilling. The designs are validated for their dimensions (width and depth), pressure performance and lipid nanoparticle (LNP) morphology. Preliminary results show that the split-and-recombine gave LNPs very similar to the ones coming from the commercial Nanoassemblr in terms of size (cca 60nm), polydispersity, concentration and tRNA encapsulation efficiency (cca 97%). Future efforts focus on analysing the effects of chip design (fewer rings, wider channels) and syringe vs. pressure driven flow on lipid nanoparticle formation.

Keywords: Lab-on-a-chip, Orphan diseases, Low cost manufacturing, Lipid Nanoparticles, Microfluidics

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SILICON MICROPUMPS LEAKAGE MEASUREMENTS WITH INSULIN BUFFER

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ABSTRACT

Continuous drug delivery enables controlled, constant-rate drug infusion and is widely used in diabetes therapy. Fraunhofer EMFT has developed piezoelectric micropumps that address both cost efficiency and dosing reliability while maintaining system miniaturization. For both implantable insulin pumps and wearable patch pumps, reverse leakage through the outlet valve is a critical safety and performance parameter. Several methods have been proposed to measure ultra-low leakage in microfluidic systems, including gravimetric methods. In this work, Nine silicon piezoelectric micropumps were assembled into a gravimetric setup while the backpressure at the pump outlet is varied stepwise. The simulated leakage rates are about 30 nl/h while the achievable resolution becomes a limiting factor when leakage rates approach clinically relevant basal delivery rates.

KEYWORDS

piezoelectric micropumps, Continuous drug delivery, Leakage rates, implantable insulin pumps, wearable patch pumps

INTRODUCTION

Piezoelectric micropumps enable highly miniaturized drug-delivery and fluid-handling systems with precisely controlled stroke volumes. Fraunhofer EMFT has developed silicon micropumps for both implantable and wearable applications, combining compact dimensions with accurate dosing performance [2]. In ultra-low-flow applications, however, the required average flow rate may be achieved by only a small number of individual pump strokes separated by comparatively long idle periods.

Under these conditions, reverse leakage through the passive valves becomes particularly important. During the intervals between pump strokes, even a very small reverse flow can become significant relative to the volume delivered by the subsequent stroke. Moreover, a pressure difference across the pump cannot generally be excluded. It may be inherent to the application, for example due to a negative-pressure reservoir or tissue backpressure or may arise locally from capillary forces and pinned gas bubbles within the fluidic system. Consequently, sufficiently low reverse leakage is a key requirement not only for the micropump itself but for the reliable

operation of the complete fluidic system.

This is particularly relevant for insulin delivery. If reverse leakage through the outlet valve is not significantly smaller than the basal delivery rate, body fluid may enter the catheter or pump outlet during the intervals between dosing events and subsequently be delivered instead of insulin. The resulting dilution may cause dosing inaccuracies and potentially affect the long-term stability of concentrated insulin formulations. With U500 insulin, the required volumetric basal flow can be only a few hundred nanoliters per hour, placing correspondingly stringent demands on valve leakage.

Characterization of such small liquid leakage rates itself is challenging. Available approaches include gravimetric measurements, capillary meniscus tracking, flow-sensor-based techniques, and pressure-decay methods. Gravimetric and optical methods can resolve very low liquid flow rates but become increasingly affected by evaporation, capillary effects, and thermal drift at nanoliter-per-hour scales [3]. Pressure-decay methods have demonstrated very high sensitivity for gas leakage through microvalves [4], but their application to liquids requires different experimental conditions. In the present work, a gravimetric approach was selected because gravimetric flow measurements are well established for liquid-flow calibration [5]. Nine silicon micropumps are characterized under controlled reverse pressure using an insulin placebo solution. The measurements are complemented by FEM analysis of the residual valve gap and analytical estimation of the resulting leakage flow.

METROLOGY

Micropumps were prepared and assembled into functional modules suitable for system-level testing (Fig. 1). The investigated devices are based on a silicon design comprising integrated valve structures, a thin actuator diaphragm with a thickness of approximately 110 μm , and a bonded piezoelectric actuator. The resulting compact device geometry is representative of miniaturized drug delivery systems and reflects key application requirements such as stable dosing, compact integration, and robustness under varying pressure conditions.

All wet parts of the fluidic path consist of PEEK, borosilicate glass and stainless steel. The pumps were flushed with the insulin placebo solution.

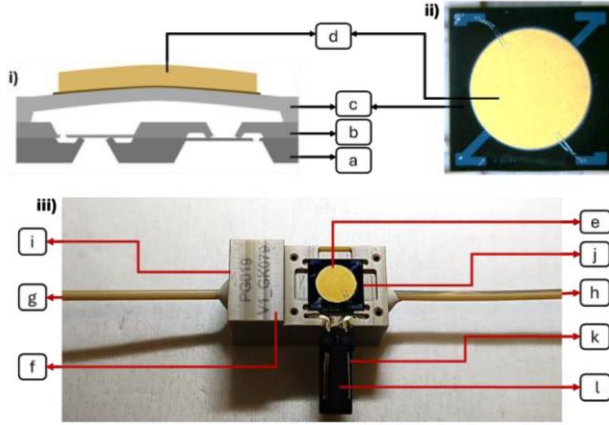


Figure 1 i) Schematic cross section of silicon piezoelectric micropump with lower valve unit (a) and upper valve unit (b) and actuator diaphragm (c) and piezoelectric ceramic (d), ii) Piezoelectric ceramic mounted pump chip and iii) partially prepared micropump module showing the pump chip (e) mounted on the PEEK housing (f) with inlet (g) and outlet (h) capillaries, steel filters (i), sealers (j), electrode pins (k) and black clamps (l).

Measurement Setup

Fig. 2 illustrates the measurement setup where the pump is placed on the balance setup, while its outlet connected via capillaries to a reservoir. The inlet reservoir stands on a microbalance (Sartorius SC 2, readability $0.1 \mu\text{g}$) inside the closed weighing chamber, and the mass signal is recorded continuously at 1.3 Hz. The outlet is connected to a sealed reservoir whose gas volume is pressurized by a Mensor CPC4000 controller (set-point accuracy 0.02 % (IntelliScale)).

Measurement protocol

The backpressure at the pump outlet increased stepwise over 1, 2, 5, 15, 20, 25, 30, 35, 40, 45 and 50 kPa. Each pressurized interval (60 s) is immediately preceded and followed by an interval of equal length at 0 kPa. During all intervals the pump was not actuated, so that only the passive reverse conductance of the closed outlet valve is probed. The bracketing of every pressure level by two zero-pressure references allows the evaporation (balance drift) rate to be tracked throughout the experiment.

Leakage estimation

Within each interval the recorded mass $m(t)$ is fitted by a straight line over the window $10 \text{ s} < t < 60 \text{ s}$; the first 10 s are discarded to exclude the settling of the pressure step and the recovery of the balance. This yields the rate m'_p during pressurization and the rates m'_b and m'_a of the preceding and following reference interval. The leakage-related mass rate is defined in Eq. (1).

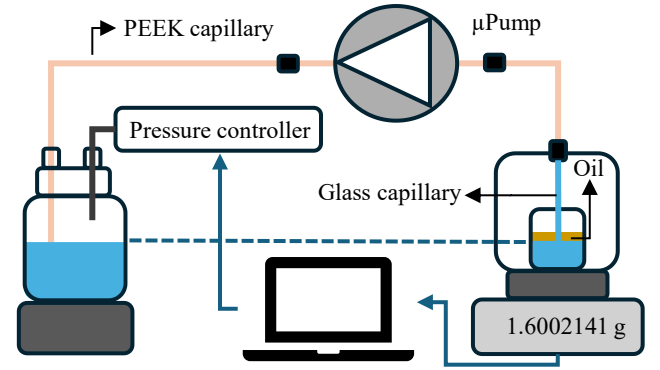


Figure 2. Measurement setup. The micropump inlet is connected to a reservoir on an analytical balance (Sartorius SC 2), outlet is connected to a pressurized reservoir with pressure controller (Mensor CPC4000).

$$m'_{leak} = m'_p - \frac{1}{2} (m'_b + m'_a) \quad (1)$$

Resolution and uncertainty

The resolution of the method is not given by the readability of the balance but by the uncertainty of a rate determined from a finite observation window. Each rate was obtained by a least-squares fit, and its standard uncertainty was taken as the square root of the corresponding diagonal element of the fit covariance matrix.

Leakage-path origin: The passive silicon flap valve

The valves flap is clamped at one edge, while its bottom side is supported by the seat. The latter spans the so-called opening area a^2 . If the force resulting from a pressure difference Δp acts on this area in the direction of opening, the flap bends, creating a gap between the flap and the valve seat. If it acts in the opposing direction (backpressure) the flap moves downward until the initial gap is closed. Further increase of the load results in the flap being pressed onto the valve seat, which causes a deformation of the flap. The resulting gaps at the corners of the valve flap, here called remaining gaps h_{corner} , cause leakages. For a detailed description of the valve see [4].

Optimized Valve

A rough estimation of the remaining gap is given as follows: With M_{xy} being the twisting moment, the corner reaction of a uniformly loaded, edge-supported plate is $R_{corner} = 2M_{xy}$ [6], amounting to $R_{corner} \approx 0.065 \Delta p a^2$ for the square plate. Because the valve seat is unilateral, this hold-down force cannot be

transmitted, and the constraint is effectively released. For a contact set that does not vary with load the response is linear [7], hence $h_{\text{corner}} \propto R_c$. Part of leakage-optimization for the valve-design used in the present pumps was reducing the opening area a^2 , minimizing h_{corner} while maintaining good opening characteristics. The precise remaining gap along the entire seat diameter for the following calculation at several different backpressures Δp is calculated using FEM.

Flow-rate calculation

Assuming Navier-Slip wall boundary conditions and Stokes-Flow, the overall leakage volume-flow Q is calculated for a rectangular microchannel geometry as:

$$Q = \frac{h_{\text{corner}}^3 b}{12 \mu L} \Delta p \left(1 + \frac{6 L_S}{h_{\text{corner}}} \right) \quad (2)$$

where b is the seat-diameter, L the seat-width, μ the fluids viscosity and L_S the slip-length. The second term in the brackets would vanish when no-slip wall conditions are assumed. However, for small channel heights as $h_{\text{corner}} \rightarrow L_S$ its contribution becomes relevant. For water on silicon surfaces, the slip-length L_S is given below 10 nm according to [8, 9]. For the following calculations, $L_S = 20$ nm is taken as it rather represents the upper limit. Furthermore, in the following leakage estimations, the maximal gap height at the corners has been taken from FEM simulation and is used as constant height around the entire perimeter of the valve seat. The calculated volume-flow is shown in Fig. 3 and should represent the upper limit on what to expect.

RESULTS

Considering a highly concentrated insulin formulation (U-500) delivered at a basal rate of 0.25 U/h, the corresponding volumetric flow rate is approximately 500 nl/h. The observed leakage rates for Pump 6 ranged from approximately 240 to 470 nl/h depending on backpressure and are therefore of the same order of magnitude as the target basal delivery rate (Fig. 4). Only Pump 1 and Pump 6 show a clear indication of reverse leakage (Table (1)).

Pump 6 yields a positive leakage contribution at all eleven pressure levels — the only device with this consistency (≈ 240 – 470 nl/h). For the remaining devices the leakage contribution was not separable from measurement artifacts. This could indicate that the actual leakage rate is below the detection limit of the measurement setup of the gravimetric balance rather than providing the absence of leakage.

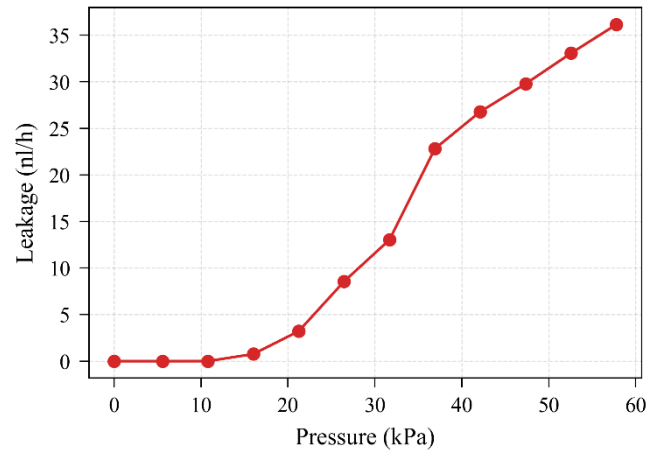


Figure 3. Calculated volume-flow through the remaining gap of the valve versus the backpressure

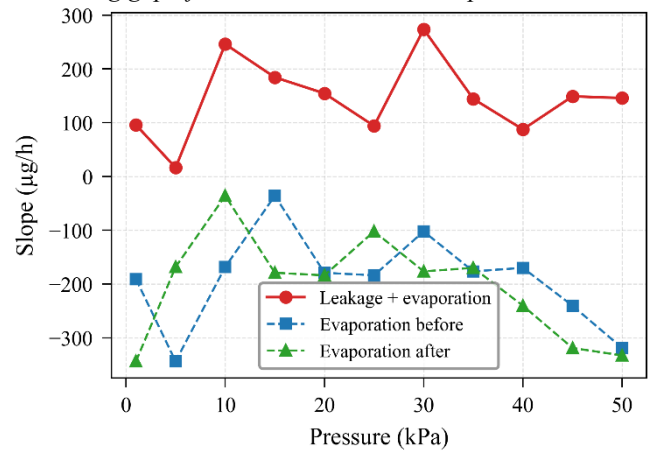


Figure 4. Measured weight-loss slopes versus applied backpressure for micropump 6. Circles show leakage plus evaporation, while squares and triangles show evaporation measured before and after each leakage measurement.

DISCUSSION

For most devices, the calculated leakage contribution fluctuated between positive and negative values of comparable magnitude. Since physical reverse leakage under applied backpressure cannot become negative, these results indicate that the measured signal is strongly affected by baseline instability. Inspection of the raw balance traces revealed several superimposed effects. long-term drift of the evaporation rate, shorter-term fluctuations on the time scale of the 60 s measurement intervals, wave-like variations, and occasional abrupt mass steps. The latter are unlikely to originate from evaporation and may be related to mechanical settling or the weighing system.

The evaporation-related variations may originate from thermal drift and time-dependent mass transfer in the headspace. Although the liquid surface was covered by an oil layer to suppress evaporation, small local openings may remain near the wetting line at the reservoir wall, providing spatially non-uniform evaporation pathways.

Table 1. Measured leakage rates for different micropump chips. Pump 1 can be considered at defect device. The leakage contribution is obtained from the difference between the pressurized measurement and the average of the two evaporation measurements. Median value of uncertainty for each pump also reported in last column.

Pressure (kPa)	Pump 1	Pump 2	Pump 3	Pump 4	Pump 5	Pump 6	Pump 7	Pump 8	Pump 9
1	5.9×10^3	420.5	-24	44	28	363	224	237	632
2	1.1×10^3	426.8	-2.3×10^3	76	256	272	-1.3×10^3	-793	98
5	20×10^3	242.1	308	2	-93	348	181	-206	183
15	30×10^3	60.6	781	-88	260	292	652	-781	-23.5
20	46×10^3	93.1	254	-150	76	336	381	-5.6	-172
25	5.9×10^3	239.3	292	-140	24	237	106	-333	129
30	63×10^3	199.6	263	-123	89	413	-124	378	-168
35	75×10^3	14.9	-265	33	-997	318	-105	66	-130
40	89×10^3	-27.6	-226	-57	121	293	-156	62	-97
45	96×10^3	-73.2	544	-218	-116	429	-156	102	-52
50	104×10^3	-16.7	-232	6	83	472	-99	12	-352
$u'_{leak} (\mu\text{g/h})$	746	22	97	32	17	36	38	44	81

These mechanisms are considered plausible explanations for the observed fluctuations but were not independently verified in the present study. The nominal balance readability of $0.1 \mu\text{g}$ therefore does not represent the practical detection limit of the measurement. Likewise, the uncertainty obtained from linear regression within an individual measurement interval primarily describes short-term scatter and does not fully account for temporal variations of the evaporation baseline.

Long-term evaporation drift can, in principle, be tracked and compensated using the preceding and subsequent baseline measurements, while isolated discontinuities can be identified and excluded as artifacts. The critical limitation is instead the variation of the evaporation-related baseline slope on approximately the same time scale as the leakage measurement itself. Such variations cannot be reliably distinguished from a small stationary leakage contribution. Consequently, while large leakage rates can be identified unambiguously, quantitative determination of leakage rates in the range of a few tens to several hundred micrograms per hour remains uncertain with the present 60 s measurement protocol.

ACKNOWLEDGMENT

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FERRULE-TYPE WORLD-TO-CHIP INTERFACES FOR MINIATURIZED MODULAR MICROFLUIDICS

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Microfluidic chips are manufactured in wafer-scale processes, where chip cost scales roughly with occupied wafer area [1]. Practical miniaturization, however, is often limited not by the microchannels but by the world-to-chip interface: conventional glass-chip holders use vises, top and bottom clamps, O-rings, and glued or inserted fluidic ports that require seating or clamping areas larger than the active fluidic structures. Current interoperability standards therefore primarily address slide-scale chip formats rather than truly miniaturized dies [2]. These interfaces add dead volume, increase chip footprint, and make modular architectures expensive to assemble and revalidate. Here we introduce a ferrule-type world-to-chip interface that makes very small microfluidic chips practical as standardized modular building blocks.

Figure 1 illustrates the operating principle. The interface consists of a port seat, a deformable ferrule with an internal receiving pocket, the chip, and an actuation element such as a nut or screw. Actuation compresses the ferrule radially around the chip perimeter, self-centering the chip while sealing multiple side ports in one step. Because sealing and tubing connection are integrated around the chip edge, a complete interface for a 5 x 5 mm glass chip can be miniaturized to 10 x 6 mm while still providing side sealing and four external fluidic tubing connections (Fig. 4). By moving the sealing plane from the top surface to the chip edge, the architecture keeps the chip face accessible for microscopy, optical coupling, electrodes, or additional sensing layers.

As a proof of concept, we fabricated more than 200 microfluidic chips on a 2-inch wafer, covering 12 design variants with channel widths from 50 to 500 μm (Fig. 3a). The chips can be placed modularly on a reusable holder with the 7.5 x 2.5 cm footprint of a conventional microscope slide (Fig. 3b). The same interface concept can be implemented in engineering thermoplastics similar to established microfluidic fittings and is compatible with scalable CNC machining or injection molding. We also tested 3D-printed interface variants, suggesting a route to robust connectors for high-resolution 3D-printed microfluidic chips, where small device footprints are otherwise difficult to interface.

Pressure-ramp and torque-dependent leakage tests were performed with deionized water using the pressure-step logic recommended for microfluidic leakage characterization [3]. Figure 2a shows the applied pressure ramp in 100 mbar steps with 20 s hold time per step, and Fig. 2b shows the simultaneously measured flow signal used for leakage quantification. At 1.4 Nm clamp torque, the measured flow returned to near zero after each pressure step up to 6.97 bar, with an average absolute flow signal of 0.15 $\mu\text{L}/\text{min}$ above 6.5 bar. Aggregating the plateau data shows that sealing

performance improves strongly with compression, reaching the predefined sealed criterion of $|Q| \leq 0.5 \mu\text{L}/\text{min}$ at the optimized torque (Fig. 2c).

The resulting architecture combines miniaturized wafer-scale chips, centimeter-scale reusable connectors, sub-0.5 μL interfacial dead volume, and pressure-validated side sealing. Together, the fabricated chips and leakage data demonstrate a viable route toward a new standard family of world-to-chip interfaces for miniaturized, modular microfluidic systems.

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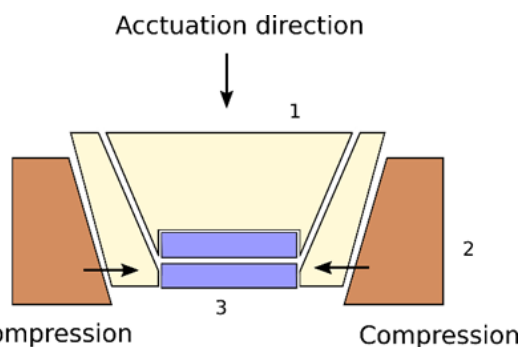


Figure 1: Basic principle of the compression ferrule. (1) Ferrule (beige) with an internal receiving pocket, (2) port seat (brown), and (3) chip (light violet). An actuation element (not shown) presses the ferrule downward. The arrows indicate the resulting radial compression, which both self-centers the chip and seals around its perimeter.

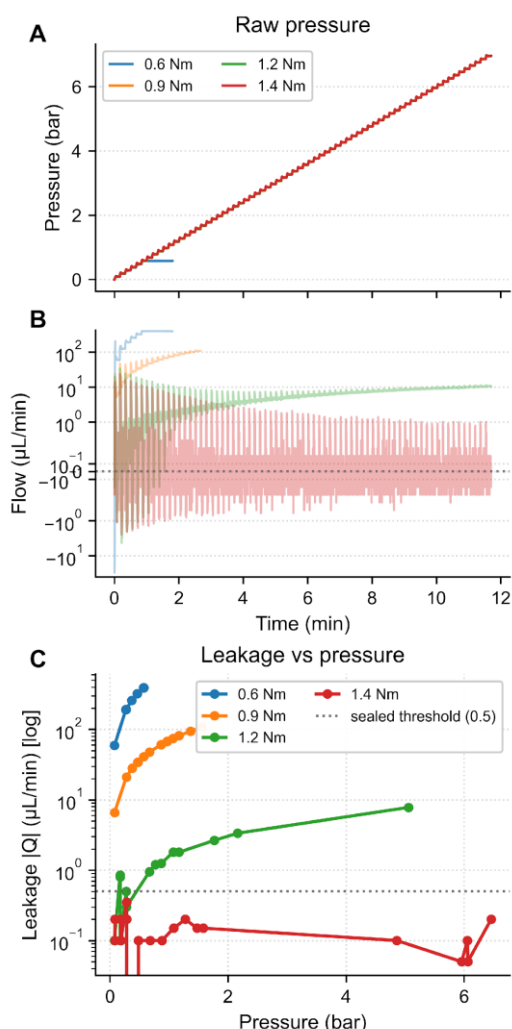


Figure 2: Measurement results of the pressure and leakage characterization of the interface. A, Applied test pressure as a time series, ramped in 100 mbar steps with a 20 s hold time per step. B, Simultaneously measured flow rate as a time series for leakage quantification. C, Aggregated leakage rate as a function of tightening torque, calculated from the flow data of the respective pressure steps.

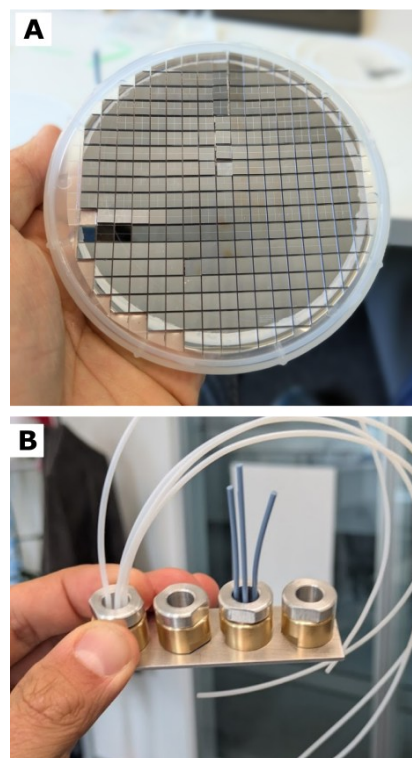


Figure 3: A, 2-inch wafer with >200 microfluidic chips comprising 12 different designs. B, Chips can be modularly placed on a holder and adopt the form factor (7.5 x 2.5 cm) of a conventional microscope slide.

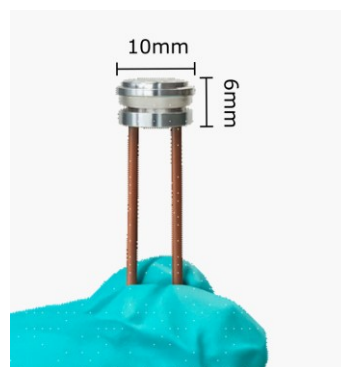


Figure 4: Miniaturization of the ferrule-type world-to-chip interface for a 5 x 5 mm glass chip to 10 x 6 mm.

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MANUFACTURING MULTI-LAYER FLUIDIC CIRCUITS DESIGNED USING NORA (NETWORK-AWARE OPTIMIZATION BY RESISTANCE ADJUSTMENT)

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ABSTRACT

Designing microfluidic networks to accommodate functional modules with specific local flow and pressure requirements within a space-constrained system presents novel challenges. Because interconnecting channels dictate the flow distribution, component placement and routing must be jointly considered. We present a workflow for designing and manufacturing Fluidic Circuit Boards (FCB) where we employ the NORA (Network-Aware Optimization by Resistance Adjustment) algorithm to generate geometry that is globally optimized to ensure specified pressures and flows. We realize an application-oriented example board and evaluate its performance in comparison to model predictions, thereby validating NORA's output and illustrating the merits of design-automation for integrated systems.

KEYWORDS

Fluidic Circuit Board, Manufacturing, Design Automation, Continuous-flow microfluidics

INTRODUCTION

Recently, microfluidics applications have seen a shift towards more multiplexed and integrated systems. Where precise liquid handling of small volumes has proven widely needed, now much cutting-edge research focuses on scaling up complexity or parallelization [1, 2]. Typically, such systems integrate multiple functional components (i.e. mixers, sensors, microreactors) in a network of fluidic channels. With the transition to increasingly large and complex networks, new challenges arise in device design.

Functional modules often come with strict pressure and flow requirements at their inlets and outlets. For example, for a passive mixer the input flows determine the mixing ratio. Flow and pressure throughout a passive system are determined by the hydraulic resistances in the fluidic network, analogous to electri-

cal networks [3]. However, changes to network resistance are implemented by redesigning channel geometry, and thereby network layout, for instance by increasing channel length. In this way, changing a resistance in one place can affect the entire network. This coupling between network layout and channel resistance complicates device design, as changes in resistance can therefore break constraints elsewhere in the network (Figure 1).

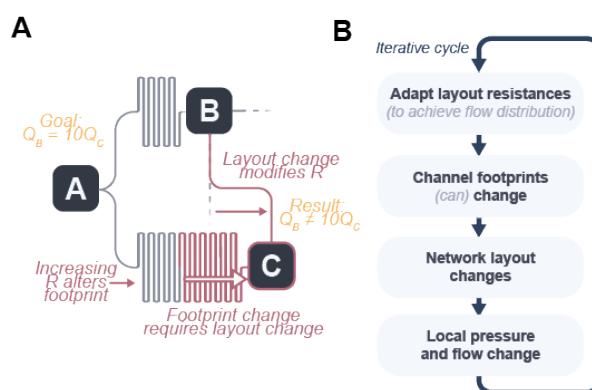


Figure 1: Microfluidic network design is a coupled hydraulics- layout problem. A) Example of coupling in fluidic circuit design. Increasing resistance AC requires a footprint change shifting C, in turn requiring resistance BC to be modified. B) The iterative design cycle in fluidic circuits arising due to the coupling of layout and resistance.

RESULTS AND DISCUSSION

Here, we present a Fluidic Circuit Board (FCB) design and manufacturing workflow using NORA (Network-Aware Optimization by Resistance Adjustment), a global algorithm that adjusts a target network to meet pressure and flow requirements. We fabricate a device for an example use-case embodying the design challenges: a parallel, combinatorial Organ-On-Chip (OoC) platform for soluble-compound testing over a broad concentration range. The device incorporates multiple cell-culture chips with membrane-separated compartments (Figure 2) - chips commonly

used to model tissues such as lung, gut, brain, and joints [4, 5] - and a passive, mixer-based serial diluter capable of generating log10-scale compound concentration gradients. This example, while heavily interconnected, requires precise input flows at the mixer inlets, as well as precise control over the trans-membrane pressure (TMP) for cell culture studies, illustrating the challenges in network design. We experimentally validate a software tool implementing NORA [6], part of the open-source Munich MicroFluidics Toolkit [7], and demonstrate how it allows our design to meet such requirements.

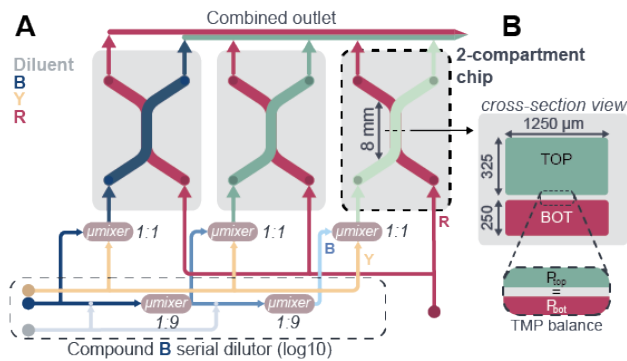


Figure 2: Schematic overview of the network description for the example case multi-OoC FCB. A) Three chips are supplied in parallel from a gradient generator. Input compound B is diluted 10x and 100x, mixed 1:1 with compound Y. B) Cross-section view of the 2-compartment chip showing the chamber configuration and TMP definition.

We choose a mixer design and determine its hydraulic properties using Computational Fluid Dynamics (CFD) simulations verified with experimental testing (Figure 3). These properties are used to formulate a *black-box* model to be used in the network optimization.

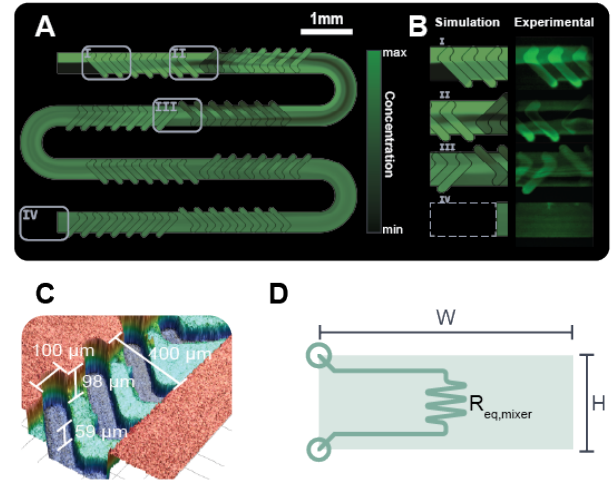


Figure 3: Constructing and experimentally validating a black-box model for the herringbone micromixers. A) CFD simulation top view. B) Side-by-side comparison of the CFD simulation and experimental fluorescence microscopy for various areas of the mixer. C) Fabricated dimensions measured using a Laser Scanning Microscope. D) Simplified resistive model.

We define an initial multi-layer network description and layout input to the tool, integrating the component models and including flow and pressure requirements. Within seconds, NORA optimizes channel routing, channel geometry and component placement together, mirroring the coupling between resistance and placement mentioned above (Figure 4). Channel depth, width, and length are adjusted, inserting meanders if space permits it, to adjust the channel resistances such that the calculated flow distribution is as designed. Because the tool takes into account fabrication constraints and spatial constraints, it can generate and export per-layer DXF-files dimensioned for manufacturing.

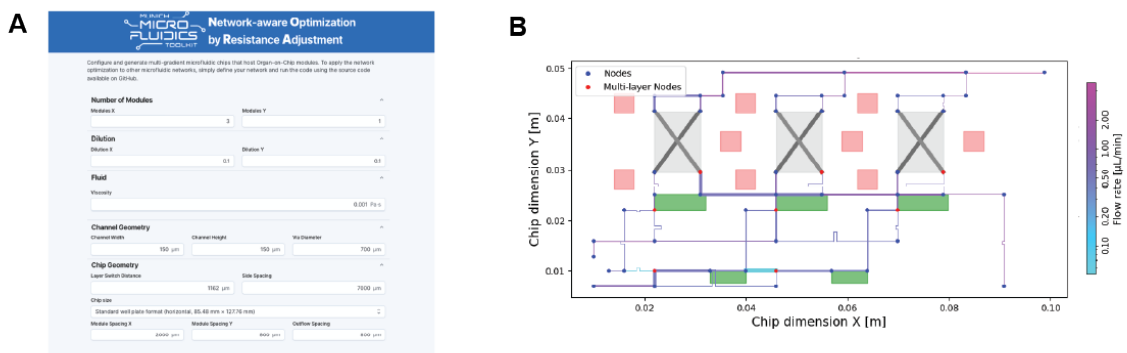


Figure 4: Applying NORA to the example case to optimize channel layout A) Screen recording of the GUI used to apply the tool to the design. B) Tool output for the multi-OoC FCB. The graph shows the final layout with added spacing, fluidic resistors, and components. The channel colour shows the calculated flowrate,

These output files are used to create Computer-Aided Design (CAD) files for micromilled parts (Figure 5A), which are fabricated and assembled into a multi-layer FCB (Figure 5B).

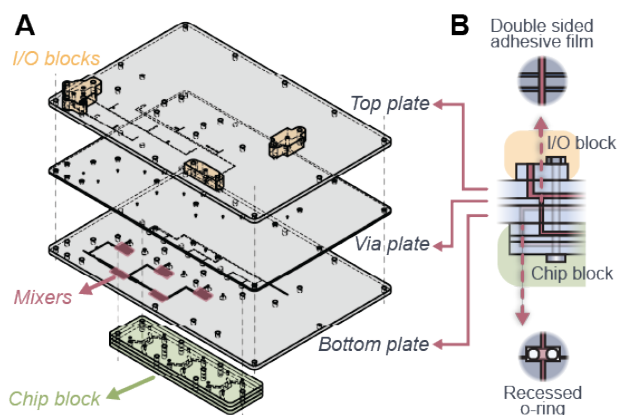


Figure 5: Component breakdown and assembly of the FCB. A) Exploded view of the FCB CAD files. B) Schematic cross-section view of the assembled board plate-stack. Adhesive film seals the board layers, interfacing with the chips is facilitated by O-rings.

We experimentally verify the tool output, supplying different dyes to the board inlets with flows as calculated by the tool, so that a concentration gradient spanning two orders of magnitude forms across the chips. (Figure 6A) We perform brightfield microscopy to quantify the dye concentrations using image-based colorimetry. In addition, we determine the flow ratio at the chip output from the flow boundary formed at the

junction (Figure 6B-D).

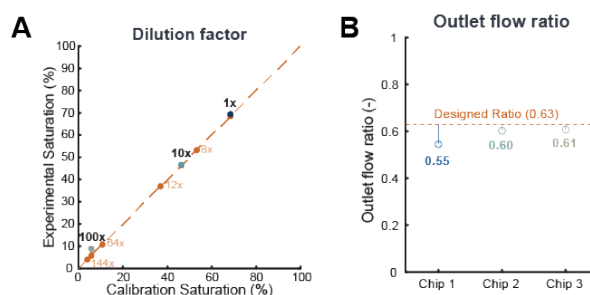


Figure 7: Validation of the experimental board. A) Comparison of saturation as a metric for dilution in experimental images and manual calibration experiments. B) Comparison of flow ratio at the chip outputs and in NORA simulation as an estimate of the TMP balance.

The saturation of the channels under experimental conditions is compared to that of channels manually loaded with known dye concentrations (Figure 7A), while the flow ratio is compared to the simulation output directly (Figure 7B). This way, we determine that the flows and pressures closely match the specified network as designed using NORA.

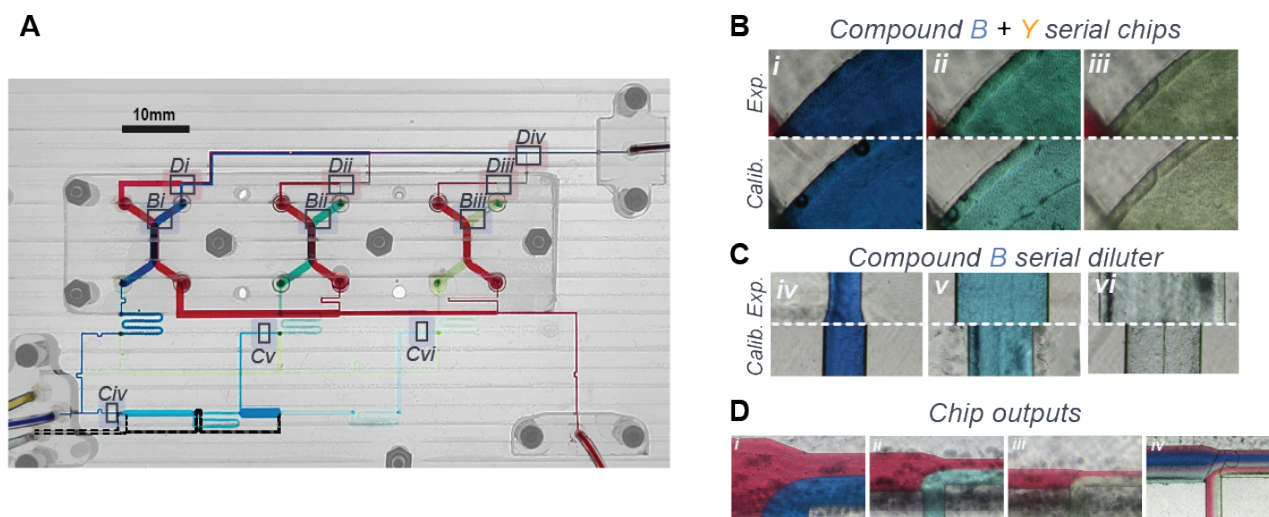


Figure 6: FCB in operation establishing dye gradient in chips. A) Top-view photograph of the fabricated board during operation at the flow rates specified by NORA. For legibility, areas outside of the channels have been masked and contrast reduced. Comparison of manually mixed dye dilutions and experimental dilutions B) on-chip and C) in channels. D) Output junctions of the 2-compartment chips showing flow boundary.

CONCLUSION

To conclude, validating this NORA generated design using our manufacturing workflow demonstrated how complex fluidic circuits can be realized without manual channel resistance optimization. As microfluidic designs continue to scale, the gap between what manual approaches can feasibly produce and theoretically realizable designs will become increasingly large. We envision that manufacturing-friendly design automation tools such as NORA are an important step in closing this gap, expanding the range of problems that can be practically solved, as well as accelerating design cycles of fluidic devices.

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A MODULAR MICROFLUIDIC DESKTOP PLATFORM FOR NEEDLE-FREE INJECTION AND DISPENSING

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ABSTRACT

A desktop injector with a modular microfluidics system for needle-free injection is presented, which reaches both low velocity regime, below 10 m/s, where only droplet dispensing takes place, and high velocity regime, above 100 m/s, where injection into the sample is achieved. Micropumps and microvalves handle the loading and the dosing of the liquid, a fiber coupled laser source generates thermocavitation in a borosilicate glass microfluidic chip deriving in a jet, and dedicated electronics synchronize pumps, stage and laser within a single control loop, under live camera monitoring. Doses between 2 and 50 nL per jet are delivered at rates higher than 100 injections per second, with a reproducibility of approximately 68% and a positioning resolution below 100 μm over a working area of 82 cm^2 . Five chip configurations fabricated in cleanroom have been mounted on a 3D printed holder, and the platform has been operated on hydrogels, in vitro tissue, ex vivo skin models and organ-on-chip devices.

KEYWORDS

Needle-free injection, droplet dispensing, jets, microfluidics automated systems, modularity, drug delivery.

INTRODUCTION

Needle-free injection (NFI) has been studied for decades as an alternative to the hypodermic needle for the delivery of drugs and vaccines, with the aim of reducing sharps waste, needle phobia and accidental injuries [1]. Among the available actuation principles, laser based injectors have received particular attention because the energy deposited in the liquid can be adjusted pulse by pulse, which provides direct control over the jet velocity and over the injected volume [1,2]. Continuous wave (CW) and pulsed laser sources have both been used to nucleate a cavitation bubble inside a microfluidic channel, and the jets generated in this way reach velocities in the order of tens to hundreds of meters per second [2,3].

The outcome of a jet does not depend only on the injector. It depends as well on the mechanical response of the receiving sample. Soft materials such as

hydrogels deform and absorb an important part of the impact energy, while stiffer samples such as skin require higher velocities before penetration occurs, and above a certain energy the jet no longer penetrates and the liquid spreads or splashes on the surface [4]. This behaviour, in addition to simple dispensing has been described for single jets under controlled conditions [4-6], and drug delivery into human ex vivo skin has been demonstrated for insulin and for liposome formulations [7]. Translating these applications or scenarios into a device that can be used routinely, on different samples and by different operators, is still a limitation in the laboratories.

The target substrate is not the only parameter varying across experiments. A formulation study ranges from aqueous solutions to emulsions or lipid based actives, and the delivery mode spans surface deposition and tissue penetration. These tasks are usually split across different instruments [7], which makes it harder to compare conditions and slows down iteration on a formulation or delivery protocol.

This work introduces the design and characterization of a modular desktop injector in which the microfluidic chip, the sample holder, and the actuation parameters are the only elements that change between applications. The same platform covers dispensing and injection, handles aqueous and oily compounds, and has been operated on samples that go from hydrogels to organ-on-chip devices. It is a flexible testing device for delivery and formulation studies, and in particular, for pre-clinical work where small volumes have to be delivered into skin models and skin-on-chip devices, where the injected volume and the position of the injection must be known.

METHODOLOGY

Modular architecture

Four modules are mounted on a common frame (Figure 1). The fluidic module (Fig. 1a) houses the inlet and outlet micropumps, check valves, a bubble trap and a DC vacuum pump, which together prime the chip and set the dose. The injector head (Fig. 1b) clamps the microfluidic chip and aligns the optical fiber that delivers laser energy into the chip and liquid; this is also where a chip is swapped for a different application.

A motorized stage (LPXY1, Thorlabs) forms the travelling system (Fig. 1c), covering an 82 cm² working area with 10 µm mechanical steps. The receiver (Fig. 1d) is a tunable sample holder that accepts multiwell plates, flat substrates and mounted tissue samples.

Chips are designed and fabricated in cleanroom. Five configurations have been produced in MEMPax borosilicate glass, each one adapted to a combination of fluid, range of velocities, dose and target sample, and all of them share the same mounting interface, so a change of chip does not require any modification of the pumping, the optical or the motion hardware.

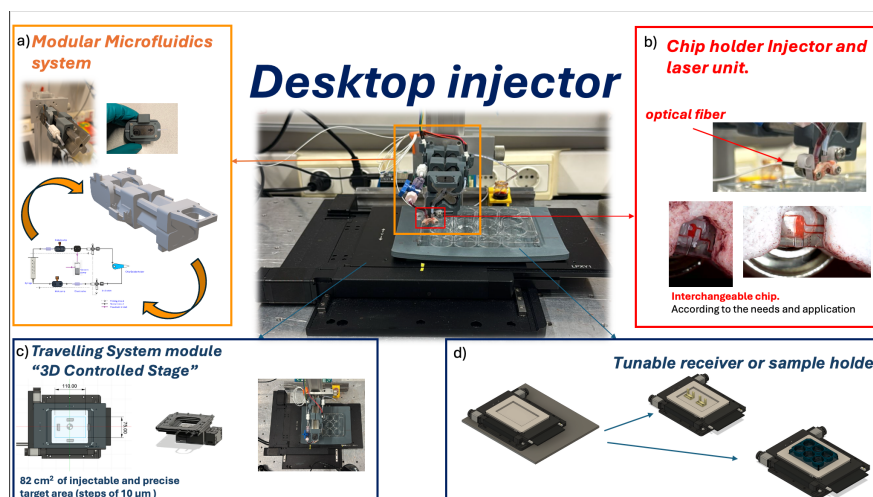


Figure 1: Overview of the desktop injector. (a) Modular microfluidic system, with the pumping and priming circuit that feeds the active chip and sets the dose. (b) Chip holder, injector and laser unit, where the optical fiber delivers the laser energy into the chip, and where the chip is interchangeable according to the needs and the application. (c) Travelling system module, 3D controlled stage, with 82 cm² of injectable and precise target area in steps of 10 µm. (d) Tunable receiver or sample holder, mounted on the same stage and adapted to hydrogel molds, well plates and mounted tissue samples.

Operating regimes

Two regimes are available on the same fluidic path. In the low energy regime, the micropumps alone drive the liquid, the CW laser is triggered delivering [10-100] mW, and droplets are formed at velocities below 10 m/s. In this condition the liquid is deposited on the sample and no penetration is expected, which is the regime used for dispensing on soft substrates and for the characterization of the formulation itself. In the high energy regime, a laser pulse with a power peak of [300-2000] mW is delivered through the optical fiber and nucleates a bubble inside the chamber, accelerating the liquid above 100 m/s and producing a jet capable of penetrating the sample. The transition between the two regimes is a parameter in the control software and not a modification of the setup, which is what allows both conditions to be compared on the same sample and with the same chip.

The velocity needed in each case depends on the stiffness of the receiver, and the window in which each regime is obtained is summarized in Figure 2. The bubble that drives the jet is generated by thermocavitation [8], so the liquid must be heated locally by the beam until the nucleation takes place [9]. When a CW laser is used, this sets a condition on the fluidic module, thermocavitation requires the liquid to

reach its superheat limit within the focal volumen [9], so any residual flow moves the deposited heat out of that volume, delaying or suppressing nucleation. The micropumps (Bartels Mikrotechnik) are therefore, stopped before triggering, with a settling time longer than the flow decay time of the circuit. Since that time is proportional to the hydraulic resistance and compliance of the chip, it is a software parameter retuned at every chip module change or every compound variation. Identifying different regimes and operation is work still in progress.

Electronics and control

Custom electronics control the micropumps, the stage motors, the camera and the laser trigger, so that dosing, positioning and jetting are coordinated in one loop instead of being synchronized by hand. The control application integrates the pump control and the stage and laser synchronization in a single interface, and the system is monitored with a live camera during the whole operation, which is used both to align the injection and to follow the result on the sample. The stopping of the pumps, the settling time, the waiting time and the duration of the laser pulse are set in this same interface.

Two working modes are implemented (Figure 3). In the automatic mode a list of coordinates and triggers

is written directly or imported from a CSV file, and the sequence is executed over the working area with the stage motion and the firing synchronized, which is the mode used to reproduce a pre-programmed pattern. In the manual mode the operator moves the stage with a joystick while a live camera image with a crosshair and a grid overlay is displayed, corrects the position on the image and fires a single jet on the selected spot. Both modes share the same coordinate system, so a position found manually can be added to an automatic sequence.

Fluids and samples

Aqueous and oily compounds with viscosities from 1 cSt to 100 cSt have been handled by the same injector head. Compatibility with one or the other fluid is obtained through the design of the microfluidic circuit, mainly the channel geometry and the surface treatment of the chip, and not through a modification of the pumping hardware. Regarding the soft samples, agarose and gelatin hydrogels, in vitro tissue constructs, ex vivo skin models and organ-on-chip devices have been used as receivers, covering a range of stiffness of several orders of magnitude (Figure 2).

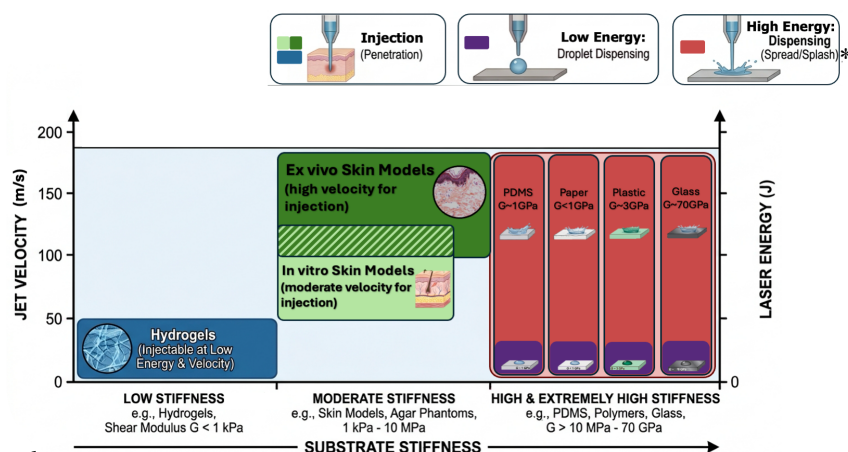


Figure 2: Working window of the platform. Jet velocity and delivered energy are represented against the stiffness of the receiving sample, showing the low energy regime where only droplet dispensing occurs (purple), the intermediate window where injection into hydrogels, in vitro tissue and ex vivo skin models takes place (blue, dark and light green), and the high energy condition on stiff materials such as PDMS, paper, plastic and glass, where the liquid spreads or splashes instead of penetrating (red). * Schematics on top are AI generated.

RESULTS AND DISCUSSION

The dose delivered in a single jet is tunable between 2 and 50 nL, depending on the chip configuration and on the actuation parameters. Repetition rates higher than 100 injections per second have been reached, which makes it possible to cover an area with many injection points in a short time. The reproducibility measured between consecutive jets (comparing theoretical volume to jet with the actual delivered volume in a jet after every laser trigger, during 40 events) is ~68%. However, single injection dose sometimes is required and the platform is flexible enough to provide a reproducible single injection in any desired target. These values can be compared with published laser based injectors, where a focused microjet working in a repetitive regime delivered jets of the order of 50 nL at frequencies between 1 and 15 Hz [8]. The platform reported here covers the same volume scale at a repetition rate almost one order of magnitude higher.

Injection position is controlled in three dimensions to a resolution below 100 μm over the full 82 cm^2 working area, with 10 μm mechanical steps. Combined with automatic sequencing, this supports continuous or discrete patterns down to a 100 μm line width. The

platform can generate spatially distributed doses, not just single-point injections. The manual mode was validated on different phantom and biological samples, with the operator aligning the injector on a chosen spot via the camera image before jetting.

Five chip configurations have been mounted and operated on the same holder, and the change between them takes a few minutes. This aspect makes the difference with a fixed injector, since a new application does not require a new instrument but a new chip and a set of parameters. Together with the two operating regimes, this modularity is what allows dispensing experiments and injection experiments to be performed consecutively on the same sample, which is difficult when the two tasks are distributed over different setups. The reproducibility of 68% is sufficient for feasibility studies and comparisons between conditions, but it is still the parameter that limits a quantitative dosing application. The sources of the shot-to-shot variation are being studied, and the fabrication tolerance between chips, the consistency of the priming step and the stability of the delivered laser energy are aspects that can be improved to enhance the machine performance. Improving the aspects mentioned is a main goal for future work.

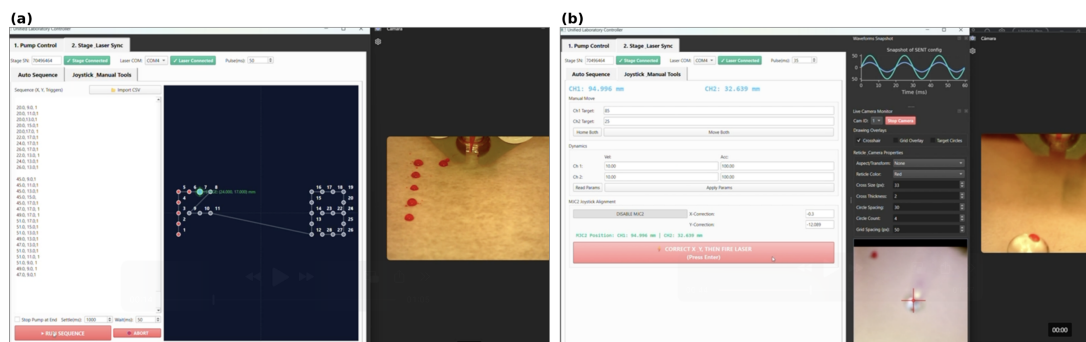


Figure 3: Operational modes of the control interface. (a) Automatic mode, where a list of coordinates and triggers imported from a CSV file is executed over the working area with the stage, the pumps and the laser synchronized, and the injection points are followed on the live camera image. The stopping of the pumps, the settling time, and the waiting time between shots are set in the same panel. (b) Manual mode, where the stage is moved with a joystick and the crosshair and the grid overlay on the live camera image are used to align the head on the selected spot before a single jet is fired.

CONCLUSIONS

A modular desktop injector has been built and characterized. It covers droplet dispensing below 10 m/s and jet injection above 100 m/s on the same fluidic path, delivers 2 to 50 nL per jet at rates above 100 injections per second, and positions the injection with a resolution below 100 μm over 82 cm^2 , with patterns down to a line width of 100 μm . Aqueous and oily compounds are handled by changing the microfluidic circuit only, and five cleanroom fabricated chips have been operated on the same holder. The samples used so far go from hydrogels to in vitro tissue, ex vivo skin models, and organ-on-chip devices. The reproducibility between consecutive jets, currently close to 68%, is the parameter that is being improved, together with the extension of the chip library to new formulations and sample types.

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