Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Biotechnology

Sensor integration into microfluidic systems: trends and challenges

Marc A Buttkewitz[1], Christopher Heuer[1,2] and Janina Bahnemann[2,3]

The combination of sensors and microfluidics has become a promising approach for detecting a wide variety of targets relevant in biotechnology. Thanks to recent advances in the manufacturing of microfluidic systems, microfluidics can be manufactured faster, cheaper, and more accurately than ever before. These advances make microfluidic systems very appealing as a basis for constructing sensor systems, and microfluidic devices have been adapted to house (bio)sensors for various applications (e.g. protein biomarker detection, cell culture oxygen control, and pathogen detection). This review article highlights several successfully integrated microfluidic sensor systems, with a focus on work that has been published within the last two years. Different sensor integration methods are discussed, and the latest trends in wearable- and smartphone-based sensors are described.

Addresses
[1] Institute of Technical Chemistry, Leibniz University Hannover, 30167 Hannover, Germany
[2] Institute of Physics, University of Augsburg, 86159 Augsburg, Germany
[3] Centre for Advanced Analytics and Predictive Sciences (CAAPS), University of Augsburg, 86159 Augsburg, Germany

Corresponding author: Bahnemann, Janina (janina.bahnemann@uni-a.de)

Current Opinion in Biotechnology 2023, **83**:102978

This review comes from a themed issue on **Analytical Biotechnology**

Edited by **Alexander Gruenberger**, **Janina Bahnemann**, and **Christian Dusny**

Available online xxxx

https://doi.org/10.1016/j.copbio.2023.102978

Introduction

In recent years, (bio)sensors have become a promising tool for the detection of a wide variety of target analytes such as cancer biomarkers, bacterial pathogens, and/or metabolites. To enable point-of-care diagnostics and reduce required volumes and space, sensor integration into microfluidic systems has become a primary focus of research [1]. Yet, such systems also hold great promise for industrial use [2,3], thanks to advances in manufacturing methods that have rendered microfluidic sensor systems surprisingly cost-effective (as little as $0.15 per device) to produce [4].

The use of microfluidic systems with integrated sensors has become particularly widespread in the field of biotechnology, and the usefulness of combining different sensor types and microfluidic systems has been well-demonstrated at this point (as shown in Table 1). For example, Arshavsky-Graham et al. [5•] integrated a silicon-based optical sensor into 3D-printed microfluidics, while Aleman et al. [6] incorporated an electrochemical impedance-based biosensor into a polydimethylsiloxane (PDMS) housing. Frey et al. have also successfully integrated different microsensors into a microbioreactor system, permitting them to monitor process parameters such as the O_2 and CO_2 concentration or the pH value during a cultivation of *Saccharomyces cerevisiae* (*S. cerevisiae)* [7]. This work highlights that the miniaturization of bioreactors or point-of-care devices also requires the miniaturization of the sensor itself, however — a fact that also poses a new challenge for (bio)sensor development. Nevertheless, a few miniaturized sensors, such as sensor plugs for bioprocess control (pH, O_2, and CO_2) [8], are already commercially available. Having said that, the sheer variety of different sensor (e.g. optical, electrochemical) and microfluidic housing (e.g. plastics, PDMS, and glass) combinations highlights that there is still no standardized method for sensor integration. Instead, different integration techniques have been developed and adapted to fit specific experimental requirements — and a number of different difficulties and challenges (including leakage issues [5•], pressure stability [9], and mechanical integrity [10]) must be considered and confronted by researchers looking to develop such a system for their own particularized use.

This review article focuses on surveying some of the recent microfluidic systems with integrated sensors that have been developed in the last two years for biotechnological/biochemical applications. Accordingly, we offer an overview of sensors employed and integration methods

Table 1

Overview of different sensors recently integrated into microfluidic systems — divided into optical versus electrochemical sensor types (since those are the two primary types reported in the literature).

Principle	Application	Housing
Optical sensors		
Colorimetric sensor	Aptamer-based pathogen detection [11]	Glass [11]
Luminescence sensor	Sensor spots for pH and oxygen control in cell culture [12•] Detection of protein biomarkers [13]	Thermoplastic polymer [12•], 3D-printed plastic [13]
Raman sensor	Analysis of cells [14]Analysis of molecules [15]	3D-printed plastic [14], PDMS [15]
Fluorescence sensor	Sensor spots for pH and oxygen control in cell culture [7,16]Glucose measurement [17]Antibody detection [18]	3D-printed plastic [7,17], PDMS [16]Combination of 3D-printed and non-3D-printed plastic [18]
Reflectance measurement	Aptamer-based biomarker detection [5•]	3D-printed plastic and PDMS [5•]
ELISA	Detection of immunoglobulin E [19]	3D-printed plastic [19]
Microring resonator	Detection of streptavidin [20]	PDMS [20]
Electrical/electrochemical sensors		
Resistive pulse sensor	Characterizing algae and microplastic particles [21]	3D-printed plastic [21]
Electrical current measurement	Exosome detection [22]	3D-printed plastic [22]
Microwave sensor	Detection of metal ions in water [23] Blood glucose measurement [24]Determination of fluid mixtures [25]	Low-temperature cofired ceramic [23]Metal [24,25]
Ultrasound sensor	Density measurement of fluids [26]	PDMS [26]
Impedance spectroscopy	Evaluating basic tastes [2]Aptamer-based pathogen detection [27]Antibody and aptamer-based detection of GTS-α and CK-MB [6]	PDMS [2,6]3D-printed plastic [22,27]

used while also flagging some of the current challenges and emerging trends in sensor integration efforts.

Integration methods — state-of-the-art

Integrating sensors into microfluidic systems is a topic of great sensitivity and importance to researchers working with such systems. Owing to the very small sizes of microfluidic systems, as well as the incredible diversity of materials that are used for microfluidics production and sensor systems [28], selecting the right integration method is something that must be given careful thought. In all cases, however, the sensor must be installed into the system in a leakage-free manner that does not impair its sensing performance.

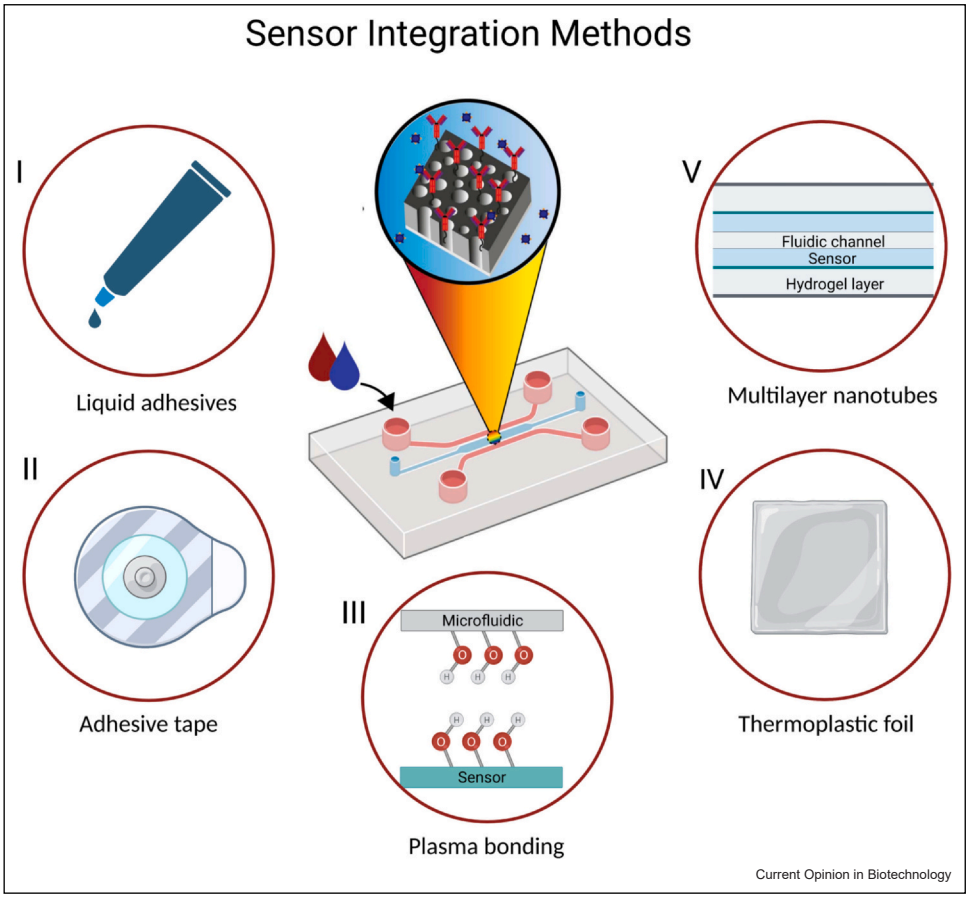
The vast majority of sensor-integrated microfluidic systems deploy a modular design [5•,29,30,31]. Put differently, these systems are manufactured in individual parts, which are then subsequently connected to form a complete system. Attempts to manufacture both the microfluidics element and the sensors in a single step are very rare, given the very different types of materials and manufacturing techniques that are typically used to develop and assemble both of those elements. An overview of the integration methods recently reported is summarized in Figure 1.

Integration of sensors into microfluidic devices is often achieved via adhesives. In their work, Arshavsky-Graham et al. [5•] spread a UV-curable liquid glue in a thickness of just a few micrometers on a transfer wafer. Subsequently, the 3D-printed microfluidic system with channels open to their bottom was placed on the adhesive and then once again removed, with the adhesive remaining on the glued area. The 3D-printed object was then placed on the silicon sensor, and bonding was achieved by curing the adhesive under UV light. The successful integration of such photonic silicon chips into a 3D-printed gradient generator to accomplish automated generation of desired antibiotic concentrations (twofold dilutions) for on-chip antimicrobial susceptibility testing has already been demonstrated by Heuer and Preuß et al. [37].

Alternatively, solid adhesives are also frequently used to form a connection. The simplest method uses double-sided adhesive tape [4,32,33••,34] or pressure-sensitive adhesive tape [38], which is cut via a suitable method (such as by using a laser cutter). The tape is then applied to the microfluidic device or the sensor and bonded to the respective counterpart [33••]. Because all tape has a certain thickness, however, this approach fundamentally limits the size of the microchannels due to the additional layer. Nevertheless, adhesive tape can also be exploited to directly create microfluidic channels and adjust the channel height [32,34].

In a different integration method, Müller et al. [12•] used a microdispenser capable of applying small volumes with pinpoint accuracy to include sensor spots into microfluidic systems. The integration was performed as follows: the microfluidic system was produced with open channels, the sensor spots were applied at the appropriate locations, and then the

Figure 1



Overview of sensor integration methods recently described in the literature. (I) Liquid adhesive can be used as a bonding agent (utilized in Ref. [5•]), or alternatively, (II) adhesive tape can be employed (utilized in Refs. [4,12•,32,33••,34]). (III) Plasma bonding is often used with PDMS-based microfluidics (utilized in Refs. [30,35]). (IV) Moreover, thermoplastic foil (utilized in Ref. [9]) or (V) multilayer nanotubes (utilized in Ref. [36••]) can be used for sensor integration.

channels were closed using a cover foil and a suitable bonding method (e.g. double-sided adhesive tape). This approach produced sensor spots with a diameter of as low as 0.5 mm and a height of just 4 µm. Another advantage of these sensor spots is that the measurement can be performed directly through the housing material (thermoplastic polymer), thereby reducing the risk of contamination — which is of course enormously important, especially in bioprocesses.

Plasma bonding [30,35] has also been widely used for establishing a connection between the sensor and the microfluidic channel system. In this approach, the microfluidic components are treated with oxygen plasma, creating a highly reactive surface. This activated surface can then be bonded to the sensor unit, creating a stable and effective connection. To date, this approach has mainly been used within PDMS-based microfluidic systems. Another integration method when using PDMS microfluidics is to insert the sensor while casting the PDMS [39].

Heidt et al. [9] describe another method of sensor integration into microfluidic systems. In this case, a channel system is fabricated exhibiting open channels. To seal the system, a thermoplastic polyethylene terephthalate glycol (PETG) film is placed on the structure of the system in a vacuum former for a precise fit. This method is suitable for the fabrication of complex geometries, and the resulting sensor system has been used for a colorimetric assay (drug detection) enabled by the excellent optical transmission of the film.

A further interesting method for integrating sensors is based on the swelling of a hydrogel layer to create microtubes. In this process, platinum electrodes are deposited on a polyimide layer, which in turn sits on a hydrogel swelling layer. By soaking the substrate in a suitable solution, the hydrogel swells and expands. The polyimide layer attached to the hydrogel does not swell, resulting in curling of the layer. The result is a microtube carrying a platinum electrode with a diameter of

25 µm inside the channel. The fabricated tubes were stabilized by a suitable drying and fixing procedure, and the authors subsequently integrated the obtained tubes into a PDMS chip [36••].

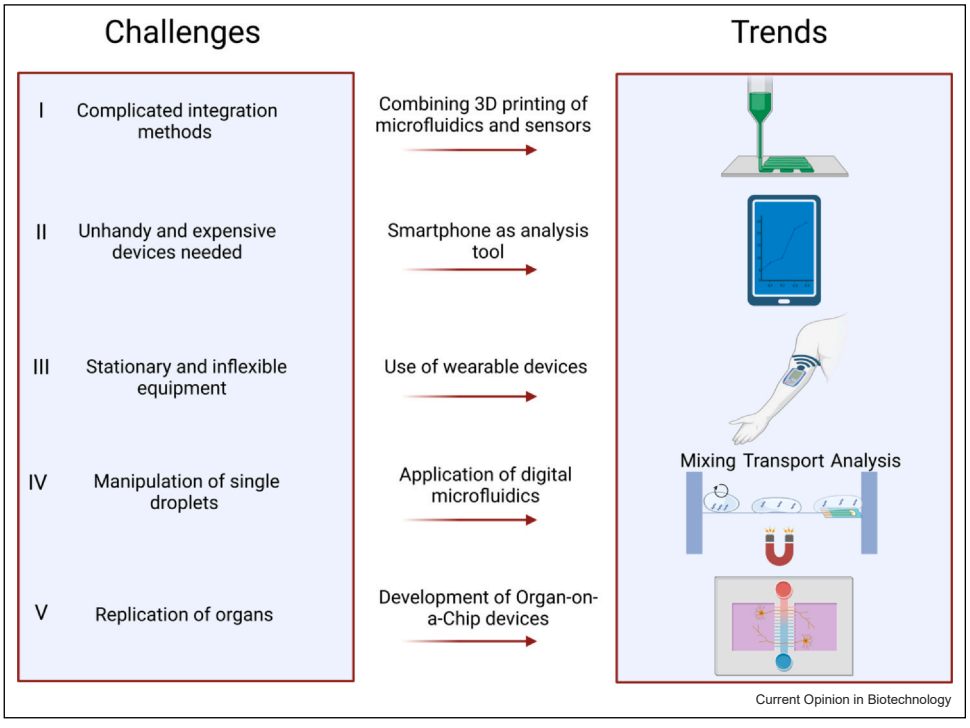
Challenges and trends

Combining and integrating sensors into microfluidic devices is rarely a simple process. A wide variety of parameters and criteria must be considered when selecting the bonding process; if an adhesive is used, then compatibility with the materials of the microfluidic system and the sensor must be verified (e.g. UV-curing adhesives may be incompatible with sensors due to the required radiation) [5•]. But the compatibility of the solvents that are to flow in the channels must also be investigated and taken into account. An overview of the recent challenges and the trends to tackle these issues is given in Figure 2.

One emerging method of sensor integration is the combined production of microfluidics and sensor systems. Inkjet printing technology, for example, can potentially facilitate the production of paper-based microfluidics in a single step [40•]. Different inks are typically used for this purpose: one ink can contain the sensor material, while another ink can print a hydrophobic barrier, and thus create channels for a water-based sample [40•]. In addition to this 2D-printing technology, a similar approach can be used for 3D printing. Here, two or more different materials might be applied to fabricate a combined microfluidic sensor system within a single step. It was, for instance, demonstrated that the use of an electrically conducting and an insulating printing material enables flow cell fabrication for electrochemical detection of target analytes (catechol, ferrocenemethanol) [41]. It is also possible to print a 3D microfluidic system directly onto a prefabricated microarray [42], so that the sensor is also directly integrated during the creation of the microfluidic system.

Challenges also extend to encompass the comparatively large periphery of required devices. Although microfluidic devices can be manufactured in very small dimensions — thus offering researchers a substantial space advantage over conventional measuring systems — large and unwieldy devices are often used to monitor and read out the measured values [24]. This can undercut the space-saving advantage of using microfluidics in the first place, and because a large number of the sensor systems

Figure 2



Overview of current challenges and emerging trends to overcome these limitations. (I) Combined 3D printing of microfluidics and sensors can be used to avoid the need for integration processes (utilized in Refs. [40•,41,42]). (II) Smartphones as analysis tools can help to cut the need for bulky analysis tools (utilized in Refs. [24,33••,43,44••]). (III) Wearable microfluidic devices for point-of-care diagnostics to replace stationary equipment (utilized in Refs. [24,45–48]). (IV) Application of DMF for single-droplet manipulation and analysis (utilized in Refs. [50•,51,52]). (V) Ooc device for the replication and simulation of tissues and organs in microfluidics (utilized in Refs. [6,16,53]).

described in the literature are intended for use in point-of-care diagnostic applications, this is not an insignificant problem. A common approach to address this issue is to use generally available devices (such as smartphones) to read out the sensors [33••,43,44••]. In general, two options are possible. The first method integrates the smartphone directly into the detection process and uses, for example, the built-in camera as an optical readout system, this is utilized by Xiao et al. [33••] for the detection of β2-microglobulin via surface plasmon resonance. By contrast, the second method utilizes a radiotransmitter that transmits the measured values to the smartphone, which then performs the analysis. This has been used to allow sweat analysis for ions such as sodium or potassium using an electrochemical sensing system [44••].

Such portable microfluidic applications [10,31] are proving to be increasingly important in the emerging field of microfluidic sensor research, since they can potentially be used to monitor critical body parameters in sick patients or in modern fitness equipment. A frequently used method is the analysis of perspiration [45] occurring on the skin. Common applications include the measurement of various anions such as sodium or potassium [46] and the pH value. In addition, molecules such as lactate [47] or glucose [24,48] can also be measured. Indeed, a portable sensor that is even able to collect blood samples by means of microneedles has been described in the literature: this sensor device enabled the detection of relevant cancer biomarkers using a biochemical fluorescence reaction [49].

Another emerging trend in microfluidic sensor systems is the field of digital microfluidics (DMF). In DMF, electrodes or magnetic particles are used to move fluids via electrowetting or magnetic interactions. This mitigates the need for pressure-driven control of the fluids, which facilitates the integration of various sensor systems that are otherwise difficult to combine with conventional systems. For example, antimicrobial susceptibility tests, immunoassays, or spectrometer-based protein quantification by the bicinchoninic acid assay have been integrated into these DMF systems [50•,51,52]. Moreover, Kanitthamniyom et al. [50•] combined a DMF system with different 3D-printed manipulating/measuring modules. The system is modularly designed and allows for plugging in different modules with different functions (mixing, particle extraction, and liquid dispensing) that enable manipulation or analysis of the fluids that are moved through the microfluidic device by magnetic force. Owing to this simple and adjustable design, it is easy to adapt the system to different experimental requirements, and also the integration/exchange of different sensors is envisioned.

Finally, the miniaturization of sensors has also become increasingly important in the field of organ-on-a-chip (OoC) systems. OoC systems allow organs to be replicated on microfluidic chips — facilitating a variety of possibilities, such as the *in vitro* evaluation of virus infection [53] or the investigation of physiologically relevant oxygen gradients [16]. Such devices also require miniaturized analytics. For this purpose, reusable electrochemical affinity-based biosensors have been developed [6] to allow universal biomarker detection in the cell culture microenvironment. In particular, the detection of the biomarkers GTS-α and CK-MB has been shown.

Conclusions

Progress in the field of designing and assembling microfluidic sensor systems has been remarkable in recent years, and a large number of different sensor types has been successfully incorporated into such systems using a wide variety of integration strategies. Several developments in particular have tremendous potential for broad application in the future: the integration of 2D/3D printing techniques into the manufacturing process allows fabricating sensors and surrounding housing in one step, avoiding the need for manual and potentially unreliable sensor integration. These techniques also permit researchers to adjust the microfluidic sensor systems to changing experimental requirements in a simple and straightforward manner. Recently, the development of wearable microfluidic- and smartphone-based sensors has become an emerging research field for potential widespread self- and point-of-care testing.

Although most reported microfluidic sensor systems remain firmly in their initial development phase, and have not yet been commercialized (or even demonstrated success in real-world field applications), we nevertheless envision that the improvement of sensor integration and its reproducibility will lead to market-wide applications of such microfluidic-integrated sensing systems in the near future.

CRediT authorship contribution statement

Marc Buttkewitz: Writing – original draft preparation. **Christopher Heuer:** Writing – review & editing. **Janina Bahnemann:** Writing – review & editing, Supervision, Funding acquisition.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the German Research Foundation (DFG) via the Emmy Noether program [project ID 346772917], the Ministry of Science and Culture of Lower Saxony and the VolkswagenStiftung via the program "Niedersächsisches Vorab: Research cooperation Lower Saxony-Israel". The graphical abstract as well as Figures. 1 and 2 were created with BioRender.com under a publication license. The open access publication of this article was supported by the DFG sponsored Open Access Fund of the University of Augsburg.

Editorial disclosure statement

Given her role as Guest Editor, Janina Bahnemann had no involvement in the peer review of the article and has no access to information regarding its peer-review. Full responsibility for the editorial process of this article was delegated to Christian Dusny.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Vicente FA, Plazl I, Ventura SPM, Žnidaršič-Plazl P: **Separation and purification of biomacromolecules based on microfluidics**. *Green Chem* 2020, **22**:4391-4410.

2. Braunger ML, Fier I, Rodrigues V, Arratia PE, Riul A: **Microfluidic mixer with automated electrode switching for sensing applications**. *Chemosensors* 2020, **8**:13.

3. Sorocki J, Piekarz I, Wincza K, Gruszczynski S, Papapolymerou J: **Broadband microwave microfluidic coupled-line sensor with 3-D-printed channel for industrial applications**. *IEEE Trans Microw Theory Tech* 2020, **68**:2808-2822.

4. Mohd Asri MA, Mak WC, Norazman SA, Nordin AN: **Low-cost and rapid prototyping of integrated electrochemical microfluidic platforms using consumer-grade off-the-shelf tools and materials**. *Lab Chip* 2022, **22**:1779-1792.

5. • Arshavsky-Graham S, Enders A, Ackerman S, Bahnemann J, Segal E: **3D-printed microfluidics integrated with optical nanostructured porous aptasensors for protein detection**. *Microchim Acta* 2021, **188**:67.

Integration of optical pours silicon-based biosensors into 3D-printed microfluidic systems. A Novel gluing technique is shown, that allows the use of a UV-curing glue without clogging of the microchannels by a precise glue distribution. The biosensor system has been used for protein detection.

6. Aleman J, Kilic T, Mille LS, Shin SR, Zhang YS: **Microfluidic integration of regeneratable electrochemical affinity-based biosensors for continual monitoring of organ-on-a-chip devices**. *Nat Protoc* 2021, **16**:2564-2593.

7. Frey LJ, Vorländer D, Ostsieker H, Rasch D, Lohse J-L, Breitfeld M, Grosch J-H, Wehinger GD, Bahnemann J, Krull R: **3D-printed micro bubble column reactor with integrated microsensors for biotechnological applications: from design to evaluation**. *Sci Rep* 2021, **11**:7276.

8. Podunavac I, Hinić S, Kojić S, Jelenčiakova N, Radonić V, Petrović B, Stojanović G: **Microfluidic approach for measurements of pH, O2, and CO_2 in saliva**. *Sens Mater* 2021, **33**:1037.

9. Heidt B, Rogosic R, Leoné N, Brás EJS, Cleij TJ, Harings JAW, Diliën H, Eersels K, van Grinsven B: **Topographical vacuum sealing of 3D-printed multiplanar microfluidic structures**. *Biosensors* 2021, **11**:395.

10. Mogera U, Guo H, Namkoong M, Rahman MS, Nguyen T, Tian L: **Wearable plasmonic paper-based microfluidics for continuous sweat analysis**. *Sci Adv* 2022, **8**:eabn1736.

11. Li T, Ou G, Chen X, Li Z, Hu R, Li Y, Yang Y, Liu M: **Naked-eye based point-of-care detection of *E.coli* O157: H7 by a signal-amplified microfluidic aptasensor**. *Anal Chim Acta* 2020, **1130**:20-28.

12. • Müller B, Sulzer P, Walch M, Zirath H, Buryška T, Rothbauer M, Ertl P, Mayr T: **Measurement of respiration and acidification rates of mammalian cells in thermoplastic microfluidic devices**. *Sens Actuators B: Chem* 2021, **334**:129664.

The integration of sensor spots based on an optical readout system into microfluidic system is shown. Miniaturization of the sensor spots is achieved by using a microdispenser, this allows to precisely localize sensor spots of sub millimeter dimensions. The microfluidic sensor system was tested in cell culture applications for oxygen and pH measurements.

13. Sharafeldin M, Chen T, Ozkaya GU, Choudhary D, Molinolo AA, Gutkind JS, Rusling JF: **Detecting cancer metastasis and accompanying protein biomarkers at single cell levels using a 3D-printed microfluidic immunoarray**. *Biosens Bioelectron* 2021, **171**:112681.

14. Santos HDA, Silva AE, Silva GC, Lima EB, Marques AS, Alexandre-Moreira MS, Queiroz AC, Jacinto C, Henrique Lopes J, Rocha U, Silva GT: **3D-printed acoustofluidic devices for raman spectroscopy of cells**. *Adv Eng Mater* 2021, **23**:2100552.

15. Nie Y, Jin C, Zhang JXJ: **Microfluidic in situ patterning of silver nanoparticles for surface-enhanced Raman spectroscopic sensing of biomolecules**. *ACS Sens* 2021, **6**:2584-2592.

16. Grant J, Lee E, Almeida M, Kim S, LoGrande N, Goyal G, Sesay AM, Breault DT, Prantil-Baun R, Ingber DE: **Establishment of physiologically relevant oxygen gradients in microfluidic organ chips**. *Lab Chip* 2022, **22**:1584-1593.

17. Nawrot W, Gzubicka W, Malecha K: **3D-Printed Microfluidic Sensor for Fluorescence Measurements**. *Periodica Polytechnica Electrical Engineering and Computer Science* (1) 2021, **65**:15-19.

18. Sathish S, Toda-Peters K, Shen AQ: **Proof-of-concept modular fluid handling prototype integrated with microfluidic biochemical assay modules for point-of-care testing**. *View* 2020, **1** e1.

19. Achille C, Parra-Cabrera C, Dochy R, Ordutowski H, Piovesan A, Piron P, van Looy L, Kushwaha S, Reynaerts D, Verboven P, *et al.*: **3D printing of monolithic capillarity-driven microfluidic devices for diagnostics**. *Adv Mater* 2021, **33**:e2008712.

20. Kim N, Han K, Su P-C, Kim I, Yoon Y-J: **A rotationally focused flow (RFF) microfluidic biosensor by density difference for early-stage detectable diagnosis**. *Sci Rep* 2021, **11**:9277.

21. Pollard M, Hunsicker E, Platt M: **A Tunable Three-Dimensional Printed Microfluidic Resistive Pulse Sensor for the Characterization of Algae and Microplastics**. *ACS Sens* 2020, **5**:2578-2586.

22. Kashefi-Kheyrabadi L, Kim J, Chakravarty S, Park S, Gwak H, Kim S-I, Mohammadniaei M, Lee M-H, Hyun K-A, Jung H-I: **Detachable microfluidic device implemented with electrochemical aptasensor (DeMEA) for sequential analysis of cancerous exosomes**. *Biosens Bioelectron* 2020, **169**:112622.

23. Liang Y, Ma M, Zhang F, Liu F, Lu T, Liu Z, Li Y: **Wireless microfluidic sensor for metal ion detection in water**. *ACS Omega* 2021, **6**:9302-9309.

24. Govind G, Akhtar MJ: **Design of an ELC resonator-based reusable RF microfluidic sensor for blood glucose estimation**. *Sci Rep* 2020, **10**:18842.

25. Fu L, Huang J, Xiang Y, Chen Y, Gu W, Wu Y: **A miniaturized differential microwave microfluidic sensor with high decoupling**. *IEEE Microw Wirel Compon Lett* 2021, **31**:909-912.

26. Roy K, Kalyan K, Ashok A, Shastri V, Jeyaseelan AA, Mandal A, Pratap R: **A PMUT integrated microfluidic system for fluid density sensing**. *J Microelectromech Syst* 2021, **30**:642-649.

27. Siller IG, Preuss J-A, Urmann K, Hoffmann MR, Scheper T, Bahnemann J: **3D-printed flow cells for aptamer-based impedimetric detection of *E. coli* crooks strain**. *Sensors* 2020, **20**:4421.

28. Akceoglu GA, Saylan Y, Inci F, Snapshot A: **A snapshot of microfluidics in point-of-care diagnostics: multifaceted integrity with materials and sensors**. *Adv Mater Technol* 2021, **6**:2100049.

29. Haghayegh F, Salahandish R, Zare A, Khalghollah M, Sanati-Nezhad A: **Immuno-biosensor on a chip: a self-powered microfluidic-based electrochemical biosensing platform for point-of-care quantification of proteins**. *Lab Chip* 2021, **22**:108-120.

30. Feng J, Wu T, Cheng Q, Ma H, Ren X, Wang X, Lee JY, Wei Q, Ju H: **A microfluidic cathodic photoelectrochemical biosensor chip for the targeted detection of cytokeratin 19 fragments 21-1**. *Lab Chip* 2021, **21**:378-384.

31. Kim T, Yi Q, Hoang E, Esfandyarpour R: **A 3D printed wearable bioelectronic patch for multi-sensing and in situ sweat electrolyte monitoring**. *Adv Mater Technol* 2021, **6**:2001021.

32. Raj W, Yang D, Priest C: **Rapid fabrication of superhydrophobic virtual walls for microfluidic gas extraction and sensing**. *Micromachines* 2021, **12**:514.

33. •• Xiao C, Eriksson J, Suska A, Filippini D, Mak WC: **Print-and-stick unibody microfluidics coupled surface plasmon resonance (SPR) chip for smartphone imaging SPR (Smart-iSRP)**. *Anal Chim Acta* 2022, **1201**:339606.

3D-printed biosensor based on surface plasmon resonance. The camera of a commercially available smartphone is used as the readout system. The detection of β2-microglobulin has been successfully performed by this system.

34. Zhu S, Zhang X, Chen M, Tang D, Han Y, Xiang N, Ni Z: **An easy-fabricated and disposable polymer-film microfluidic impedance cytometer for cell sensing**. *Anal Chim Acta* 2021, **1175**:338759.

35. Chen S, Wang Z, Cui X, Jiang L, Zhi Y, Ding X, Nie Z, Zhou P, Cui D: **Microfluidic device directly fabricated on screen-printed electrodes for ultrasensitive electrochemical sensing of PSA**. *Nanoscale Res Lett* 2019, **14**:71.

36. •• Egunov AI, Dou Z, Karnaushenko DD, Hebenstreit F, Kretschmann N, Akgün K, Ziemssen T, Karnaushenko D, Medina-Sánchez M, Schmidt OG: **Impedimetric microfluidic sensor-in-a-tube for label-free immune cell analysis**. *Small* 2021, **17**:e2002549.

A self-assembling sensor-in-a-tube system is proposed. The method is based on the swelling of a hydrogel layer, platinum electrodes are deposited on a polyimide layer which in turn sits on a hydrogel swelling layer. By soaking the substrate in a suitable solution, the hydrogel expands, which leads to the curling of the layer, creating microtubes. The sensor system is used as an impedimetric sensor.

37. Heuer C, Preuss J-A, Buttkewitz M, Scheper T, Segal E, Bahnemann J, 3D-printed A: **microfluidic gradient generator with integrated photonic silicon sensors for rapid antimicrobial susceptibility testing**. *Lab Chip* 2022, **22**:4950-4961.

38. Hassanpour-Tamrin S, Sanati-Nezhad A, Sen A: **A simple and low-cost approach for irreversible bonding of polymethylmethacrylate and polydimethylsiloxane at room temperature for high-pressure hybrid microfluidics**. *Sci Rep* 2021, **11**:4821.

39. Javidanbardan A, Azevedo AM, Chu V, Conde JP, Systematic A: **Approach for developing 3D high-quality PDMS microfluidic chips based on micromilling technology**. *Micromachines* 2021, **13**:6.

40. • Deng Y, Li Q, Zhou Y, Qian J: **Fully inkjet printing preparation of a carbon dots multichannel microfluidic paper-based sensor and its application in food additive detection**. *ACS Appl Mater Interfaces* 2021, **13**:57084-57091.

In this study, the single-step production of paper based microfluidic system has been shown. Ink jet printing is utilized to print the microfluidic system as well as fluorescence-based sensor system. Custom made inks have been used to print the combined system for the detection of food additives.

41. O'Neil GD, Ahmed S, Halloran K, Janusz JN, Rodríguez A, Terrero Rodríguez IM: **Single-step fabrication of electrochemical flow cells utilizing multi-material 3D printing**. *Electrochem Commun* 2019, **99**:56-60.

42. Su R, Wen J, Su Q, Wiederoder MS, Koester SJ, Uzarski JR, McAlpine MC: **3D printed self-supporting elastomeric structures for multifunctional microfluidics**. *Sci Adv* 2020, **6**:eabc984.

43. Anderson S, Hadwen B, Brown C: **Thin-film-transistor digital microfluidics for high value in vitro diagnostics at the point of need**. *Lab Chip* 2021, **21**:962-975.

44. •• Paul B, Demuru S, Lafaye C, Saubade M, Briand D: **Printed iontophoretic-integrated wearable microfluidic sweat-sensing patch for on-demand point-of-care sweat analysis**. *Adv Mater Technol* 2021, **6**:2000910.

A wearable microfluidic sensor system is shown. This system allows the on-demand analysis of body sweat in terms of common physiologically relevant ions such as sodium or potassium. Wireless transmission of the sensor signal to a smartphone allows the readout with a wide spread device.

45. Padash M, Carrara S: **A 3D printed wearable device for sweat analysis**. In *Proceedings of the MeMeA 2020 Conference*. IEEE; 2020:1–5.

46. Zhang S, Zahed MA, Sharifuzzaman M, Yoon S, Hui X, Chandra Barman S, Sharma S, Yoon HS, Park C, Park JY: **A wearable battery-free wireless and skin-interfaced microfluidics integrated electrochemical sensing patch for on-site biomarkers monitoring in human perspiration**. *Biosens Bioelectron* 2021, **175**:112844.

47. Vinoth R, Nakagawa T, Mathiyarasu J, Mohan AMV: **Fully printed wearable microfluidic devices for high-throughput sweat sampling and multiplexed electrochemical analysis**. *ACS Sens* 2021, **6**:1174-1186.

48. Bolat G, La Paz E, de, Azeredo NF, Kartolo M, Kim J, de Loyola e Silva AN, Rueda R, Brown C, Angnes L, Wang J, Sempionatto JR: **Wearable soft electrochemical microfluidic device integrated with iontophoresis for sweat biosensing**. *Anal Bioanal Chem* 2022, **414**:1-11.

49. Chu T, Wang H, Qiu Y, Luo H, He B, Wu B, Gao B: **3D printed smart silk wearable sensors**. *Analyst* 2021, **146**:1552-1558.

50. • Kanitthamniyom P, Zhou A, Feng S, Liu A, Vasoo S, Zhang Y, 3D-printed A: **modular magnetic digital microfluidic architecture for on-demand bioanalysis**. *Micro Nanoeng* 2020, **6**:48.

Use of digital magnetic microfluidics to build a modular microfluidic sensor system. The device is designed to be fast adjustable. This is enabled by the interchangeability of the different modules, such as the sensing or dispensing modules. This adjustability allows the sensor system to be used in a wide variety of sensing applications.

51. Qiu W, Nagl S: **Automated miniaturized digital microfluidic antimicrobial susceptibility test using a chip-integrated optical oxygen sensor**. *ACS Sens* 2021, **6**:1147-1156.

52. Jin K, Hu C, Hu S, Hu C, Li J, Ma H: **"One-to-three" droplet generation in digital microfluidics for parallel chemiluminescence immunoassays**. *Lab Chip* 2021, **21**:2892-2900.

53. Gard AL, Luu RJ, Miller CR, Maloney R, Cain BP, Marr EE, Burns DM, Gaibler R, Mulhern TJ, Wong CA, *et al*.: **High-throughput human primary cell-based airway model for evaluating influenza, coronavirus, or other respiratory viruses in vitro**. *Sci Rep* 2021, **11**:14961.