Review scientific paper
https://doi.org/10.33180/InfMIDEM2021.101

Informacije MIDEM
Journal of Microelectronics,
Electronic Components and Materials
Vol. 51, No. 1(2021), 3 – 23

Microfluidics: a review

Borut Pečar, Drago Resnik, Matej Možek, Danilo Vrtačnik

University of Ljubljana, Faculty of Electrical Engineering, Laboratory of Microsensor Structures and Electronics, Ljubljana, Slovenia

Abstract: Microfluidics technologies have become a powerful tool in life science research laboratories over the past three decades. This review discusses three important segments of the field from origins and current status to future prospective: a) materials and microfabrication technologies from the field, b) research and development of essential microfluidic components and c) integration of components into complex microfluidic systems that will, according to some forecasts, play a key role in improving the quality of life for future generations. The most sophisticated microfluidic systems developed by now are Point-of-Care systems, that are based on Lab-on-Chip technologies. As these subfields are very extensive and go beyond the scope of this review, some carefully chosen additional review papers are provided.

Keywords: microfluidics; materials; technologies; micropumps; flowmeters; microneedles; fuel steam reformers; microdosing systems; LOC; POC

Mikrofluidika: pregled področja

Izvleček: Mikrofluidne tehnologije so v zadnjih treh desetletjih postale nepogrešljivo orodje sodobne znanosti. Pregledni članek pokriva tri pomembne segmente področja: a) materiale in tehnologije za izdelavo mikrofluidnih naprav, b) raziskave in razvoj osnovnih mikrofluidnih komponent in c) integracijo komponent v kompleksne mikrofluidne sisteme, ki bodo po napovedi mnogih imeli ključno vlogo pri zagotavljanju višje kakovosti življenja prihodnjih generacij. Med najnaprednejše mikrofluidne sisteme uvrščamo sisteme za hitro analizo na samem mestu odvzema vzorca, ki temeljijo na tehnologijah »laboratorija na čipu«. Ker področja teh sistemov presegajo obseg tega dela, smo podali nekaj dodatnih skrbno izbranih preglednih člankov s področij.

Ključne besede: Mikrofluidika; materiali; tehnologije; mikročrpalke; merilniki pretoka; mikroigle; mikroprocesorji goriva; mikrodozirni sistemi; LOC; POC

* *Corresponding Author's e-mail: borut.pecar@fe.uni-lj.si*

1 Introduction

Since Richard Feynman's thought-provoking 1959 speech "There's Plenty of Room at the Bottom", humanity has witnessed the most rapid technology development in its history—the miniaturization of devices [1]. Microelectronics was one of the most significant enabling technology of the last century. Until recently, the development of miniaturized transducer and fluidic devices lagged behind this miniaturization trend in microelectronics. In the late 1970s, silicon technology was extended to 3-D machining of mechanical microdevices, which later came to be known as microelectromechanical systems (MEMS) [2]. The development of microvalves, micropumps and microflow sensors in the late 1980s dominated the early stage of microfluidics. Since then, microfluidics is rapidly emerging as a breakthrough technology that finds applications in diverse fields ranging from biology, chemistry, pharmacy, biomedicine to information technology and optics [3].

Microfluidics can be defined as the science and technology of manipulating small amount of fluids in channels with dimensions of tens to hundreds of micrometers [4]. Due to their small scale, microfluidic devices have advantages over conventional devices. Among the advantageous properties are, large surface area to volume ratio, which lowers the diffusional distances dramatically and very low reagent consumption [4]. Consequently, they can enhance the reaction efficiency, reduce the analysis time, simplify procedures and provide highly portable systems [5]. Furthermore, they can be easy to use, cheap to fabricate and disposable [6].

The purpose of this review is to give a broad overview of the field, summarizing recent advances in materials and microfabrication technologies in relation to the field, addressing the essential microfluidic components and outlining the integration of components into wide variety of miniature-sophisticated systems capable of performing even the most demanding tasks. The remainder of the review paper is organized as follows:

Section 2 covers relevant materials and technologies for microfluidic applications. Correspondingly, silicon, glass and polymer materials will be addressed. Focus will be on precedent research activities in the field of reactive and deep reactive ion etching of silicon, dry and wet etching of glass and polymers micromachining. Since most microfluidic devices require bonding of substrates with additional functional layers to create enclosed volumes, various bonding processes such as silicon-silicon, silicon-glass and thermoplastic–polydimethylsiloxane bonding will be reviewed.

Section 3 is devoted to microfluidic components. First, an overview of micropumps, microvalves and microactuators will be given. Regarding micropump integration into modern polydimethylsiloxane (PDMS) microfluidic systems that require miniaturization and autonomy, focus in this subsection will be on PDMS elastomeric micropumps, especially on microthrottle pumps and peristaltic micropumps. Moreover, additional micropump functionalities such as bidirectional pumping and low pulsating flow will be discussed. Second, flowmeters for microfluidic applications will be outlined. Various flowmeter measurement principles and reported functional devices will be summarized. Focus will be on thermal mass microflowmeters, which have been fabricated on a wide variety of substrates. Here, past efforts which led to improvements of flowmeters sensitivity and response time, will be reviewed. Third, heaters, coolers and temperature sensors for microfluidic platforms will be addressed. Temperature is a critical parameter in managing many physical, chemical and biological microfluidic applications therefore many interesting approaches to this issue have been proposed. Fourth, overview of microneedles will be made. The microneedles are essential in microfluidic systems for transdermal drug delivery applications. They have been made from various materials using different fabrication processes and were applied using many approaches to enhance the drug delivery through the skin.

Section 4 deals with microfluidic systems, where microfluidic components discussed in Section 3 are integrated and functionally interconnected into advanced microfluidic platforms. Such systems can execute even the most demanding tasks required by the modern science. Here, several most representative microfluidics systems will be addressed, starting with micro fuel reformers, more specific with methanol steam reformers, which convert methanol solution into a hydrogen rich gas needed for fuel cells to generate electricity. Many different approaches related to this field and which have been reported in the last sixteen years and greatly improved conversing efficiency, will be reviewed. Temperature control and fuel supply for micro fuel reformers will be also addressed from the microfluidic aspect. Next, microdosing systems for drug delivery, which typically comprises several integrated microfluidic components such as micropumps, microfluidic channels, reservoirs and microneedle arrays, will be suggested. In this subsection, innovative bubble-type, shape memory alloy and other non-mechanical microdosing systems will also be tackled. At the end of the Section 4, Lab-on-Chip (LOC) and Point-of-Care (POC) systems, which are the most sophisticated microfluidic systems developed by now, will be described. As these subfields are very extensive and go beyond the scope of this review, we will provide some additional carefully chosen review papers in conjunction with foodborne pathogens detection, drug development, stem cell analysis, cardiovascular disease prevention, infectious disease diagnostics etc. Few examples of successful transformations of LOC technologies into actual POC devices will follow. Our conclusions are drawn in the final Section 5.

2 Materials and technologies for microfluidic applications

Microfluidic devices originate from microelectronics fabrication sector [7]. Silicon has been most frequently used as the base substrate material for fabrication of microfluidic devices in the past. However, silicon substrate is relatively expensive and optically opaque at certain wavelengths, limiting its applications in optical detection. To combat these shortcomings, glass and polymer materials have been introduced into microfluidic devices [7]. Polymer materials in microfluidics include polymethylmethacrylate (PMMA), polystyrene (PS), polycarbonate (PC), polyethylene terephthalate (PET), polyethylene (PE) and PDMS. Amongst these polymer materials, PDMS has been one of the most widely used materials for fabricating microfluidic devices due to its flexibility in moulding and stamping, optical transparency and biocompatibility [8].

The literature on microfabrication techniques for microfluidic applications shows a variety of approaches. Silicon microfabrication is a process that involves the removal of silicon material using wet chemical or dry plasma etching processes such as reactive ion etch-

ing (RIE) or deep reactive ion etching (DRIE) in order to create 3-D silicon or non-silicon microstructures for microfluidic devices [9]. An excellent overview of techniques involved in advanced microfabrication of silicon was written by Resnik et al. [10]. RIE has limitations in producing deep vertical silicon structures and is more often used for etching thin inorganic and organic layers. To overcome these limitations, Vrtačnik et al. [11] studied and optimized RIE of deep silicon microchannels for microfluidic applications. Optimal set of etching parameters resulted in high silicon etching rate (2 µm/min), good anisotropy close to 90°, lateral undercut less than 6% and surface roughness of less than 1 µm.

DRIE process was first introduced by Bosch in the mid-nineties and commercialized by several equipment manufactures. DRIE is capable of forming vertically smooth sidewalls at high etch rate (>10 µm min^{-1}) [12]. An improved DRIE process for ultra high aspect ratio silicon trenches with reduced undercut was reported by Owen et al. [13]. By ramping process pressure, etch power and switching time, authors were able to produce 5.7 µm trenches with an aspect ratio of 70. Giang et al. [14] reported microfabrication of shallow concave pits or deep spherical cavities in PDMS using DRIE silicon molds. Effect of DRIE process parameters on the surface morphology and mechanical performance of silicon structures were studied by Chen et al. [15]. Authors designed and performed a set of experiments to fully characterize surface morphology and mechanical behavior of silicon samples produced with different DRIE operating conditions. Similarly, Vrtačnik et al. [16] performed optimization of Bosch process for DRIE silicon microstructures. After optimization, directional Si etching resulted in etch rate of 3.0 µm min^{-1}, profile angle close to 90°, roughness of sidewalls less than 150 nm and aspect ratio higher than 10 (see test pillar structures in Fig. 1).

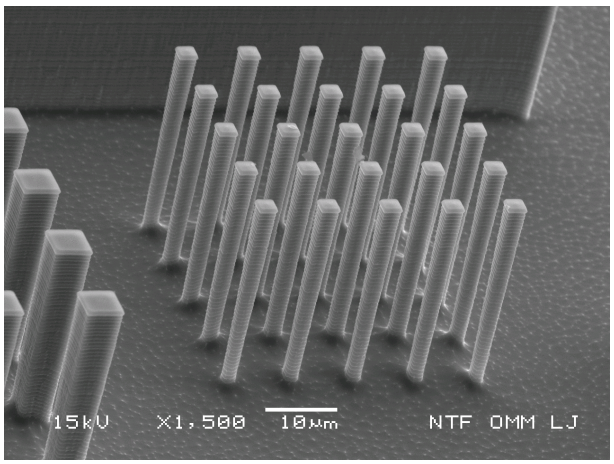

Figure 1: SEM image of test Si pillar structures fabricated by optimized DRIE etching. Source: Vrtačnik et al. [16].

For glass microfabrication, three major groups of techniques are used: mechanical treatment, dry and wet etching. Mechanical treatments include traditional drilling, ultrasonic drilling, electrochemical discharge and powder blasting. The dry etching technique of Pyrex glass using SF_6 was reported by Li et al. [17]. Authors fabricated small through holes in Pyrex glass wafers intended for electrical feed-throughs. The disadvantage of glass etching by DRIE was relatively low etching rate, which extended etching time to 10 hours. Wet etching of glass is the most common method and was reported by Stjernström and Roeraade [18]. In this work, capillary electrophoretic chips were fabricated in glass using photoresist as the mask layer. Excellent review on wet etching of glass for microfluidics was given by Iliescu [19].

For polymers micromachining, soft lithography [20], hot embossing [21], injection molding [22], casting [23], laser micromachining [24] and milling [25] are the most commonly applied.

Most microfluidic devices require bonding of substrates to create enclosed volumes for fluid handling. Therefore, various bonding processes have been developed in the last thirty years to mutually bond silicon, glass and polymer layers. Direct silicon wafer-to-wafer bonding without the use of intermediate adhesive layer was employed by Thompson et al. [26]. To heat silicon wafers above 1000 °C before they were brought into contact, electromagnetic induction was applied. Typical power consumption was in the range of 900 to 1300 W for silicon wafers with the diameter values between 75 and 100 mm. Low temperature direct bonding of silicon and silicon dioxide by surface activation method was investigated by Takagi et al. [27]. Neutralized high-energy Ar beam etching (FAB 110, Atom Tech, UK) was used to create a clean surface which had strong bonding ability. The specimens were brought in contact and bonded in vacuum. Modified process for low temperature direct silicon bonding was reported by Quenzer and Benecke [28]. After a hydrophilic pretreatment, a diluted solution of sodium silicate in water was spun onto one of the two surfaces and the two wafers were brought into contact. Resnik et al. [29,30] studied direct bonding of (111) and (100) oriented silicon wafers performed in the range of temperatures from 80 to 400 °C in nitrogen, oxygen and low vacuum atmosphere. Authors found that bond strengthening in nitrogen ambient exhibited about 25% higher tensile strength compared to bonding performed in vacuum or oxygen.

The combination of glass and silicon is a common choice for fabrication of microfluidic systems. Glass can be bonded to silicon with fusion bonding process or anodic bonding process. Fusion bonding process

as applied by Xiao et al. [31] comprises thorough silicon wafers cleaning during which Si–O–Si bonds of the native oxide on the silicon surface.The Si–O–Si bonds on the glass surface are cleaved by the attack of OH^- and H^+ ions. The new Si–OH groups on wafer surfaces are formed after the silicon and glass wafers are put together face to face in a clean room at room temperature. Resnik et al. [32,33] focused on issues accompanied with defect free anodic bonding of multilayer glass-Si-glass microfluidic structures. Pyrex 7740 and Borofloat 33 glass wafers were bonded to bare Si and Si/SiO2 terminated structures in the temperature range 350-400 °C in the air ambient under applied anodic voltages between 800-1200 V. Authors concluded that appropriate configuration of bonding electrodes was mandatory to avoid debonding effects in multilayer bonding process.

Thermoplastic–polydimethylsiloxane assemblies in the field of microfluidics gained popularity in the last ten years [34]. Many strategies for plastic–PDMS bonding have been previously reported, such as sol–gel coating approach, chemical gluing approach and organofunctional silanes approach [35, 36]. First approach requires a multiple coating procedures as well as a complex technology. Second approach creates chemically robust amine–epoxy bonds at the interface at room temperature, however, two silane-coupling reagents are required and both surfaces had to be oxidized prior to chemical modification. Third approach requires only one coupling agent. In this approach, the most widely used organofunctional silane is 3-amino propyltriethoxysilane (APTES), aminosilane frequently employed in covalent bonding of organic films to metal oxides [37]. Pečar et al. [38] studied, optimized and applied two room-temperature bonding processes for thermoplastic - PDMS polymer covalent bonding based on organofunctional silanes APTES and amine-PDMS linker (Fig. 2).

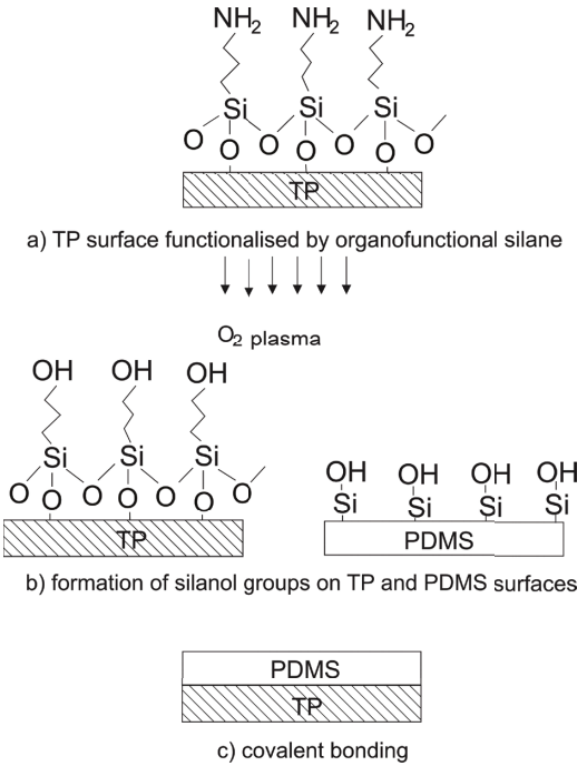

Figure 2: Process flow for thermoplastic (TP)-PDMS covalent bonding via organofunctional silanes e.g. APTES or amine-PDMS linker. Formation of Si–OH groups on both surfaces is provoked by oxygen plasma. Covalent bond is established when both surfaces are brought in contact. Source: Pečar et al. [38].

Both bonding processes were applied on piezoelectric micropumps where glass substrate was replaced by thermoplastic substrate. Water initiated the hydrolysis of covalent bonds established via the modified APTES bonding process while micropumps employing amine-PDMS linker exhibited no deterioration in their performance after eight weeks of continuous operation.

3 Microfluidic components

3.1 Micropumps

The most often encountered components in microfluidic systems are micropumps [39]. They are incorporated into the system separately as discrete components or integrated into the microfluidic platform. Division of micropumps based on Krutzch classification [40] is shown in Fig.3.

Micropumps employing displacement principle exert pressure forces on the working fluid through one or more moving boundaries, while the onesemploying dynamic principle add energy to the working fluid in a manner that increases either its momentum or its pressure. First, reciprocating micropumps require valves for its operation. Passive valves operate based on the pressure gradient, while active valves require outside actuation. In 1988, van Linte et al. [41] introduced diaphragm passive check valve. Seven years latter, Carrozza et al. reported ball valve [42]. Each ball valve consisted of a cylindrical chamber connected to a hemispherical chamber, which contained a mobile ball. First cantilever flap was reported by Koch et al. in 1998 [43]. For this flap, deep boron diffusion together with KOH etching was employed. Recently, Pečar et al. [44] proposed venous-valves micropump with valves that mimic the operation of biological venous valves. Next, reciprocating micropumps require an actuator to perform pumping function. For this purpose, piezo-

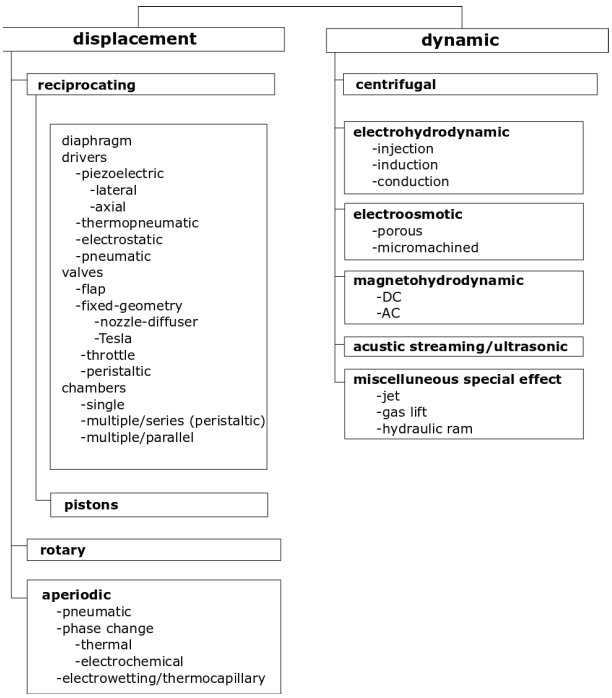

Figure 3: Division of micropumps based on Krutzch classification [40] where throttle and peristaltic pumps were additionally assigned to "valves" category.

electric, electrostatic, electromagnetic, shape memory alloy and pneumatic or thermopneumatic actuators have been applied. Piezoelectric actuation with lead zirconate titanate (PZT) has been widely utilized for micropump actuation due to small size, low power consumption, absence of electromagnetic interference and relatively low fabrication costs [45]. An effective method for reducing the excitation signal amplitudes in piezoelectric micropumps might be the use of highly efficient piezoelectric materials. The microcylinder pumps employing piezoelectric actuators based on relaxor-ferroelectric $0.57Pb(Sc_{1/2}Nb_{1/2})O_3–0.43PbTiO_3$ (PSN–43PT) was reported by Pečar et al. [46]. The performance results indicate that PSN–43PT is a promising material for high performance portable, wearable, or implantable micropump applications, where operation amplitude has to be kept low for reasons of safety and smaller plus more economic driver circuits.

A special subgroup of displacement micropumps are pumps without check valves (fixed geometry, throttle, peristaltic). Rectifying effect is accomplished (a) by geometrically asymmetric channels or structures such as diffusers [47], Tesla valves [48] or oscillating sharp-edge structures [49] shown in Fig. 4, (b) by principle of peristaltics or (c) by use of throttle rectifying elements.

Over the last decade, PDMS has become virtually the default material for forming microfluidic devices due to its simplicity of casting and bonding to the glass

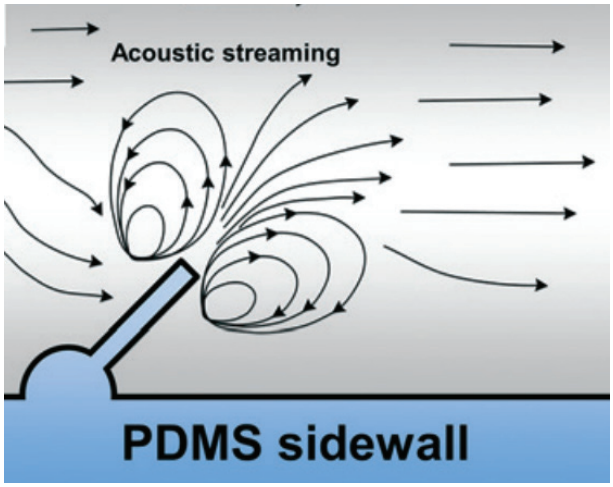

Figure 4: Acoustic streaming phenomenon around the tip of a tilted oscillating sharp-edge structure in acoustofluidic pumping device actuated by piezoelectric transducer. Source: Huang et al. [49].

substrate [50]. Regarding micropump integration into modern PDMS microfluidic systems that are required to be miniature and autonomous, micropumps fabricated on PDMS elastomer are considered as the most appropriate. Incorporation of PDMS micropumps into microfluidic systems can be found widely in the recent literature. Wang et al. [51] proposed a check valve micropump for implantable drug delivery application. A magnetic nanoparticle-PDMS composite membrane is actuated in a magnetic field to release a drug. For the same application, Gadad et al. [52] reported a dual-chamber valveless PDMS micropump. It produced 1.7 ml min^{-1} of water flowrate at excitation frequency of 14.8 Hz. Kawun et all. [53] reported a thin PDMS nozzle/diffuser micropump for biomedical applications. The pump comprised a cast PDMS body, a spin coated PDMS membrane and commercial silicone tubing, all bonded together with PDMS. The pump produced a peak flowrate of 135 µl min^{-1} and a maximum backpressure of 2.5 mbar at excitation frequency of 12 Hz and duty cycle of 25%. Chien et al. [54] proposed a ball valve PDMS/PC micropump on LOC microfluidic devices. It comprised a pair of ball valves implemented by confining a micro-ball within nozzle. Micropump exhibited maximum flowrate of 389 ml min^{-1} and a maximum backpressure of 41.5 mbar.

Regarding advanced microfluidic systems that require additional pumping capabilities and functionalities, several solutions were recently proposed. In 2018, Ye et al. [55] reported a PDMS check valve improvement for piezoelectric PDMS pumps. Authors achieved a considerable increase in the micropump flowrate performance by adding a blocking edge over conventional polydimethylsiloxane (PDMS) check valve. Generally, micropumps drive the fluid in only one direction. How-

ever, bidirectional capability is an important feature in the development of chemical analysis especially in the fluid handling application such as mixing, circulation and metering [56]. For instance, in a chemical analysis, to mix two chemical compounds, a single directional flow micropump needs an additional active rotational mechanism to create turbulent flow in mixing process. With the bidirectional flow functionality, the microfluidic system can be made in more efficient and compact structure, which merits from reducing the chemical analysis time and complexity. Recently, a research group from Malysia [57] reported a PDMS bidirectional flow dual-chamber micropump for LOC applications. Authors implemented a dispersing depth between the microchannel chamber and inlet/outlet channel in order to achieve a bidirectional flow.

For microfluidic systems where steady, low pulsating flow is required, a PDMS micropump system with additional PDMS fluidic capacitor was proposed [58]. Two single pneumatic micropumps connected in parallel exhibited maximum flowrate of 496 µl min^{-1}. It was shown, that the PDMS structure with its elastic mechanical properties smoothened pulsating flow with a smoothing factor of 0.6. In addition, Gidde and Pawar [59] addressed PDMS material properties and their influence on PDMS micropumps performance.

One sub-group of micropumps that does not employ check-valves are peristaltic micropumps. Conventional piezoelectric peristaltic micropumps comprise a series of sequentially actuated segments that deform fluidic channel on the principle of peristalsis to induce a net flow. The first piezoelectric peristaltic micropump with three piezoelectric actuators was reported by Smits in 1990 [60]. In 2003, Berg et al. [61] reported first peristaltic micropump with two piezoelectric actuators. Here, an established mechanical traveling wave was induced by a proper signal phasing of two actuation sequences. Such provoked flow-rates were comparable to three-stage peristaltic micropumps. A two-stage micropump was patented in 2010 (U.S. 20100059127 A1). A first piezoelectric peristaltic micropump with a single piezoelectric actuator was reported by Pečar et al. [62]. The fabricated prototypes featured high water / air flowrate performance (up to 0.24 ml min^{-1}/up to 0.84 ml min^{-1}) and backpressure performance (up to 360 mbar/up to 80 mbar). Furthermore, bubble tolerance and self-priming capability have been proved, together with valve regime of operation that enables sealing of the fluidic path when appropriate dc voltage was applied.

Another sub-group of micropumps that does not employ check-valves are throttle micropumps [63]. Their main advantage is high tolerance to clogging caused by mechanical particles or aggregates in the pumping medium, omitting the need for filters, which introduce significant pressure drop and increase system complexity. Furthermore, incomplete closing of rectifying elements (throttling) prevents damage to sensitive biological samples. Compared to peristaltic micropumps, microthrottle pumps exhibit superior backpressure and flowrate performance. A novel design of a strip-type microthrottle pump with a rectangular actuator geometry was proposed by Pečar et al. [64], with more efficient chip surface consumption compared to existing micropumps with circular actuators. Measured characteristics proved expected micropump operation, achieving maximal flow-rate 0.43 mL min^{-1} and maximal backpressure 12.4 kPa at 300 V excitation. In 2014, Pečar et al. [65] introduced a novel concept of microthrottle pump, named "microcylinder pump". Improved version of microcylinder pump was embedded in professional housing (see Fig. 5). Novel concept offers numerous advantages over conventional microthrottle design including self-priming ability, high level of bubble tolerance, inhibition of the cavitation occurrence and valve regime of operation.

3.2 Flowmeters

Flowmeters are prerequisite for proper operation of a wide range of microfluidics devices. Four measurement principles are frequently employed in these devices, namely thermal dilution in a flow stream, transit time measurement of a tracer injected into the flow, pressure difference measurement across a restriction and force measurement on an element placed in the stream [66].

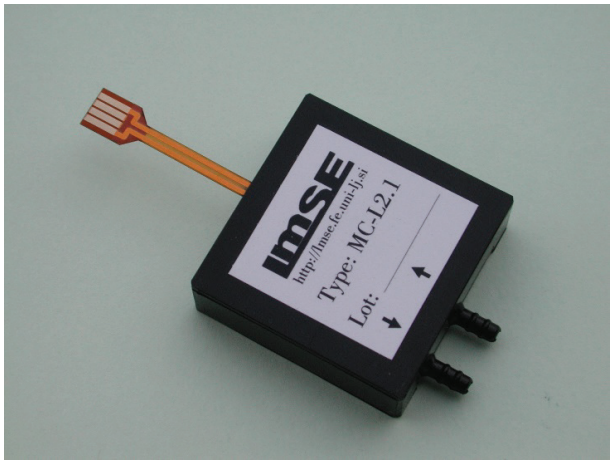

Figure 5: Piezoelectric microcylinder pump in a professional housing.

Wang et al. [67] demonstrated an electrolytic-bubble-based approach. Authors measured pressure difference (and thus flow rate) in real time by simultaneously generating two gas bubbles electrochemically along a

channel. Nezhard et al. [68] fabricated PDMS microcantilever flow sensor suitable for integration in LOC. The author's attention was focused on a high aspect ratio microcantilever, which was fabricated using a multilayer PDMS fabrication process. The device was capable of measuring flowrates as low as 35 $\mu L\ min^{-1}$. Amnache et al. [69] reported microflowmeter for moderate flowrates of gases based on a differential pressure measurement. It consisted of a microfabricated silicon–glass rectangular micro-orifice plate and two pressure sensors. Richter et al. [70] studied microflowmeter based on the micromachined electrohydrodynamic injection pump. Method is based on the measurement of the ion transit time between two grids. Another unique approach was demonstrated by Accoto et al. [71]. Their PDMS microflowmeter for closed-loop management of biological samples detected the streaming potential associated with the liquid flow by means of interface between polymeric surfaces and polar liquids and yielded a linear response. Nie et al. [72] reported microflowmeter which operated in the range of 30–250 nl min^{-1} for water. The principle was based on determining the evaporation rate of the liquid via reading the number of wetted pore array structures in a microfluidic system, through which continuous evaporation took place.

Thermal detection principles are widely used for air and gas flow sensors. An excellent state-of-the-art review in the field of thermal mass flowmeters was given by van Oudheusden [73] with the references therein. Typically, thermal mass flowmeter comprises a heating element which creates a local temperature increase and sensing elements that aim to measure the distortion in the temperature profile along the channel as induced by the fluid flow [74]. Several Si-based thermal flow sensors are currently available for measuring gas and liquid flowrates [75-77]. To enhance the device sensitivity and to improve corresponding response time, heat dissipation to the substrate should be minimized [78]. Due to the high thermal conductivity of the silicon substrate, various schemes have been implemented in order to achieve the thermal isolation of the sensing elements, such as freestanding structures, vacuum cavities and formation of porous silicon, or thin silicon nitride membranes [78]. Baek et al. [79] reported a vacuum-isolated thermal microflowmeter for *in vivo* drug delivery. Flowmeter used an arsenic-doped polysilicon heater/sensor, supported on dielectric membrane over the flow channel. Heater/sensor was capped by a vacuum-sealed microchamber to minimize heating of the surrounding structure and maximize heating efficiency.

To provide highly effective thermal isolation of the heating/sensing elements without the need for above-mentioned thermal insulation approaches and additional MEMS fabrication processes, attempts have been made to substitute silicon substrate with organic materials such as epoxy-based negative photoresist SU8 [79], polyimide [80, 81], Kapton® [82] and parylene [83]. Pečar et al. [84] proposed thermal microflowmeter for microfluidic applications where a PDMS elastomer was employed as heat insulative substrate between heater/sensor elements (Fig. 6). Device is suitable for integration on common microfluidic platform with additional PDMS fluidic components.

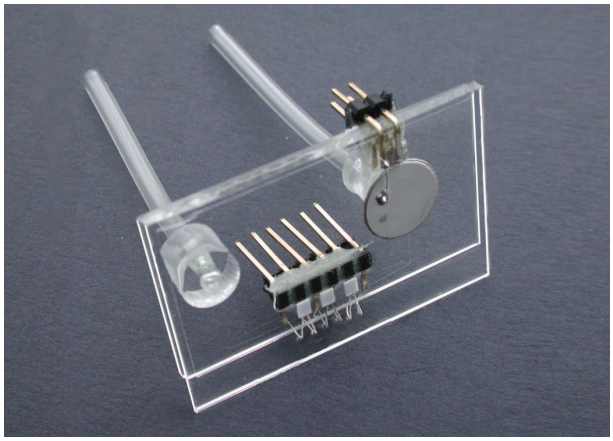

Figure 6: Thermal microflowmeter for microfluidic applications and piezoelectric micropump on common substrate by Pečar et al. [84]. PDMS elastomer is employed as heat insulative substrate between heater/sensor elements.

3.3 Heaters, coolers and temperature sensors for microfluidic platforms

Modern microfluidic systems require integration of multiple functions within a compact platform. One of such functionalities is the control of temperature, either in terms of profile or accessible range [85]. The temperature is a critical parameter in managing many physical, chemical and biological microfluidic applications such as Polymerase Chain Reaction (PCR), Electrophoresis (TGF), digital microfluidics, mixing and protein crystallization. The most commonly employed heating or cooling technologies exploit Peltier element, microwaves, pre-heated liquids, integrated wires or lasers, chemical reactions and Joule heating.

Matsu et al. [86] reported application of temperature gradient concentrator in a PDMS/glass hybrid microfluidic chip. By the combination of a temperature gradient along a microchannel using two Peltie elements, an applied electric field, and a buffer with a temperature-dependent ionic strength, Oregon Green 488 carboxylic acid was concentrated approximately 30 times as high as the initial concentration. Kempitiya et al. [87] explored the potential of microwave heating for appli-

cations requiring parallel deoxyribonucleic acid (DNA) amplification platforms. For this purpose, authors delivered microwave power at 6 GHz to the chamber via copper transmission line in a microstrip configuration. Temperatures up to 72 °C were achieved with less than 400 mW power consumption. An approach by using preheated and precooled liquids to generate a linear temperature gradient across a series of samples was employed by Mao et al. [88]. The three channel device (see Fig. 7) comprises a sandwich of glass and PDMS layers. Hot and cold fluids were introduced through the brass tubing using standard water bath circulators. The advantages of optical heating with laser are absence of the electric connections and the heating locations are more controllable comparing to the resistive electrodes. Optical approach was employed by Zhang et al. [89]. They used continuous wave laser induced heat to substitute microvalves and micropumps in microfluidic platform. Authors demonstrated effective blocking of microfluidic channels and bi directional pumping of fluid at a flow rate of 7.2–28.8 µl h^{-1}.

The interesting approach to heating and cooling in microfluidics, especially in PCR, was proposed by Guijt et al. [90]. In that work, chemical and physical processes were employed to locally regulate temperature. Cooling and heating of the microchannel was achieved by evaporation of acetone (endothermic process) and by dissolution of concentrated sulfuric acid in water (exothermic process), respectively.

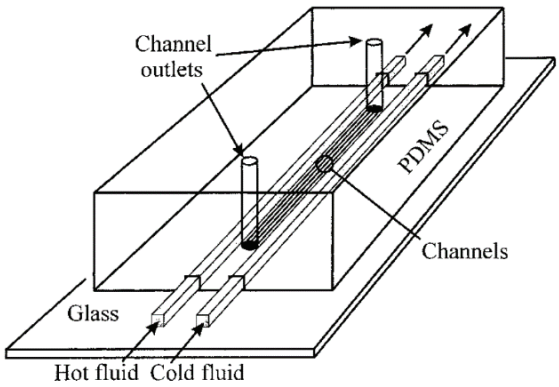

Figure 7: Three-channel device using preheated and precooled liquids by Mao et al. [88]. Reprinted with permission from [88]. Copyright (2019) American Chemical Society.

Regarding Joule heating, Mavraki et al. [91] reported low cost microfluidic device with integrated microheaters on a thin flexible polymeric substrate suitable to perform DNA amplification on a chip. The heating/sensing elements were formed on the Cu layer on the Pyralux substrate. Electrical measurements proved the functionality of the microheaters both as temperature sensors and thermal elements. Selva et al. [92] demonstrated Joule heating with electrical resistors that were fabricated by evaporating chromium (15 nm) and gold (150 nm) on the glass wafer. By applying improved optimization algorithms, the shape of resistors was optimized to generate high-temperature gradients with a linear temperature profile. Hserh et al. [93] proposed a new approach to increase the temperature uniformity inside a microthermal cycler, especially for PCR, by using new array-type microheaters with active compensation units. In this study, platinum was used as material for the microheaters and the temperature sensors. Resnik et al. [94] reported thin film Ti/Pt heaters and integrated temperature sensors on a Si microfluidic platform (Fig. 8). Heaters and sensors were fabricated by the combination of DC sputtering, lift-off process and thermal annealing of the deposited layers. Heater was able to provide vaporization of input liquid between 120 and 150 ◦C. Integrated Pt temperature sensors exhibited a typical TCR of 2200 ± 100 ppm/°C when annealed at 700 °C and proved stable during the prolonged operation.

3.4 Microneedle arrays

Microneedles are essential in microfluidic systems for drug delivery application. They are used for delivering drug through the transdermal route and for overcoming the limitations of conventional drug delivery approaches [95].

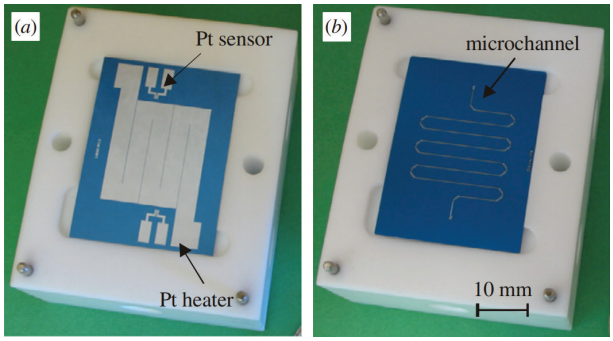

Figure 8: fabricated microfluidic platform with the meandered microchannel on the rear side (left) and a Ti/Pt heater and sensors on the front side (right) in PTFE housing.

Microneedles differ in design and composition. Currently, four distinct types of microneedles exist [96]: (a) solid microneedles often used to pretreat the skin prior to the administration of bioactives; (b) drug-coated solid microneedles for drug dissolution in the skin; (c) hollow microneedles for drug injections; and (d) dissolving microneedles prepared from a polymer in which the drug or vaccine is embedded in the polymer matrix for the controlled or rapid release in the skin. In the early

period microneedles used for drug delivery were made from silicon wafers through deep reactive ion etching and photolithography [97, 98]. Chen et al. [99] and Lin and Pisano [100] reported silicon microneedles with biodegradable tips and 6 mm-long silicon microneedles for localized chemical analysis, respectively. In the last fifteen years, various titanium [101], stainless steel [102], glass, ceramics [103] and polymeric [104-106] microneedles were introduced.

Since the diffusion of substances through the skin layers is a gradual process, microneedles systems use various approaches to enhance the drug delivery through the skin. Common methods practice electroporation, iontophoresis, sonophoresis [107], use of chemical enhancers [108], high velocity jet injection, ablation, tape stripping, vibratory, or impact assisted approaches [109]. Resnik et al. [110] reported investigation of skin penetration efficacy by a silicon microneedle array. When impact assisted penetration of microneedle array was applied instead of incremental increase of applied force, a significant impedance reduction of up to 50% on animal skin and 95% on human skin was obtained, which was a strong evidence of successful skin penetration.

Several publications have appeared in recent years documenting many successful microneedle arrays applications. In recent study, Deng et al. [111] for the first time evaluated the ability of solid silicon microneedle array for punching holes to deliver cholesterol-modified housekeeping gene (GAPDH) siRNA to the mouse ear. Such development of siRNA therapies has significant potential for the treatment of skin conditions (alopecia, allergic skin diseases, hyperpigmentation, psoriasis, skin cancer, pachyonychia congenital) caused by aberrant gene expression. In 2020, Kim et al. [112] delivered coronaviruses-S1 subunit vaccines by dissolving microneedle array. MERS-S1 subunit vaccines elicited strong and long-lasting antigen-specific antibody responses in mice, implyingthat it is a promising immunization strategy against coronavirus infection. For diabetic patients, insulin delivery using hollow microneedle array is very desirable. In experimental study of in vivo insulin delivery conducted by Resnik et al. [113], two types of fast-acting insulin were used to provide evidence of efficient delivery by hollow microneedle array to a human subject (Fig. 9). Results of *in vivo* insulin delivery proved successful infusion of fast-acting insulin as shown by blood analyses. Recently, a new cell transplantation method to inject donor cells into tissues to treat certain diseases using an array of ultrathin microneedles was reported by Iliescu et al. [114]. Here, an array of silicon microneedles was successfully employed to inject fluorescently labeled Mardin–Darby canine kidney cells into rat liver tissue.

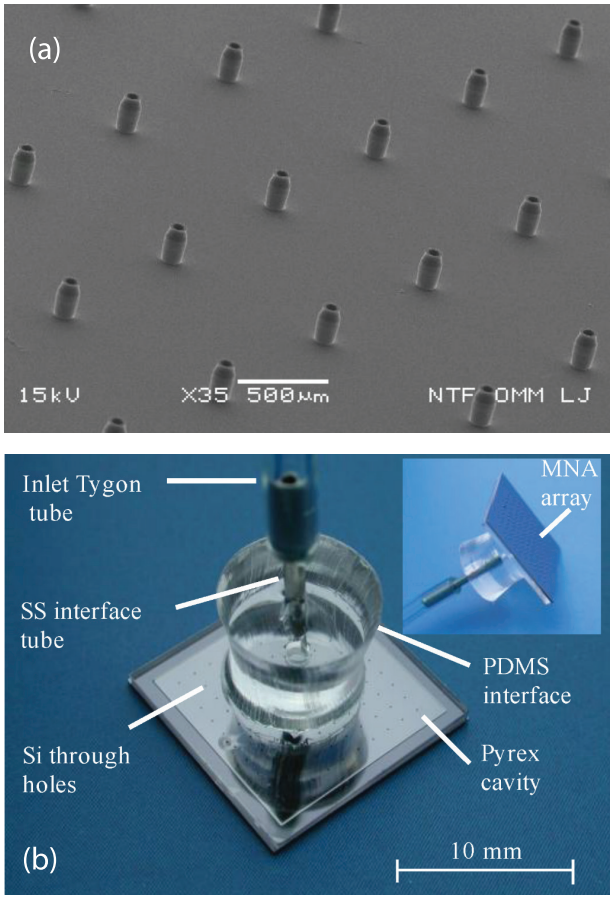

Figure 9: SEM image of hollow Si microneedles array fabricated by DRIE etching (a) and assembled microinjection device with 100 microneedles (b) view from the rear side, showing fluidic connection, distribution cavity and through holes. Source: Resnik et al. [113].

4 Microfluidic systems

4.1 Micro fuel reformers

With the rapid advancement in technology, everyday application of electronic devices such as laptops, cell phones, music players and other portable devices has become inevitable. Li-ion batteries are good options for providing the required energy for such devices. However, they require time-consuming recharging and are generally difficult to be recycled [115]. In contrast, liquid hydrocarbon fuels contains enormous energy per volume and weight compared to the best existing batteries, refueling is more convenient than recharging and recyclable fuel cartridges are more environmentally friendly. From the above reasons, various approaches were proposed to convert liquid hydrocarbon fuels to electrical power at micro-scale, such as using miniature gas turbine generators, fuel cells, thermo electric generators, a thermophotovoltaic generator and a thermi-

onic generator [116]. Among them, a miniature hydrogen fuel cell system combined with a microfluidic fuel reformer seems one of promising candidates to power mobile devices. Microfluidics technologies enabled fabrication of catalyst coated microchannels with large surface area to volume ratio, which greatly increased fuel conversion efficiency. Methanol is one of the best choices for the hydrogen production since it is a liquid at room temperature and can be easily stored in small cartridges premixed with water.

In 2004, Pacific Northwest National Laboratory developed a micro integrated methanol reformer, which was equipped with a microcombustor, an evaporator and a CO methanizer [117]. It was small enough for portable electronics but limited to 3.55 ml min^{-1} hydrogen production. Kamura et al. [118] reported a miniaturized methanol reformer with $Cu/ZnO/Al_2O_3$ catalyst-based microreactor shown in Fig. 10. The microreactor (25 × 17 × 1.3 mm^3) was constructed from glass and silicon substrates. The use of the high-performance catalyst allowed for higher hydrogen production rates than using a commercial Cu/ZnO catalyst. The microreactor was demonstrated to be capable maintaining a hydrogen production rate suitable for powering 1 W-class devices.

Hsueh et al. [119] presented a numerical investigation of the transport phenomena and performance of a plate methanol steam micro-reformer with serpentine flow field as a function of wall temperature, fuel ratio and Reynolds number. Jeong et al. [120] studied hydrogen production by steam reforming of methanol over Cu/Zn-based catalysts. Among the catalysts tested, $Cu/ZnO/ZrO_2/Al_2O_3$ exhibited the highest methanol conversion and the lowest CO concentration in the outlet gas.

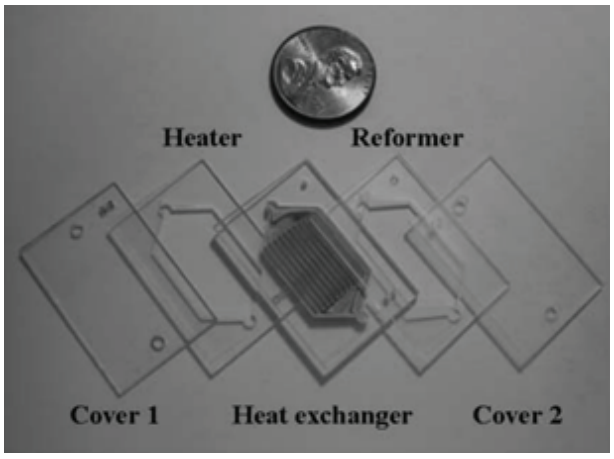

Figure 10: Individual glass wafers of MEMS methanol reformer heated by decomposition of hydrogen peroxide. Source: Kim et al. [121].

Kim et al. [121] proposed micro methanol reformer with a heat source. The micro system consists of the methanol steam-reforming reactor, the hydrogen peroxide catalytic decomposition reactor and a heat exchanger between the two reactors. Catalyst loaded supports were inserted in the cavity made on the glass wafer. The total hydrogen production rate was 23.5 ml min^{-1}. This amount of hydrogen can produce 1.5 W of power on a typical proton-exchange membrane fuel cells.

To improve the energy conversion of a micro-channel reactor, Mei et al. [122] proposed and fabricated an innovative microchannel catalyst support with a microporous surface. Results showed that the microchannel catalyst support with micro-porous and non-porous surfaces had a hydrogen production rate of 18.07 ml min-1 and 9.65 m min-1, respectively at 573 K under the inlet flowrate of 30 µl min-1. Huang et al. [123] studied the fractal channel pattern design and the gradient catalyst layer in relation to their effects on the performance of a methanol micro steam reformer. Compared to a uniform catalyst layer, the fractal design effectively increased the conversion ratio by 8.5% and decrease CO by 11% when the inlet liquid flow rate was fixed at 1.0 cc min-1. Recently, Sarafraz et al. [124] conducted series of experiments for the hydrogen production via steam reforming of methanol with Cu–SiO2 porous catalyst coated on the internal walls of a micro-reactor with parallel micropassages. Wang et al. [125] proposed a partial oxidation methanol micro reformer with finger-shaped channels for low operating temperature and high conversing efficiency. Micro reformer supplied hydrogen to fuel cells by generating 2.23 J min-1 for 80% H2 utilization and 60% fuel cell efficiency at 2 ml min-1 of supplied reactant gas.

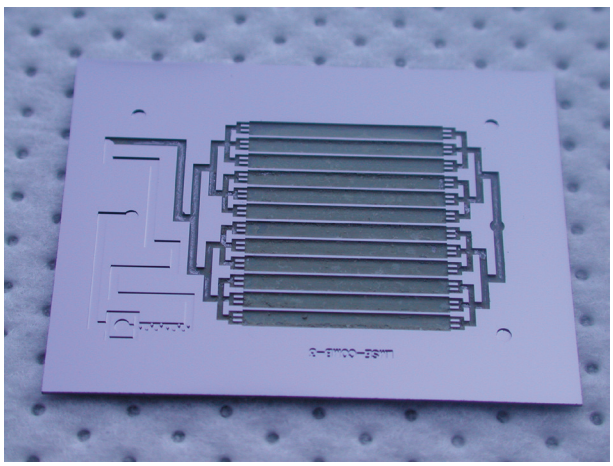

Figure 11: Si based micro catalytic methanol–oxygen combustor with thin film nanostructured Pt/CeO_2 catalyst in microchannels.

To maintain the required reactions taking place in micro reformer unit, a micro combustor is commonly

employed. The most convenient approach is to utilize the same energy source (methanol) for steam reforming process and for catalytic combustion. In this case the methanol–air or methanol–oxygen mixture should be provided for combusting process. Correspondingly, Resnik et al. [126] studied Si based micro catalytic methanol–oxygen combustor with thin film nanostructured Pt/CeO_2 catalyst (Fig. 11). The goal of the study was to reduce the catalyst load and to maximize the catalyst effectiveness through better mass transfer by implementing of the new high performance mesoporous Pt/CeO_2 catalyst with multiple layer deposition method and by the proposed micro combustor design.

For proper operation of methanol fuel microreactor, precise temperature control and uninterrupted fuel supply is mandatory. Temperature control of methanol fuel microreactor for hydrogen production was reported by Peruško et al. [127]. The temperature control was achieved by on-off control with an adjustable hysteresis. The heater actuation circuit comprised a boost converter, controlled by pulse width modulated signal from the microcontroller. The output of the boost converter was applied to the platinum (Pt) heater in the microreactor evaporation stage. To pump the fuel into microreformer, a fuel supply system is required. Pečar et al. [128] proposed a low cost, energy efficient flow-generator for hydrogen production in microreactors. The proposed approach is energy efficient and suitable for implementation into a compact hybrid device, small enough to fit on microreactor housing.

4.2 Micro dosing systems for drug delivery

A typical microdosing system comprises micropump, microsensor, microfluidic channel, reservoir and electronics. It is mainly aimed at serious chronic diseases, such as diabetes, melancholia, malignant lymphoma, etc., or abrupt life threats, such as heart attack, stroke, septicaemia etc. [129]. With the automatic dosing system, the patients are protected from sudden death or irregular/incorrect taking medicine. Microdosing systems are fabricated using bio-compatibile materials such as poly methyl methacrylate, poly-pimethylsiloxane, SU-8 photo resist, or parylene C [129].

Bubble-type and other non-mechanical microdosing systems need no physical actuation components but its effectiveness, due to long time delay and slow response, are much devalued [129]. Bohm et el. [130] proposed a closed-loop controlled micromachined dosing system for accurate manipulation of liquids in microsystems down to the nanoliter range via expanding electrochemically generated gas bubbles. Another solution was described by Reynaerts et al. [131]. An implantable drug-delivery system based on shape memory alloy micro-actuation was based on a precisely controlled discontinuous release from a pressurized reservoir by using a shape memory actuated microwave system. One dose can be controlled with accuracy up to 5 µl. However, shape memory alloys dosing systems suffer from a relatively low flowrate and insufficient bio-compatibility [129]. A microdosing device comprising a dosing chamber, dispensing opening and vibration unit was patented by Koerner et al. [132]. Vibration unit was connected to at least one boundary surface of the dosing chamber. Consequently, boundary surface oscillated for the purpose of a dispensing operation. A plastic micro drug delivery system was successfully demonstrated by Ianchulev et al. [133], utilizing the principle of osmosis without any electrical power consumption. The system had an osmotic microactuator and a polydimethylsiloxane (PDMS) microfluidic cover compartment consisting of a reservoir, a microfluidic channel and a delivery port. Induced osmotic pressure could extend up to 25 MPa to overcome possible blockages caused by cells or tissues during drug delivery operations. Than et al. [134] reported a strategy using an eye patch equipped with an array of detachable microneedles. Microneedles penetrated the ocular surface tissue, and served as implanted microreservoirs for controlled drug delivery. System comprised micro-seized membrane in sealed microfluidic reservoir, piezoelectric microcylinder pump and array of hollow Si microneedles. Biocompatible components were covalently bonded to each other to form a compact wearable system. Complete emptying of 590 µl sealed reservoir needed suction pressure of less than 50 millibars which minimized power consumption that is crucial for long device autonomy.

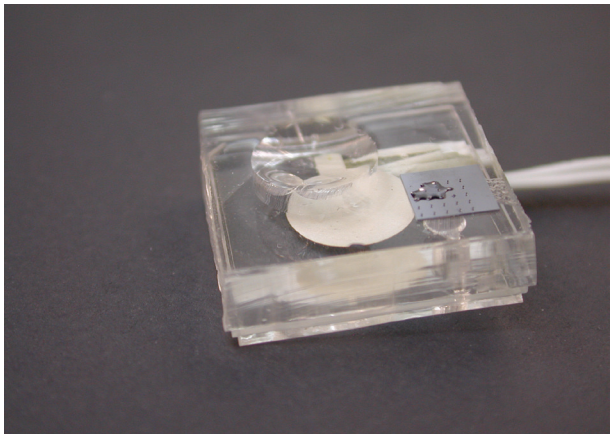

Figure 12: Wearable integrated microdosing system for transdermal drug delivery by Vrtačnik et al. [136,137].

Kabata et al. [135] fabricated insulin pump using the volume change of hydrogen bubbles and conducted experiments using rats. To monitor the blood glu-

cose level, a glucose sensor was employed. Recently, Vrtačnik et al. [136, 137] proposed and patented wearable integrated microdosing system with a microneedle array for transdermal drug delivery (Fig. 12).

4.3 Lab-on-Chip and Point-of-Care systems

One of the main objectives of microfluidic technologies is to provide a total solution, from sample input to display of the analyzed results [138]. Complete analytical protocols, from sample pretreatment through to sample and reagent manipulation, separation, reaction and detection can be performed automatically on well-designed and integrated miniaturized devices such as LOC systems. LOC devices are a subset of MEMS devices and often indicated by "Micro Total Analysis Systems" (μTAS) as well [139]. LOC devices comprise microchannels, integrated pumps, electrodes, valves, sensors and electronics to perform required tasks [140]. The term "Lab on Chip" was probably first used [141] by Moser et al. from Technical University Vienna [142] to describe the miniaturized thin film glutamate and glutamine biosensors developed by them. Research on LOC focuses on several applications including human diagnostics, DNA analysis and synthesis of chemicals [140]. The miniaturization of biochemical operations normally handled in a laboratory has numerous advantages, such as cost efficiency, parallelization, ergonomics, diagnostic speed and sensitivity.

LOC systems offer advantages for pathogen, toxin and virus detection. A review by Yoon et al. [143] summarized the requirements of LOCs for foodborne pathogens detection and gave an overview on immunoassay and PCR-based LOC biosensors. A review by Weigl et al. [144] highlights LOCs for drug development, advances in LOC technology for flow-injection analysis, electrokinesis, cell manipulation, proteomics, sample preconditioning, immunoassays, electrospray ionization mass spectrometry, and polymerase chain reaction. Overview on LOC technologies for stem cell analysis was presented by Ertl et al. [145]. Authors focused on the advantages of the microfluidic devices to overcome most of the challenges associated with stem cell identification, expansion and differentiation. Por et al. [146] focused on the latest developments in environmental LOC monitoring devices and provided future perspectives to overcome the challenges using printing technologies. Wu et al. [147] made a short review on LOC platforms for detection of cardiovascular disease and cancer biomarkers. Ai et al. [148] summarized recent progress in LOCs for pharmaceutical analysis and pharmacological/toxicological tests. Authors gave insight into the challenges and possible breakthrough of Pharm-LOCs development.

POC diagnostic systems are instruments that can rapidly provide in vitro diagnostic results by non-trained personnel at a patient site, in the physician's office, in the field, at home, in an ambulance, or in a hospital [149]. There has been a growing need to provide diagnostic results at the point of care, for prompt treatment of acute diseases such as acute myocardial infarction and for home-care diagnostics such as diabetes monitoring. In many ways, the features of microfluidics and LOC technologies are a natural fit for POC diagnostics devices [150]. Bringing the LOC technology to life through POC devices is a challenging task. So far, there have been only a few successes in the transformation of LOC technology to the actual POC devices with a real life application [151]. A review of POC diagnostic systems using microfluidic LOC technologies was recently given by Sia at al.[152]. This review covers advances in POC technologies, commercially available POC diagnostic systems and microfluidic LOC technologies. Park et al. [153] summarized advances in microfluidic PCR for POC infectious disease diagnostics. In this review, authors discussed practical issues and perspectives related to implementing microfluidic PCR technologies into infectious disease diagnostics. Further on, in recent years, paper-based microfluidics has emerged as a multiplexable POC platform [154]. Paper-based microfluidics is considered a low-cost, lightweight, and disposable technology [155]. A review on paper-based microfluidic POC diagnostic devices was given by Yetisen et al. [156], covering fabrication of paper-based microfluidic devices, functionalization of microfluidic components and quantitative readouts via handheld devices and camera phones.

Examples of successful transformations of the LOC technologies into an actual POC devices are encouraging. Ahn et al. [157] demonstrated a disposable plastic biochip incorporating smart passive microfluidics with embedded on-chip power sources and integrated biosensor array for applications in clinical diagnostics and POC testing. Neuzil et al. [158] demonstrated a high performance polymerase chain reaction system in portable LOC for POC. Sun et al. [159] designed, fabricated, and tested miniature 96 sample ELISA-LOC for immunological detection of Staphylococcal Enterotoxin B. Their simple POC system is useful for carrying out various immunological assays and other complex medical assays without a laboratory. Upaassana et al. [160] reported highly sensitive LOC immunoassay for protein biomarker that causes lung inflammation (see Fig. 13). Authors drastically reduced analysis time to about 30 min as opposed to hours in conventional methods. Recently, several authors demonstrated an integrated POC solution for noninvasive diagnosis and therapy monitoring of heart failure patients [161]. KardiaPOC™ is an easy to use portable device with a disposable LOC

for the rapid, accurate, non-invasive and simultaneous quantitative assessment of four heart failure related biomarkers from saliva samples.

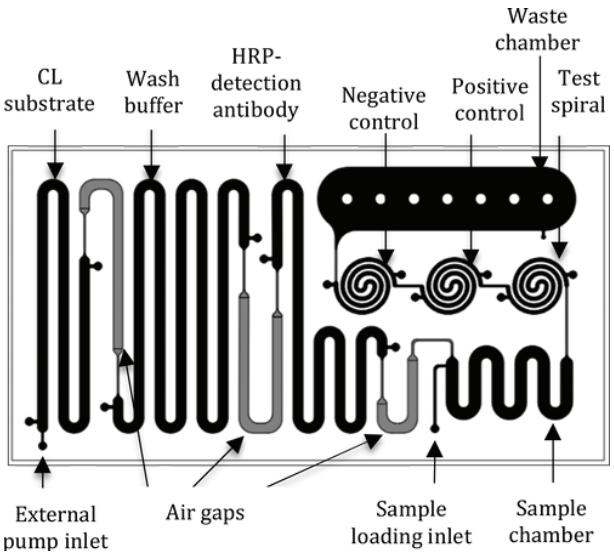

Figure 13: Schematic diagram of the highly sensitive LOC for POC immunoassay for protein biomarker that causes lung inflammation by Upaassana et al. [160]. On-chip reservoirs store assay reagents. Air gaps isolate reagents and prevent mixing while in storage and during the assay. Reprinted with permission from [160]. Copyright (2019) American Chemical Society.

5 Conclusions: Future perspective of the field

The field of microfluidics has grown into a mature technology capable of producing the most complex microfluidics systems that push the boundaries of today's scientific and technological advances. Many challenges still lie ahead, but the main challenge remains how to translate a wide variety of successful microfluidic concepts from laboratory prototypes to robust end-user products in order to be more accessible. Many fabrication processes currently employed in laboratory environment, including manually performed PDMS soft lithography techniques, are inappropriate for mass production of microfluidic devices due to speed and cost concerns. There is a need to overcome these limitations in the future. Advances in bioinspired smart materials are leading to next-generation fabrication technologies for microfluidic devices such as 4-D printing, which adds a time dimension to the conventional 3-D printing and offer the capability to control size, shape and structure post-manufacture [162]. With the continuous development of novel fabrication technologies including 4-D printing, it is expected that the future microfluidic devices, will be less expensive, more integrated, more customizable and will incorporate a higher level of quality control [163]. Given the current state of the field, we can expect that future advances, particularly in POC systems, will have a transformative impact on the global health care system, which will improve the quality of life especially for elder people and people in developing countries [164]. Some exciting futuristic aspects for the field of microfluidics was given by Tian et al. [165] as follows:

»Microfluidics will provide autonomous distributed monitors for public health and surveillance for biothreats. The aging population will use health kits to provide preventive medicine. Medical checkups will be performed daily. Healthcare costs will be reduced due to the availability of microfluidics instruments. Chronic disease patients will possess home diagnostics systems and high risk patients (e.g. post surgical) will enjoy the comfort of being at home knowing that LOC devices will be monitoring risks of infection, blood clots, etc. Microfluidic devices will increase the efficacy and safety of medical treatments by assisting in the prescription and administration of drugs. Artificial cells, synthetic hybrid biomolecules and synthetic biomaterials will require the development of sophisticated microfluidic platforms down to the true nanometer scale dimensions.«

6 Acknowledgments

The authors would like to thank the Slovenian Research Agency/ARRS and the Ministry of Education, Science, Culture and Sport for their support of this work (Grant No P2-0244).

7 Conflict of Interest

The authors declare no conflict of interest.

8 Permission statement

The authors declare they have permission from the rightsholders to re-use the material.

9 References

1. R. P. Feynman, "There's plenty of room at the bottom", Journal of Microelectromechanical Systems,

Vol. 1, Issue 1 , pp. 60-66, Mar 1992, https://doi.org/10.1109/84.128057.
2. K. E. Petersen, "Silicon as a mechanical material", Proc.IEEE, Vol. 70, No. 5, pp. 420-457, 1982, https://doi.org/10.1109/PROC.1982.12331.
3. P. S. Dittrich and A. Manz, "Lab-on-a-chip: microfluidics in drug discovery," Nat Rev Drug Discov, vol. 5, no. 3, pp. 210–218, Mar. 2006, https://doi.org/10.1038/nrd1985.
4. N. T. Nguyen and S. T. Wereley, "Fundamentals and applications of microfluidics," Artech House. Boston, MA, USA: Inc, 2006
5. S. Lai, S. Wang, J. Luo, L. J. Lee, S.-T. Yang, and M. J. Madou, "Design of a Compact Disk-like Microfluidic Platform for Enzyme-Linked Immunosorbent Assay," Anal. Chem., vol. 76, no. 7, pp. 1832–1837, Apr. 2004, https://doi.org/10.1021/ac0348322.
6. A. M. Streets and Y. Huang, "Chip in a lab: Microfluidics for next generation life science research," Biomicrofluidics, vol. 7, no. 1, p. 011302, Jan. 2013, https://doi.org/10.1063/1.4789751.
7. K. F. Lei, "Chapter 1. Materials and Fabrication Techniques for Nano- and Microfluidic Devices," Royal Society of Chemistry, pp. 1–28.
8. M. P. Wolf, G. B. Salieb-Beugelaar, and P. Hunziker, "PDMS with designer functionalities—Properties, modifications strategies, and applications," Progress in Polymer Science, vol. 83, pp. 97–134, Aug. 2018, https://doi.org/10.1016/j.progpolymsci.2018.06.001.
9. M. Elwenspoek and H. V. Jansen, "Cambridge studies in semiconductor physics and microelectronic engineering: Silicon micromachining series number 7," Cambridge, England: Cambridge University Press, 2004.
10. D. Resnik, U. Aljančič, D. Vrtačnik, M. Cvar, and S. Amon, "Mikroobdelava silicija," Vakuumist, vol. 1, no. let 18, pp. 4–11, 1998.
11. D. Vrtačnik et al. "RIE of deep silicon microchannels for microfluidic applications," Proceedings, 44th International Conference MIDEM, September 2008.
12. M. Tilli, "Silicon wafers preparation and properties," in Handbook of Silicon Based MEMS Materials and Technologies, Elsevier, 2020, pp. 93–110, https://doi.org/10.1016/b978-0-12-817786-0.00004-9
13. K. J. Owen, B. VanDerElzen, R. L. Peterson, and K. Najafi, "High aspect ratio deep silicon etching," presented at the 2012 IEEE 25th International Conference on Micro Electro Mechanical Systems (MEMS), Jan. 2012, https://doi.org/10.1109/memsys.2012.6170138.
14. U.-B. T. Giang, D. Lee, M. R. King, and L. A. DeLouise, "Microfabrication of cavities in polydimethylsiloxane using DRIE silicon molds," Lab Chip, vol. 7, no. 12, p. 1660, 2007, https://doi.org/10.1039/b714742b.
15. Kuo-Shen Chen, A. A. Ayon, Xin Zhang, and S. M. Spearing, "Effect of process parameters on the surface morphology and mechanical performance of silicon structures after deep reactive ion etching (DRIE)," J. Microelectromech. Syst., vol. 11, no. 3, pp. 264–275, Jun. 2002, https://doi.org/10.1109/jmems.2002.1007405.
16. D. Vrtačnik et al. "Optimization of DRIE silicon microstructures with Bosch process," Proceedings, 47th International Conference MIDEM, september 2011.
17. X. Li, T. Abe, Y. Liu, and M. Esashi, "Fabrication of high-density electrical feed-throughs by deep-reactive-ion etching of Pyrex glass," J. Microelectromech. Syst., vol. 11, no. 6, pp. 625–630, Dec. 2002, https://doi.org/10.1109/jmems.2002.805211.
18. M. Stjernström and J. Roeraade, "Method for fabrication of microfluidic systems in glass," J. Micromech. Microeng., vol. 8, no. 1, pp. 33–38, Mar. 1998, https://doi.org/10.1088/0960-1317/8/1/006.
19. C. Iliescu, "Microfluidics in glass: technologies and applications," Informacije MIDEM, 2006, 36(4), 204, http://www.dlib.si/details/URN:NBN:SI:doc-U408KBPW.
20. Y. Xia and G. M. Whitesides, "SOFT LITHOGRAPHY," Annu. Rev. Mater. Sci., vol. 28, no. 1, pp. 153–184, Aug. 1998, https://doi.org/10.1146/annurev.matsci.28.1.153.
21. V. N. Goral, Y.-C. Hsieh, O. N. Petzold, R. A. Faris, and P. K. Yuen, "Hot embossing of plastic microfluidic devices using poly(dimethylsiloxane) molds," J. Micromech. Microeng., vol. 21, no. 1, p. 017002, Dec. 2010, https://doi.org/10.1088/0960-1317/21/1/017002.
22. M. Matteucci, T. L. Christiansen, S. Tanzi, P. F. Østergaard, S. T. Larsen, and R. Taboryski, "Fabrication and characterization of injection molded multi level nano and microfluidic systems," Microelectronic Engineering, vol. 111, pp. 294–298, Nov. 2013, https://doi.org/10.1016/j.mee.2013.01.060.
23. P. Sethu, "Cast epoxy-based microfluidic systems and their application in biotechnology," Sensors and Actuators B: Chemical, vol. 98, no. 2–3, pp. 337–346, Mar. 2004, https://doi.org/10.1016/j.snb.2003.09.036.
24. P. P. Shiu, G. K. Knopf, M. Ostojic, and S. Nikumb, "Rapid fabrication of tooling for microfluidic devices via laser micromachining and hot embossing," J. Micromech. Microeng., vol. 18, no. 2, p. 025012, Jan. 2008, https://doi.org/10.1088/0960-1317/18/2/025012.

25. V. Shukla, S. N. Akhtar, S. K. Subbu, and J. Ramkumar, "Fabrication of Complex Micro Channels by Micro Electric Discharge Milling (μ-ED Milling)," presented at the ASME 2013 International Mechanical Engineering Congress and Exposition, Nov. 2013, https://doi.org/10.1115/imece2013-64031.
26. K. Thompson, Y. B. Gianchandani, J. Booske, and R. F. Cooper, "Direct silicon-silicon bonding by electromagnetic induction heating," J. Microelectromech. Syst., vol. 11, no. 4, pp. 285–292, Aug. 2002, https://doi.org/10.1109/jmems.2002.800929.
27. H. Takagi, R. Maeda, T. R. Chung, and T. Suga, "Low-temperature direct bonding of silicon and silicon dioxide by the surface activation method," Sensors and Actuators A: Physical, vol. 70, no. 1–2, pp. 164–170, Oct. 1998, https://doi.org/10.1016/s0924-4247(98)00128-9.
28. H. J. Quenzer and W. Benecke, "Low-temperature silicon wafer bonding," Sensors and Actuators A: Physical, vol. 32, no. 1–3, pp. 340–344, Apr. 1992, https://doi.org/10.1016/0924-4247(92)80009-r.
29. D. Resnik, D. Vrtačnik, U. Aljančič, and S. Amon, "Study of low-temperature direct bonding of (111) and (100) silicon wafers under various ambient and surface conditions," Sensors and Actuators A: Physical, vol. 80, no. 1, pp. 68–76, Mar. 2000, https://doi.org/10.1016/s0924-4247(99)00299-x.
30. D. Resnik, D. Vrtačnik, U. Aljančič, and S. Amon, "Study of low-temperature direct bonding of (111) and (100) silicon wafers under various ambient and surface conditions," Sensors and Actuators A: Physical, vol. 80, no. 1, pp. 68–76, Mar. 2000, https://doi.org/10.1016/s0924-4247(99)00299-x.
31. Z.-X. Xiao, G.-Y. Wu, Z.-H. Li, G.-B. Zhang, Y.-L. Hao, and Y.-Y. Wang, "Silicon–glass wafer bonding with silicon hydrophilic fusion bonding technology," Sensors and Actuators A: Physical, vol. 72, no. 1, pp. 46–48, Jan. 1999, https://doi.org/10.1016/s0924-4247(98)00197-6.
32. D. Resnik, U. Aljancic, D. Vrtacnik, M. Mozek, B. Pecar, and S. Amon, "Microfluidic platforms realized by micromachining and anodic bonding of Si and glass substrates," presented at the 2012 International Caribbean Conference on Devices, Circuits and Systems (ICCDCS), Mar. 2012, https://doi.org/10.1109/iccdcs.2012.6188939.
33. D. Resnik, M. Možek, T. Dolžan, S. Amon and D. Vrtačnik, "Spajanje podlag silicij-steklo z anodnim bondiranjem, "Vakuumist, 2012, 3(32), pp. 4-11.
34. C.-W. Tsao, "Polymer Microfluidics: Simple, Low-Cost Fabrication Process Bridging Academic Lab Research to Commercialized Production," Micromachines, vol. 7, no. 12, p. 225, Dec. 2016, https://doi.org/10.3390/mi7120225.
35. Y. Suzuki, M. Yamada, and M. Seki, "Sol–gel based fabrication of hybrid microfluidic devices composed of PDMS and thermoplastic substrates," Sensors and Actuators B: Chemical, vol. 148, no. 1, pp. 323–329, Jun. 2010, https://doi.org/10.1016/j.snb.2010.04.018.
36. C.-W. Tsao and D. L. DeVoe, "Bonding of thermoplastic polymer microfluidics," Microfluid Nanofluid, vol. 6, no. 1, pp. 1–16, Nov. 2008, https://doi.org/10.1007/s10404-008-0361-x.
37. K. S. Lee and R. J. Ram, "Plastic–PDMS bonding for high pressure hydrolytically stable active microfluidics," Lab Chip, vol. 9, no. 11, p. 1618, 2009, https://doi.org/10.1039/b820924c.
38. B. Pečar, M. Možek, and D. Vrtačnik, "Ther-moplastic-PDMS polymer covalent bonding for microfluidic applications,"Informacije MIDEM, 2017, vol. 47, no. 3, pp. 147–154.
39. J. P. Conde et al., "Lab-on-chip systems for integrated bioanalyses," Essays in Biochemistry, vol. 60, no. 1, pp. 121–131, Jun. 2016, https://doi.org/10.1042/ebc20150013.
40. W. C. Krutzsch and P. Cooper, "Introduction: classification and selection of pumps," Pump Handbook, 2001.
41. H. T. G. van Lintel, F. C. M. van De Pol, and S. Bouwstra, "A piezoelectric micropump based on micromachining of silicon," Sensors and Actuators, vol. 15, no. 2, pp. 153–167, Oct. 1988, https://doi.org/10.1016/0250-6874(88)87005-7.
42. M. C. Carrozza, N. Croce, B. Magnani, and P. Dario, "A piezoelectric-driven stereolithography-fabricated micropump," J. Micromech. Microeng., vol. 5, no. 2, pp. 177–179, Jun. 1995, https://doi.org/10.1088/0960-1317/5/2/032.
43. M. Koch, N. Harris, A. G. R. Evans, N. M. White, and A. Brunnschweiler, "A novel micromachined pump based on thick-film piezoelectric actuation," Sensors and Actuators A: Physical, vol. 70, no. 1–2, pp. 98–103, Oct. 1998, https://doi.org/10.1016/s0924-4247(98)00120-4.
44. B. Pečar, M. Možek, and D. Vrtačnik, "Piezoelektrična mikročrpalka z ventiloma, ki posnemata delovanje bioloških venskih zaklopk," patent SI 25227 (A), 2017-12-29. Ljubljana: Urad RS za intelektualno lastnino, 2017
45. R. Ardito, E. Bertarelli, A. Corigliano, and G. Gafforelli, "On the application of piezolaminated composites to diaphragm micropumps," Composite Structures, vol. 99, pp. 231–240, May 2013, https://doi.org/10.1016/j.compstruct.2012.11.041
46. B. Pečar et al., "Microcylinder pump employing 0. 57 Pb (Sc1/2Nb1/2) O3–0. 43 PbTiO3 piezoelectric actuator,"Journal of Optoelectronics and Advanced Materials, 2017, vol. 19, pp. 617–622.

47. B Pečar et al., "Silicon piezoelectric vaveless micropumps", MIT & SLIM, 2011 : proceedings of the 11th International Conference on Management of Innovative Technologies & 2nd International Conference
48. Z. Jin, Z. Gao, M. Chen, and J. Qian, "Parametric study on Tesla valve with reverse flow for hydrogen decompression," International Journal of Hydrogen Energy, vol. 43, no. 18, pp. 8888–8896, May 2018, https://doi.org/10.1016/j.ijhydene.2018.03.014.
49. P.-H. Huang et al., "A reliable and programmable acoustofluidic pump powered by oscillating sharp-edge structures," Lab Chip, vol. 14, no. 22, pp. 4319–4323, 2014, https://doi.org/10.1039/c4lc00806e.
50. M. Tanyeri and S. Tay, "Viable cell culture in PDMS-based microfluidic devices," in Methods in Cell Biology, Elsevier, 2018, pp. 3–33, https://doi.org/10.1016/bs.mcb.2018.09.007.
51. C. Wang, J. Kim, and J. Park, "Micro check valve integrated magnetically actuated micropump for implantable drug delivery," presented at the 2017 19th International Conference on Solid-State Sensors, Actuators and Microsystems (TRANSDUCERS), Jun. 2017, https://doi.org/10.1109/transducers.2017.7994396
52. N. Gadad et al., "Fabrication and development of magnetically actuated PDMS micropump for drug delivery," IOP Conf. Ser.: Mater. Sci. Eng., vol. 376, p. 012128, Jun. 2018, https://doi.org/10.1088/1757-899x/376/1/012128
53. P. Kawun, S. Leahy, and Y. Lai, "A thin PDMS nozzle/diffuser micropump for biomedical applications," Sensors and Actuators A: Physical, vol. 249, pp. 149–154, Oct. 2016, https://doi.org/10.1016/j.sna.2016.08.032.
54. H.-L. Chien and Y.-C. Lee, "A ball valve micro-pump based on axially symmetrical nozzle fabricated by excimer laser micromachining technology," Int. J. Precis. Eng. Manuf., vol. 18, no. 10, pp. 1315–1320, Oct. 2017, https://doi.org/10.1007/s12541-017-0156-7.
55. Y. Ye, J. Chen, Y. J. Ren, and Z. H. Feng, "Valve improvement for high flow rate piezoelectric pump with PDMS film valves," Sensors and Actuators A: Physical, vol. 283, pp. 245–253, Nov. 2018, https://doi.org/10.1016/j.sna.2018.09.064.
56. A. Mashayek, C. P. Caulfield, and W. R. Peltier, "Role of overturns in optimal mixing in stratified mixing layers," J. Fluid Mech., vol. 826, pp. 522–552, Aug. 2017, https://doi.org/10.1017/jfm.2017.374.
57. M. Rusli, P. S. Chee, R. Arsat, K. X. Lau, and P. L. Leow, "Electromagnetic actuation dual-chamber bidirectional flow micropump," Sensors and Actuators A: Physical, vol. 282, pp. 17–27, Oct. 2018, https://doi.org/10.1016/j.sna.2018.08.047.
58. A. T. Al-Halhouli, S. Demming, A. Dietzel, and S. Büttgenbach, "Design, Fabrication, and Characterization of a Continuous Flow Micropump System," Journal of Thermal Science and Engineering Applications, vol. 8, no. 2, Dec. 2015, https://doi.org/10.1115/1.4031922.
59. R. R. Gidde and P. M. Pawar, "On effect of viscoelastic characteristics of polymers on performance of micropump," Advances in Mechanical Engineering, vol. 9, no. 2, p. 168781401769121, Feb. 2017, https://doi.org/10.1177/1687814017691211.
60. J. G. Smits, "Piezoelectric micropump with three valves working peristaltically," Sensors and Actuators A: Physical, vol. 21, no. 1–3, pp. 203–206, Feb. 1990, https://doi.org/10.1016/0924-4247(90)85039-7.
61. J. M. Berg, R. Anderson, M. Anaya, B. Lahlouh, M. Holtz, and T. Dallas, "A two-stage discrete peristaltic micropump," Sensors and Actuators A: Physical, vol. 104, no. 1, pp. 6–10, Mar. 2003, https://doi.org/10.1016/s0924-4247(02)00434-x.
62. B. Pečar, D. Križaj, D. Vrtačnik, D. Resnik, T. Dolžan, and M. Možek, "Piezoelectric peristaltic micropump with a single actuator," J. Micromech. Microeng., vol. 24, no. 10, p. 105010, Sep. 2014, https://doi.org/10.1088/0960-1317/24/10/105010
63. M. J. Davies, I. D. Johnston, C. K. L. Tan, and M. C. Tracey, "Whole blood pumping with a microthrottle pump," Biomicrofluidics, vol. 4, no. 4, p. 044112, Dec. 2010, https://doi.org/10.1063/1.3528327.
64. B. Pečar et al., "A Strip-Type Microthrottle Pump: Modeling, Design and Fabrication," Sensors, vol. 13, no. 3, pp. 3092–3108, Mar. 2013, https://doi.org/10.3390/s130303092.
65. B. Pečar et al., "Piezoelektrična mikrocilindrska črpalka," SI 24234 A, 2014-05-30. Ljubljana: Urad RS za intelektualno lastnino, 2014. 13 str., P 201300185 2013-07-05
66. P. Gravesen, J. Branebjerg, and O. S. Jensen, "Microfluidics-a review," Journal of microme-chanics and microengineering, 1993, vol. 3, no. 4, p. 168, https://doi.org/10.3390/s130303092.
67. J. Wang, M. Sullivan and S. Z. Hua, "Electro-lytic-bubble-based flow sensor for microfluidic systems," J Microelectromech Syst, 2007, vol. 16, no. 5, pp. 1087–1094, https://doi.org/10.1109/jmems.2007.906078
68. A. S. Nezhad, M. Ghanbari, C. G. Agudelo, M. Packirisamy, R. B. Bhat, and A. Geitmann, "PDMS Microcantilever-Based Flow Sensor Integration for Lab-on-a-Chip," IEEE Sensors J., vol. 13, no. 2, pp. 601–609, Feb. 2013, https://doi.org/10.1109/jsen.2012.2223667.

69. A. Amnache, M. Omri, and L. G. Fréchette, "A silicon rectangular micro-orifice for gas flow measurement at moderate Reynolds numbers: design, fabrication and flow analyses," Microfluid Nanofluid, vol. 22, no. 6, May 2018, https://doi.org/10.1007/s10404-018-2077-x.
70. A. Richter, K. A. Hofmann, A. Plettner, and H. Sandmaier, "The electrohydrodynamic micro flow meter," presented at the TRANSDUCERS '91: 1991 International Conference on Solid-State Sensors and Actuators. Digest of Technical Papers, https://doi.org/10.1109/sensor.1991.149042.
71. D. Accoto et al., "A micro flow-meter for closed-loop management of biological samples," presented at the 2005 IEEE Engineering in Medicine and Biology 27th Annual Conference, 2005, https://doi.org/10.1109/iembs.2005.1615614.
72. C. Nie, A. J. H. Frijns, R. Mandamparambil, M. A. G. Zevenbergen, and J. M. J. den Toonder, "An evaporation based digital microflow meter," J. Micromech. Microeng., vol. 25, no. 11, p. 115008, Sep. 2015, https://doi.org/10.1088/0960-1317/25/11/115008
73. B. W. van Oudheusden, "Silicon thermal flow sensors," Sensors and Actuators A: Physical, vol. 30, no. 1–2, pp. 5–26, Jan. 1992, https://doi.org/10.1016/0924-4247(92)80192-6.
74. A. Petropoulos and G. Kaltsas, "Study and Evaluation of a PCB-MEMS Liquid Microflow Sensor," Sensors, vol. 10, no. 10, pp. 8981–9001, Oct. 2010, https://doi.org/10.3390/s101008981.
75. Y. Valizadeh Yaghmourali, N. Ahmadi, and E. Abbaspour-sani, "A thermal-calorimetric gas flow meter with improved isolating feature," Microsyst Technol, vol. 23, no. 6, pp. 1927–1936, Mar. 2016, https://doi.org/10.1007/s00542-016-2915-2.
76. W. Ke, M. Liu, T. Li, and Y. Wang, "MEMS thermal gas flow sensor with self-test function," J. Micromech. Microeng., vol. 29, no. 12, p. 125009, Oct. 2019, https://doi.org/10.1088/1361-6439/ab4aef.
77. W. Kang, H.-M. Choi, and Y.-M. Choi, "Development of MEMS-based thermal mass flow sensors for high sensitivity and wide flow rate range," J Mech Sci Technol, vol. 32, no. 9, pp. 4237–4243, Sep. 2018, https://doi.org/10.1007/s12206-018-0822-4.
78. G. Kaltsas et al., "A novel microfabrication technology on organic substrates – application to a thermal flow sensor," J. Phys.: Conf. Ser., vol. 92, p. 012046, Dec. 2007, https://doi.org/10.1088/1742-6596/92/1/012046.
79. Y. Li, K. Baek, M. Gulari, D. Lin, and K. D. Wise, "A Vacuum-Isolated Thermal Microflowmeter for In-Vivo Drug Delivery," presented at the IEEE Sensors, 2005., https://doi.org/10.1109/icsens.2005.1597787.
80. P. Liu, R. Zhu, and R. Que, "A Flexible Flow Sensor System and Its Characteristics for Fluid Mechanics Measurements," Sensors, vol. 9, no. 12, pp. 9533–9543, Nov. 2009, https://doi.org/10.3390/s91209533.
81.]R. Ahrens and K. Schlote-Holubek, "A micro flow sensor from a polymer for gases and liquids," J. Micromech. Microeng., vol. 19, no. 7, p. 074006, Jun. 2009, https://doi.org/10.1088/0960-1317/19/7/074006.
82. C. Li, P.-M. Wu, J. Han, and C. H. Ahn, "A flexible polymer tube lab-chip integrated with microsensors for smart microcatheter," Biomed Microdevices, vol. 10, no. 5, pp. 671–679, May 2008, https://doi.org/10.1007/s10544-008-9178-3.
83. J. T. W. Kuo, L.-Y. Chang, P.-Y. Li, T. Hoang, and E. Meng, "A microfluidic platform with integrated flow sensing for focal chemical stimulation of cells and tissue," Sensors and Actuators B: Chemical, vol. 152, no. 2, pp. 267–276, Mar. 2011, https://doi.org/10.1016/j.snb.2010.12.019.
84. B. Pečar et al., "Microflowmeter for microfluidics applications, " Conference proceedings, 52nd International Conference MIDEM, September 28 - 30 2016, pp. 122-126.
85. V. Miralles, A. Huerre, F. Malloggi, and M.-C. Jullien, "A Review of Heating and Temperature Control in Microfluidic Systems: Techniques and Applications," Diagnostics, vol. 3, no. 1, pp. 33–67, Jan. 2013, https://doi.org/10.3390/diagnostics3010033.
86. T. Matsui, J. Franzke, A. Manz, and D. Janasek, "Temperature gradient focusing in a PDMS/glass hybrid microfluidic chip," Electrophoresis, vol. 28, no. 24, pp. 4606–4611, Dec. 2007, https://doi.org/10.1002/elps.200700272.
87. A. Kempitiya, D. A. Borca-Tasciuc, H. S. Mohamed, and M. M. Hella, "Localized microwave heating in microwells for parallel DNA amplification applications," Appl. Phys. Lett., vol. 94, no. 6, p. 064106, Feb. 2009, https://doi.org/10.1063/1.3078273.
88. H. Mao, T. Yang, and P. S. Cremer, "A Microfluidic Device with a Linear Temperature Gradient for Parallel and Combinatorial Measurements," J. Am. Chem. Soc., vol. 124, no. 16, pp. 4432–4435, Apr. 2002, https://doi.org/10.1021/ja017625x.
89. K. Zhang, A. Jian, X. Zhang, Y. Wang, Z. Li, and H. Tam, "Laser-induced thermal bubbles for microfluidic applications," Lab Chip, vol. 11, no. 7, p. 1389, 2011, https://doi.org/10.1039/c0lc00520g.
90. R. M. Guijt, A. Dodge, G. W. K. van Dedem, N. F. de Rooij, and E. Verpoorte, "Chemical and physical processes for integrated temperature control in

microfluidic devices," Lab Chip, vol. 3, no. 1, p. 1, 2003, https://doi.org/10.1039/b210629a.
91. E. Mavraki, D. Moschou, G. Kokkoris, N. Vourdas, S. Chatzandroulis, and A. Tserepi, "A continuous flow µPCR device with integrated microheaters on a flexible polyimide substrate," Procedia Engineering, vol. 25, pp. 1245–1248, 2011, https://doi.org/10.1016/j.proeng.2011.12.307.
92. B. Selva, J. Marchalot, and M.-C. Jullien, "An optimized resistor pattern for temperature gradient control in microfluidics," J. Micromech. Microeng., vol. 19, no. 6, p. 065002, May 2009, https://doi.org/10.1088/0960-1317/19/6/065002.
93. T.-M. Hsieh, C.-H. Luo, F.-C. Huang, J.-H. Wang, L.-J. Chien, and G.-B. Lee, "Enhancement of thermal uniformity for a microthermal cycler and its application for polymerase chain reaction☆," Sensors and Actuators B: Chemical, vol. 130, no. 2, pp. 848–856, Mar. 2008, https://doi.org/10.1016/j.snb.2007.10.063.
94. D. Resnik, D. Vrtačnik, M. Možek, B. Pečar, and S. Amon, "Experimental study of heat-treated thin film Ti/Pt heater and temperature sensor properties on a Si microfluidic platform," J. Micromech. Microeng., vol. 21, no. 2, p. 025025, Jan. 2011, https://doi.org/10.1088/0960-1317/21/2/025025.
95. E. Larrañeta, R. E. M. Lutton, A. D. Woolfson, and R. F. Donnelly, "Microneedle arrays as transdermal and intradermal drug delivery systems: Materials science, manufacture and commercial development," Materials Science and Engineering: R: Reports, vol. 104, pp. 1–32, Jun. 2016, https://doi.org/10.1016/j.mser.2016.03.001.
96. Y.-C. Kim, J.-H. Park, and M. R. Prausnitz, "Microneedles for drug and vaccine delivery," Advanced Drug Delivery Reviews, vol. 64, no. 14, pp. 1547–1568, Nov. 2012, https://doi.org/10.1016/j.addr.2012.04.005.
97. W. H. Smart and K. Subramanian, "The Use of Silicon Microfabrication Technology in Painless Blood Glucose Monitoring," Diabetes Technol. Ther., vol. 2, no. 4, pp. 549–559, Dec. 2000, https://doi.org/10.1089/15209150050501961.
98. H. J. G. E. Gardeniers et al., "Silicon micromachined hollow microneedles for transdermal liquid transport," J. Microelectromech. Syst., vol. 12, no. 6, pp. 855–862, Dec. 2003, https://doi.org/10.1109/jmems.2003.820293.
99. B. Chen, J. Wei, F. E. H. Tay, Y. T. Wong, and C. Iliescu, "Silicon microneedle array with biodegradable tips for transdermal drug delivery," Microsyst Technol, vol. 14, no. 7, pp. 1015–1019, Jan. 2008, https://doi.org/10.1007/s00542-007-0530-y.
100. Liwei Lin and A. P. Pisano, "Silicon-processed microneedles," J. Microelectromech. Syst., vol. 8, no. 1, pp. 78–84, Mar. 1999, https://doi.org/10.1109/84.749406.
101. W. Martanto, J. S. Moore, T. Couse, and M. R. Prausnitz, "Mechanism of fluid infusion during microneedle insertion and retraction," Journal of Controlled Release, vol. 112, no. 3, pp. 357–361, May 2006, https://doi.org/10.1016/j.jconrel.2006.02.017.
102. S. Doddaballapur, "Microneedling with dermaroller," J Cutan Aesthet Surg, vol. 2, no. 2, p. 110, 2009, https://doi.org/10.4103/0974-2077.58529.
103. L. Wei-Ze et al., "Super-short solid silicon microneedles for transdermal drug delivery applications," International Journal of Pharmaceutics, vol. 389, no. 1–2, pp. 122–129, Apr. 2010, https://doi.org/10.1016/j.ijpharm.2010.01.024.
104. M. A. L. Teo, C. Shearwood, K. C. Ng, J. Lu, and S. Moochhala, "In Vitro and In Vivo Characterization of MEMS Microneedles," Biomed Microdevices, vol. 7, no. 1, pp. 47–52, Mar. 2005, https://doi.org/10.1007/s10544-005-6171-y.
105. S. P. Davis, W. Martanto, M. G. Allen, and M. R. Prausnitz, "Hollow Metal Microneedles for Insulin Delivery to Diabetic Rats," IEEE Trans. Biomed. Eng., vol. 52, no. 5, pp. 909–915, May 2005, https://doi.org/10.1109/tbme.2005.845240.
106. J.-H. Park, M. G. Allen, and M. R. Prausnitz, "Polymer Microneedles for Controlled-Release Drug Delivery," Pharm Res, vol. 23, no. 5, pp. 1008–1019, May 2006, https://doi.org/10.1007/s11095-006-0028-9.
107. S. H. Bariya, M. C. Gohel, T. A. Mehta, and O. P. Sharma, "Microneedles: an emerging transdermal drug delivery system," Journal of Pharmacy and Pharmacology, vol. 64, no. 1, pp. 11–29, Nov. 2011, https://doi.org/10.1111/j.2042-7158.2011.01369.x
108. P. Karande, A. Jain, and S. Mitragotri, "Relationships between skin's electrical impedance and permeability in the presence of chemical enhancers," Journal of Controlled Release, vol. 110, no. 2, pp. 307–313, Jan. 2006, https://doi.org/10.1016/j.jconrel.2005.10.012.
109. M. R. Prausnitz and R. Langer, "Transdermal drug delivery," Nat Biotechnol, vol. 26, no. 11, pp. 1261–1268, Nov. 2008, https://doi.org/10.1038/nbt.1504.
110. D. Resnik et al., "Characterization of skin penetration efficacy by Au-coated Si microneedle array electrode," Sensors and Actuators A: Physical, vol. 232, pp. 299–309, Aug. 2015, https://doi.org/10.1016/j.sna.2015.05.020.
111. Deng et al., "Transdermal Delivery of siRNA through Microneedle Array," Sci Rep, vol. 6, no. 1, Feb. 2016, https://doi.org/10.1038/srep21422.

112. E. Kim et al., "Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development," EBioMedicine, vol. 55, p. 102743, May 2020, https://doi.org/10.1016/j.ebiom.2020.102743.
113. D. Resnik et al., "In Vivo Experimental Study of Noninvasive Insulin Microinjection through Hollow Si Microneedle Array," Micromachines, vol. 9, no. 1, p. 40, Jan. 2018, https://doi.org/10.3390/mi9010040.
114. F. S. Iliescu, J. C. M. Teo, D. Vrtacnik, H. Taylor, and C. Iliescu, "Cell therapy using an array of ultrathin hollow microneedles," Microsyst Technol, vol. 24, no. 7, pp. 2905–2912, Nov. 2017, https://doi.org/10.1007/s00542-017-3631-2.
115. Z. Li, A. Khajepour, and J. Song, "A comprehensive review of the key technologies for pure electric vehicles," Energy, vol. 182, pp. 824–839, Sep. 2019, https://doi.org/10.1016/j.energy.2019.06.077.
116. S. Tanaka, K.-S. Chang, K.-B. Min, D. Satoh, K. Yoshida, and M. Esashi, "MEMS-based components of a miniature fuel cell/fuel reformer system," Chemical Engineering Journal, vol. 101, no. 1–3, pp. 143–149, Aug. 2004, https://doi.org/10.1016/j.cej.2004.01.017.
117. J. D. Holladay, E. O. Jones, R. A. Dagle, G. G. Xia, C. Cao, and Y. Wang, "High efficiency and low carbon monoxide micro-scale methanol processors," Journal of Power Sources, vol. 131, no. 1–2, pp. 69–72, May 2004, https://doi.org/10.1016/j.jpowsour.2004.01.003.
118. Y. Kawamura, N. Ogura, T. Yamamoto, and A. Igarashi, "A miniaturized methanol reformer with Si-based microreactor for a small PEMFC," Chemical Engineering Science, vol. 61, no. 4, pp. 1092–1101, Feb. 2006, https://doi.org/10.1016/j.ces.2005.08.014.
119. C.-Y. Hsueh, H.-S. Chu, W.-M. Yan, and C.-H. Chen, "Transport phenomena and performance of a plate methanol steam micro-reformer with serpentine flow field design," Applied Energy, vol. 87, no. 10, pp. 3137–3147, Oct. 2010, https://doi.org/10.1016/j.apenergy.2010.02.027.
120. H. Jeong, K. I. Kim, T. H. Kim, C. H. Ko, H. C. Park, and I. K. Song, "Hydrogen production by steam reforming of methanol in a micro-channel reactor coated with Cu/ZnO/ZrO2/Al2O3 catalyst," Journal of Power Sources, vol. 159, no. 2, pp. 1296–1299, Sep. 2006, https://doi.org/10.1016/j.jpowsour.2005.11.095.
121. T. Kim, J. S. Hwang, and S. Kwon, "A MEMS methanol reformer heated by decomposition of hydrogen peroxide," Lab Chip, vol. 7, no. 7, p. 835, 2007, https://doi.org/10.1039/b700040e.
122. D. Mei, Y. Feng, M. Qian, and Z. Chen, "An innovative micro-channel catalyst support with a micro-porous surface for hydrogen production via methanol steam reforming," International Journal of Hydrogen Energy, vol. 41, no. 4, pp. 2268–2277, Jan. 2016, https://doi.org/10.1016/j.ijhydene.2015.12.044.
123. Y.-X. Huang, J.-Y. Jang, and C.-H. Cheng, "Fractal channel design in a micro methanol steam reformer," International Journal of Hydrogen Energy, vol. 39, no. 5, pp. 1998–2007, Feb. 2014, https://doi.org/10.1016/j.ijhydene.2013.11.088.
124. M. M. Sarafraz, M. R. Safaei, M. Goodarzi, and M. Arjomandi, "Reforming of methanol with steam in a micro-reactor with Cu–SiO2 porous catalyst," International Journal of Hydrogen Energy, vol. 44, no. 36, pp. 19628–19639, Jul. 2019, https://doi.org/10.1016/j.ijhydene.2019.05.215.
125. H.-S. Wang, K.-Y. Huang, Y.-J. Huang, Y.-C. Su, and F.-G. Tseng, "A low-temperature partial-oxidation-methanol micro reformer with high fuel conversion rate and hydrogen production yield," Applied Energy, vol. 138, pp. 21–30, Jan. 2015, https://doi.org/10.1016/j.apenergy.2014.10.033.
126. D. Resnik, S. Hočevar, J. Batista, D. Vrtačnik, M. Možek, and S. Amon, "Si based methanol catalytic micro combustor for integrated steam reformer applications," Sensors and Actuators A: Physical, vol. 180, pp. 127–136, Jun. 2012, https://doi.org/10.1016/j.sna.2012.04.029.
127. D. Peruško et al., "Temperature control of methanol fuel microreactor for hydrogen production,"Proceedings of the 34th International Convention MIPRO (pp. 141-144), 2011, pp. 141–144.
128. B. Pečar et al., "Microflow-generator for fuel-cell methanol hydrogen microreactor," 33rd International Convention MIPRO , IEEE, 2010, pp. 110–115.
129. C. Tsai and C.-Y. Sue, "Review of MEMS-based drug delivery and dosing systems," Sensors and Actuators A: Physical, vol. 134, no. 2, pp. 555–564, Mar. 2007, https://doi.org/10.1016/j.sna.2006.06.014.
130. S. Böhm, B. Timmer, W. Olthuis, and P. Bergveld, "A closed-loop controlled electrochemically actuated micro-dosing system," J. Micromech. Microeng., vol. 10, no. 4, pp. 498–504, Oct. 2000, https://doi.org/10.1088/0960-1317/10/4/303.
131. D. Reynaerts, J. Peirs, and H. Van Brussel, "An implantable drug-delivery system based on shape memory alloy micro-actuation," Sensors and Actuators A: Physical, vol. 61, no. 1–3, pp. 455–462, Jun. 1997, https://doi.org/10.1016/s0924-4247(97)80305-6.
132. J. Koerner, M. Helmlinger and H. Schuerle (2009). U.S. Patent No. 7,584,903. Washington, DC: U.S. Patent and Trademark Office.

133. Y.-C. Su and L. Lin, "A Water-Powered Micro Drug Delivery System," J. Microelectromech. Syst., vol. 13, no. 1, pp. 75–82, Feb. 2004, https://doi.org/10.1109/jmems.2003.823215.
134. A. Than et al., "Self-implantable double-layered micro-drug-reservoirs for efficient and controlled ocular drug delivery," Nat Commun, vol. 9, no. 1, Nov. 2018, https://doi.org/10.1038/s41467-018-06981-w.
135. A. Kabata, H. Suzuki, Y. Kishigami, and M. Haga, "Micro System for Injection of Insulin and Monitoring of Glucose Concentration," presented at the IEEE Sensors, 2005, https://doi.org/10.1109/icsens.2005.1597663.
136. D. Vrtačnik et al. "Micro-sized PDMS membranes in sealed microfluidic reservoirs, " in Conference proceedings 2016. 52nd International Conference MIDEM, September 28 - 30 2016, Ankaran, Slovenia.
137. D. Vrtačnik et al. "Nosljiv integrirani mikrodozirni sistem s poljem silicijevih mikroigel za transdermalni vnos zdravil, " patent SI24564 (A), 2015-06-30. Ljubljana: Urad RS za intelektualno lastnino, 2015.
138. K. F. Lei, "Chapter 1. Materials and Fabrication Techniques for Nano- and Microfluidic Devices," in Microfluidics in Detection Science, Royal Society of Chemistry, pp. 1–28.
139. M. Barbooti, Ed., "Environmental Applications of Instrumental Chemical Analysis." Apple Academic Press, Apr. 15, 2015, https://doi.org/10.1201/b18376.
140. "Microfluidics innovation center,"Elveflow.com, 31-Jul-2019. [Online]. Available: https://www.elveflow.com. [Accessed: 12-Mar-2021].
141. J. Sengupta and C. M. Hussain, "Graphene and its derivatives for Analytical Lab on Chip platforms," TrAC Trends in Analytical Chemistry, vol. 114, pp. 326–337, May 2019, https://doi.org/10.1016/j.trac.2019.03.015.
142. I. Moser et al., "Miniaturized Thin Film Glutamate and Glutamine Biosensors," in Biosensors '94, Elsevier, 1994, p. 170, https://doi.org/10.1016/b978-1-85617-242-4.50137-3
143. J.-Y. Yoon and B. Kim, "Lab-on-a-Chip Pathogen Sensors for Food Safety," Sensors, vol. 12, no. 8, pp. 10713–10741, Aug. 2012, https://doi.org/10.3390/s120810713.
144. B. H. Weigl, R. L. Bardell, and C. R. Cabrera, "Lab-on-a-chip for drug development," Advanced Drug Delivery Reviews, vol. 55, no. 3, pp. 349–377, Feb. 2003, https://doi.org/10.1016/s0169-409x(02)00223-5.
145. P. Ertl, D. Sticker, V. Charwat, C. Kasper, and G. Lepperdinger, "Lab-on-a-chip technologies for stem cell analysis," Trends in Biotechnology, vol. 32, no. 5, pp. 245–253, May 2014, https://doi.org/10.1016/j.tibtech.2014.03.004.
146. R. Pol, F. Céspedes, D. Gabriel, and M. Baeza, "Microfluidic lab-on-a-chip platforms for environmental monitoring," TrAC Trends in Analytical Chemistry, vol. 95, pp. 62–68, Oct. 2017, https://doi.org/10.1016/j.trac.2017.08.001.
147. J. Wu, M. Dong, S. Santos, C. Rigatto, Y. Liu, and F. Lin, "Lab-on-a-Chip Platforms for Detection of Cardiovascular Disease and Cancer Biomarkers," Sensors, vol. 17, no. 12, p. 2934, Dec. 2017, https://doi.org/10.3390/s17122934.
148. Y. Ai, F. Zhang, C. Wang, R. Xie, and Q. Liang, "Recent progress in lab-on-a-chip for pharmaceutical analysis and pharmacological/toxicological test," TrAC Trends in Analytical Chemistry, vol. 117, pp. 215–230, Aug. 2019, https://doi.org/10.1016/j.trac.2019.06.026.
149. W. Jung, J. Han, J.-W. Choi, and C. H. Ahn, "Point-of-care testing (POCT) diagnostic systems using microfluidic lab-on-a-chip technologies," Microelectronic Engineering, vol. 132, pp. 46–57, Jan. 2015, https://doi.org/10.1016/j.mee.2014.09.024.
150. S. K. Sia and L. J. Kricka, "Microfluidics and point-of-care testing," Lab Chip, vol. 8, no. 12, p. 1982, 2008, https://doi.org/10.1039/b817915h.
151. T. Nguyen, S. Zoëga Andreasen, A. Wolff, and D. Duong Bang, "From Lab on a Chip to Point of Care Devices: The Role of Open Source Microcontrollers," Micromachines, vol. 9, no. 8, p. 403, Aug. 2018, https://doi.org/10.3390/mi9080403.
152. S. K. Sia and L. J. Kricka, "Microfluidics and point-of-care testing," Lab Chip, vol. 8, no. 12, p. 1982, 2008, https://doi.org/10.1039/b817915h.
153. S. Park, Y. Zhang, S. Lin, T.-H. Wang, and S. Yang, "Advances in microfluidic PCR for point-of-care infectious disease diagnostics," Biotechnology Advances, vol. 29, no. 6, pp. 830–839, Nov. 2011, https://doi.org/10.1016/j.biotechadv.2011.06.017
154. B. J. Toley et al., "Multidimensional Paper Networks: A New Generation of Low-Cost Pump-Free Microfluidic Devices," J Indian Inst Sci, vol. 98, no. 2, pp. 103–136, May 2018, https://doi.org/10.1007/s41745-018-0077-1.
155. A. Böhm and M. Biesalski, "Paper-based microfluidic devices: A complex low-cost material in high-tech applications," MRS Bull., vol. 42, no. 05, pp. 356–364, May 2017, https://doi.org/10.1557/mrs.2017.92.
156. A. K. Yetisen, M. S. Akram, and C. R. Lowe, "Paper-based microfluidic point-of-care diagnostic de-

vices," Lab Chip, vol. 13, no. 12, p. 2210, 2013, https://doi.org/10.1039/c3lc50169h.
157. C. H. Ahn et al., "Disposable Smart Lab on a Chip for Point-of-Care Clinical Diagnostics," Proc. IEEE, vol. 92, no. 1, pp. 154–173, Jan. 2004, https://doi.org/10.1109/jproc.2003.820548.
158. P. Neuzil, J. Pipper, and T. M. Hsieh, "Disposable real-time microPCR device: lab-on-a-chip at a low cost," Mol. BioSyst., vol. 2, no. 6–7, p. 292, 2006, https://doi.org/10.1039/b605957k.
159. S. Sun, M. Yang, Y. Kostov, and A. Rasooly, "ELISA-LOC: lab-on-a-chip for enzyme-linked immunodetection," Lab Chip, vol. 10, no. 16, p. 2093, 2010, https://doi.org/10.1039/c003994b.
160. V. T. Upaassana et al., "Highly Sensitive Lab on a Chip (LOC) Immunoassay for Early Diagnosis of Respiratory Disease Caused by Respirable Crystalline Silica (RCS)," Anal. Chem., May 2019, https://doi.org/10.1021/acs.analchem.9b00582.
161. E. E. Tripoliti et al., "KardiaTool: An Integrated POC Solution for Non-invasive Diagnosis and Therapy Monitoring of Heart Failure Patients," presented at the 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Jul. 2018, https://doi.org/10.1109/embc.2018.8513298.
162. X. Hou et al., "Erratum: Interplay between materials and microfluidics," Nat Rev Mater, vol. 2, no. 5, May 2017, https://doi.org/10.1038/natrevmats.2017.28.
163. A. Bohr, S. Colombo, and H. Jensen, "Future of microfluidics in research and in the market," in Microfluidics for Pharmaceutical Applications, Elsevier, 2019, pp. 425–465.
164. R. Lo, "Microfluidics technology: future prospects for molecular diagnostics," AHCT, vol. Volume 3, pp. 3–17, Feb. 2017, doi: 10.2147/ahct.s94024.
165. W.-C. Tian and E. Finehout, "Current and Future Trends in Microfluidics within Biotechnology Research," in Microfluidics for Biological Applications, Springer US, pp. 385–411.

Arrived: 04. 12. 2021
Accepted: 19. 03. 2021