PERSPECTIVE

Reconfigurable microfluidics

Federico Paratore[¥,1], Vesna Bacheva[¥1,2], Moran Bercovici*[,2] and Govind V. Kaigala*[,1]
[1]IBM Research Europe [2]Technion – Israel Institute of Technology
[¥]Equal contribution *Corresponding author

Abstract

The field of microfluidics has enabled a wide range of discoveries and technologies in the biological and chemical sciences. However, despite three decades of research, the vision of lab-on-a-chip, a microscale device capable of replacing large-scale chemical and biological laboratories, remains elusive. Here we argue that a major gap toward achieving this goal is the lack of reconfigurability and programmability of existing microfluidic platforms. We portray a vision of a fully reconfigurable microfluidic device, which can change its shape and function dynamically, thus allowing researchers to 'put their hands' into a microscale experiment and enabling real-time decision making. We review existing technologies that can dynamically control microscale flows, suggest additional physical mechanisms that could be leveraged towards the goal of reconfigurable microfluidics, and call on the broad scientific community to join in this effort.

1. Introduction

The field of lab-on-a-chip seeks to take large-scale chemical and biochemical laboratories, and reduce them to the size of a small microfluidic chip. Figure 1 presents a timeline of the trends and major achievements in this field. While examples of chemical analysis on microfabricated wafer-based substrates date back to as far as the late '70s[1], the birth of the field is largely attributed to developments in the early '90s where the maturity of microfabrication techniques significantly lowered the technological barriers for the creation of such devices and paved the way to an explosion in research on the use of microscale systems for bio/chemical analysis. During these times, Manz, Graber, and Widmer published their seminal paper on a vision of integrating multiple laboratory steps in devices on the μm-mm scale[2], coining the term 'micro total analysis systems' (μTAS), now commonly referred to as lab-on-a-chip. Lab-on-a-chip systems have clear advantages including compact size and portability, small sample and reagent volumes, in addition to new functionalities enabled by the microscale. However, despite three decades of research, the grand vision of a complete lab operating at a microscale remains elusive.

A key element of any lab-on-a-chip system is the ability to drive fluids and control fluidic paths, enabling core functionalities such as liquid mixing, splitting, and the transport of molecules and particles. Lab-on-a-chip devices are commonly divided into two main families: continuous phase devices, and discrete phase (e.g. droplets) devices (see Box 1). A large number of physical mechanisms (e.g. electro-wetting[3,4], dielectrophoresis (DEP)[5], and thermocapillary[6]) are available to precisely control two-phase systems on a large scale, with digital microfluidic technologies[7] being the most prominent. However, many processes, including chromatographic and electrophoretic separations, as well as live cell assays, rely on continuous single-phase flows, whose control remains a substantial challenge[8].

Single-phase microfluidic chips are largely still single-purpose “protocols on chips” rather than true “labs on chips”: they do not allow the flexibility and real-time experimental decision-making essential to scientific work. After carrying out a predetermined protocol, it is rarely possible to perform unplanned follow-up experiments based on the obtained results on the same sample or on the same system. We believe that rapid progress in research depends on the ability to make real-time experimental decisions, in which the observations from the current step direct subsequent steps in the experiment – a level of flexibility unattainable with current microfluidic tools. In this perspective we portray our vision of creating single-phase reconfigurable systems and focus on actuation mechanisms that could potentially be leveraged to achieve this goal.

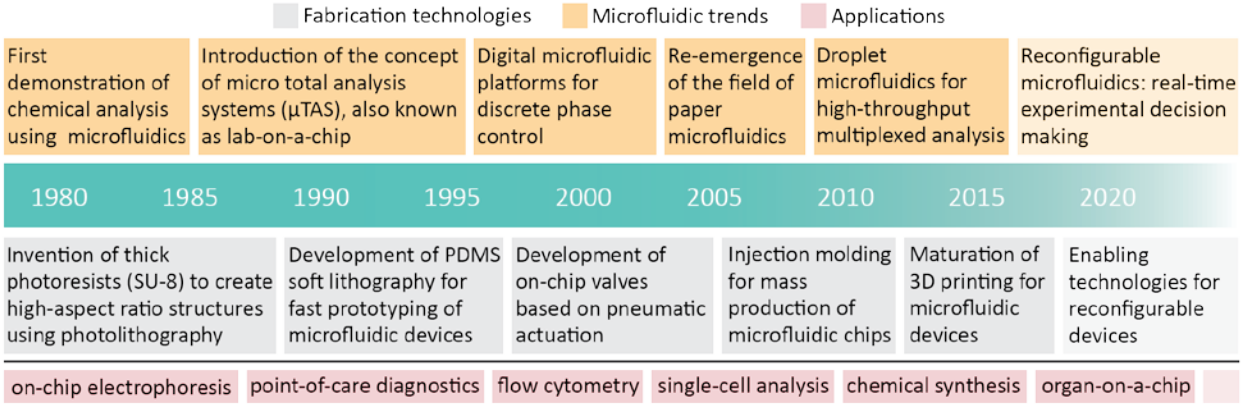
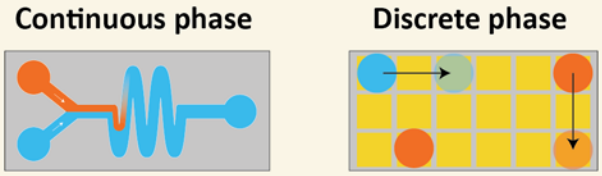


Figure 1 | Timeline of key achievements and trends in the development of microfluidic technologies. *Microfluidic trends*: The first implementation of an on-chip chemical analysis is often attributed to the work of Terry *et al.* in 1979[1] who demonstrated on-chip chromatography. The concept of micro total analysis (μTAS) was introduced by Manz *et al.* in their 1990 paper[2]. In 1998, Washizu[9] introduced the use of electrowetting to transport droplets in microsystems, laying the foundation for digital microfluidics[7]. In 2007, Whitesides’ group popularized paper-based analytical devices[10], particularly for point of care diagnostics in low resource settings[11]. At the same time, droplet microfluidics, which uses a large number of droplets as independent reaction containers, became a central theme in microfluidics[12]. *Fabrication technologies:* In 1987, IBM invented the SU-8 photoresist for high-aspect ratio structures[13]. This enabled the development of PDMS-based soft lithography by Whitesides’ group in 1998[14], which quickly became the *de-facto* standard for microfluidic prototyping. In turn, soft lithography led to the implementation of on-chip pneumatic valves[15–17], which provided the ability to reconfigure a microfluidic device for the first time. The early 2000s also saw a fast development of injection molding for the mass production of microfluidic chips[18]. More recently, 3D printing technologies have been taking center stage as prototyping methods for microfluidic devices[19]. Throughout the years the development of new technologies has enabled new applications, particularly in biochemical analysis. The development of reconfigurable microfluidic systems will enable additional functionalities that are not possible with current tools.

Box 1 | Primary classes of microfluidic devices.



Continuous phase microfluidics relies on the manipulation of a single liquid, i.e. one phase, or molecules within this phase to provide functional processes such as transport, mixing, and separation. The level of flow reconfigurability to date is highly limited as it is dictated by the fixed device geometry.

Discrete phase microfluidics utilizes immiscible phases to define discrete volumes of liquid that can be individually manipulated to merge, mix and split. This type of microfluidics already offers a high-level of reconfigurability and operational flexibility.

2. Vision and need for a reconfigurable system for single-phase microfluidics

Figure 2 illustrates our vision of a reconfigurable microfluidic platform in which the flow field can be arbitrarily controlled in real time by the user. This could be achieved either by shaping physical boundaries in the chip and forcing the liquid through the resulting networks, or by directly manipulating the liquid using body or surface forces. Both approaches should allow the microchip to be configured to drive fluids along *ad-hoc* fluidic networks, and provide a variety of desired functionalities, including mixing, splitting, merging, confining, stagnating, shearing, and pumping. In addition, the physical boundaries approach should also allow the creation of structural elements such as chambers, traps and posts.

Figure 2 further depicts the range of bioanalytical applications that could be significantly advanced and enhanced by using such a reconfigurable platform. It could, for example, (1) close a major gap in the field of single-cell analysis where current technologies are limited in their ability to dynamically compartmentalize, manipulate, and analyze single cells; (2) unlock new degrees of freedom in microscale chemistry, by enabling programmable synthesis and separations on continuous flow streams; (3) accelerate the development of microfluidic chips for diagnostic applications, by allowing developers to rapidly test a large number of configurations without the time and cost associated with lithography cycles. In the future, such a configuration may also present an unprecedented opportunity to link artificial-intelligence capabilities with biological experiments, providing experimental decisions and optimizations in real-time.

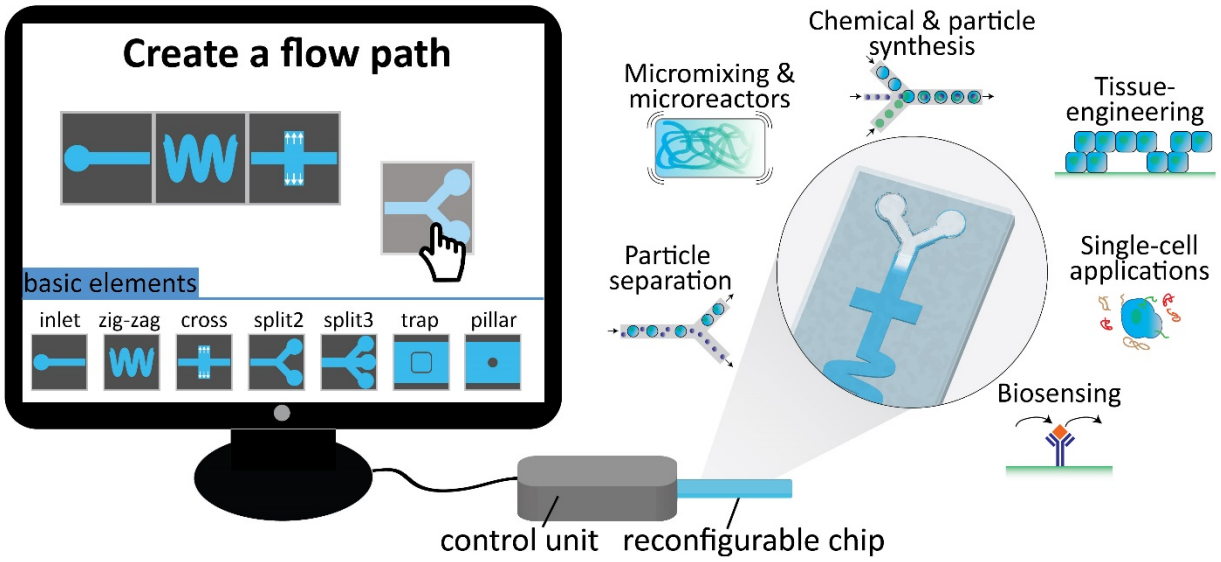
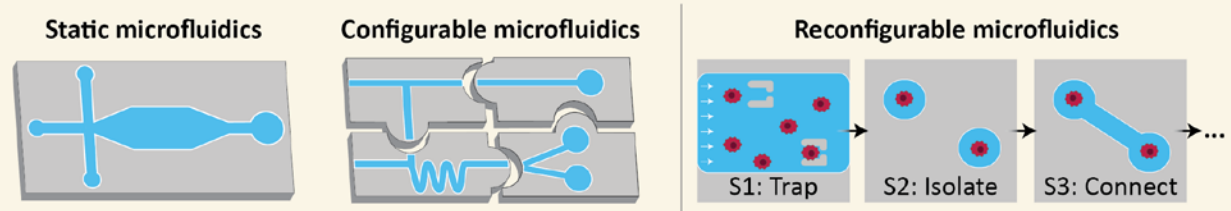


Figure 2 | Illustration of our vision for a reconfigurable microfluidic platform. The user will be able to draw any desired microfluidic configuration on a computer, and this design will be instantaneously implemented on the reconfigurable chip. The ideal reconfigurable system would be able to rapidly switch between a large number of states and functionalities, thus allowing the user to dynamically interact with the on-chip experiment. The ability to reconfigure a chip in real-time will open the door to a wide range of applications in chemical and biological analysis, from chemical synthesis through medical diagnostics to single-cell research.

3. State-of-the-art of reconfigurable systems

Box 2 presents the classification of microfluidic devices based on their configurability. Traditionally, continuous-flow microfluidic devices consist of static microfluidic networks, where fluids are pumped through channels actively (e.g. by pressure gradients, electroosmotic flow) or passively (e.g. capillary-driven), limiting them to a predefined functionality. These devices are typically produced using techniques such as lithography, micro milling, laser ablation, and injection molding. Configurable systems rely on a physical actuation mechanism to transform a device from its baseline state to a desired functional state. Examples include modular assembly[20–22], oleophilic/hydrophobic boundaries[23,24], and paraffin structuring[25]. In contrast, a *re*configurable system is one which enables multiple transitions between a large number of states and can do so in real-time during its operation. While configurable devices are undoubtedly useful, real-time decision-making in experiments will only be possible with reconfigurable systems, and we focus solely on their state-of-the-art here, summarized in Figure 3.

Box 2 | Classification of microfluidic devices based on their configurability.



Static microfluidics. The geometry of the device is fixed during the fabrication process (e.g. lithography, 3D printing, injection molding). Once the device is fabricated, the user does not have further control over its geometry.

Configurable microfluidics. The user can configure the device to certain states. Modifying the configuration is possible, but requires disassembly or resetting of the original device, and cannot be performed in real-time.

Functionality is set by a fixed geometry.

The user can set any desired state of the device in real-time. The transition between states provides additional functionalities while the device remains operational and the experiment is running. Reconfigurable platforms will open the door to new on-chip applications with experimental decisions and optimizations in real-time.

Functionality can be changed in real-time.

The first reconfigurable systems, developed in the early 2000s, were based on a fixed microfluidic network supplemented by on-chip valves controlling the flow paths[17]. While a large number of mechanisms exist for valve actuation, including electrostatic, magnetic, piezoelectric, and thermal, the best-known example is the pneumatic valve[15–17], composed of a flexible membrane that deflects under pneumatic actuation to close or open a fluidic channel. Routing fluid in a predefined fluidic network could also be achieved by subjecting the fluid itself to surface or body forces that direct its path through the network. For example, electroosmotic flow (EOF) has been used to direct the flow, either by controlling the electric field distribution in the network[26], or by controlling the surface potential in different branches[27]. Achieving a similar functionality, yet using a different physical mechanism, Lemoff and Lee introduced the use of magneto-hydrodynamics (MHD) for pumping fluids in microchannels[28]. Bau *et al.* later demonstrated the use of MHD to direct liquid within a fluidic network by controlling the electric current in individual branches[29].

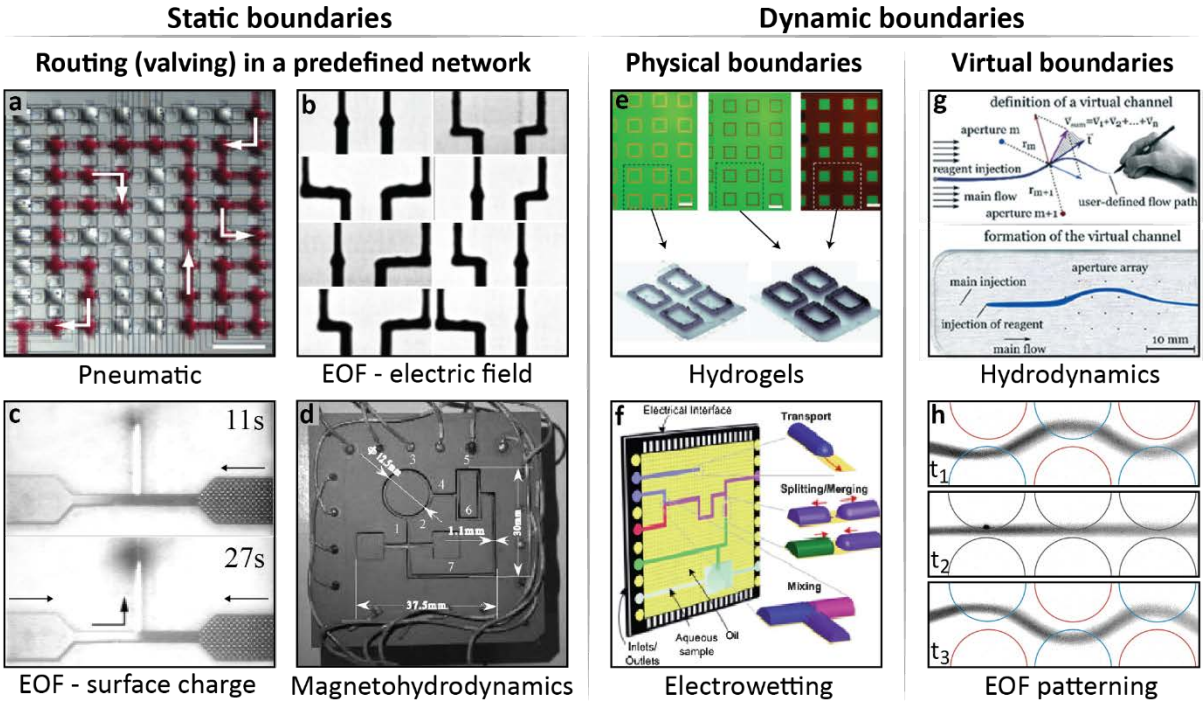


Figure 3 | State-of-the-art in reconfigurable systems. We classify existing approaches for reconfigurable microfluidics into those that route the fluids through desired paths within a predefined network (static boundaries), and those that rely on the dynamic creation or manipulation of the boundaries (dynamic boundaries). Prominent examples of the former rely on valving mechanisms such as (a) mechanical deformations[30] , (b-c) electroosmotic flow [26,27], and (d) magnetohydrodynamics[29]. The latter can be further classified to physical boundaries that are solid as in the case of (e) hydrogels[31] or liquid such as in (f) electrowetting[32], and to virtual boundaries where the fluid itself is manipulated as in (g) hydrodynamics[33] or (h) electroosmotic flow patterning[34].

Fluidic routing can be obtained not only by redirecting flows within a fixed network, but also through the creation of the physical network itself. For example, Papautsky and his colleagues demonstrated the creation of water-in-oil channels, wherein the liquid-liquid interface serves as the channel boundary, allowing to then drive liquids using standard pressure-driven flow. Utilizing electrowetting, fluidic paths could be created or erased in real-time by controlling the voltage on the electrodes[32,35]. Another technology enabling real-time creation of physical boundaries leverages phase-transition elements such as stimuli-responsive (e.g. pH, temperature) hydrogels. This approach was introduced for self-regulating the flow in simple microfluidic networks[36] and has recently been expanded by D'Eramo *et al.* to large-scale active actuation of an array of traps[31].

An alternative to having physical boundaries is to guide the liquid through a network of virtual channels, defined by imposing a pressure distribution within the chamber itself. One mechanism for achieving this is microscale electrokinetic flow control that has its roots in the work of Schasfoort *et al.*; they demonstrated the a way to start, stop, and control the magnitude of electroosmotic flow by using a gate electrode in a fluidic channel[27]. Recently, our team demonstrated the use of local electroosmotic flow control to create more complex flows in an unobstructed chamber, showing dynamic real-time flow patterning[34,37]. Another mechanism for creating virtual channels is hydrodynamic flow control, which has

been implemented by Cooksey *et al.*; they used individually controlled reservoirs, located at the edges of a microfluidic chamber, to shape the flow streamlines and direct them towards the desired inlets to the desired outlets[38]. Building on this work, Taylor *et al.* placed the flow sources/sinks at the floor of a Hele-Shaw chamber, thus providing additional degrees of freedom[33]. With this approach, additional functionalities such as streamline splitting and re-merging, as well as more precise control over streamline paths, were achieved. In contrast to electrokinetic techniques, hydrodynamic flows do not strongly depend on fluid properties, yet require external and bulky fluidic instrumentation, such as pressure controllers or pumps, which are not easy to scale down.

4. Potential mechanisms for future reconfigurable systems

In addition to the systems discussed in the previous section, we believe that a large number of actuation mechanisms have the potential to create powerful reconfigurable systems, yet have not been fully explored. Some of these mechanisms have already been used to route liquid through a preexisting network, while others have only been explored for basic fluid transport.

While devices that route liquids through preexisting networks are undoubtedly useful for a variety of applications, they do not represent the ultimate reconfigurable system as they are based on channels with pre-set dimensions, resulting in a finite number of fluidic routes. Moreover, the flow is transported unidirectionally in each channel with a physical wall between flow streams, precluding more complex flow patterns and mass transport between streamlines. Here, we therefore focus on what we consider the most advanced form of reconfigurability – the dynamic shaping of boundaries, either through manipulation of physical boundaries (liquid or solid) or through the application of forces to the liquid itself (virtual boundaries). We provide a brief review of such mechanisms, summarized in Figure 4, and speculate how they could be further developed for reconfigurable systems.

Physical boundaries

As discussed in Section 3, electrowetting was shown to be an effective method for the dynamic creation of microfluidic channels. While demonstrations have so far been limited to few channels, it is foreseeable that this approach could be scaled up based on the infrastructure developed for droplet microfluidics[7] where fairly large arrays of electrodes have been developed[39]. However, flow within liquid boundaries is inherently limited to relatively low pressures, dictated by the Laplace pressure that can be sustained by the interface. Furthermore, from a practical perspective, handling two phases adds an additional level of complexity over single phases. As an alternative, we envision a reconfigurable system in which none of the physical boundaries are fixed. Instead, the ceiling and/or floor of the chip is deformed arbitrarily, thus defining the fluidic path. Such deformations could potentially be achieved by responsive materials or by mechanical actuations.

Phase-transition hydrogels. Volume phase-transition is a process in which hydrogels shrink or expand in response to a certain stimulus, either physical (e.g. temperature, electric/magnetic fields, light, pressure), or chemical (e.g. pH, salt concentration)[40]. The change in volume is usually reversible and its magnitude, which can vary by more than an order of magnitude, depends on the hydrogel characteristics, such as chemical composition and degrees of cross-linkage, as well as on the intensity of the external stimulus.

An early and elegant incorporation of hydrogels within microfluidics was demonstrated by Beebe *et al.* who implemented a self-regulated valving system, where the opening/closing of the valve was governed

by the pH of the solution[36,41]. They fabricated the hydrogels *in situ*, within the microfluidic networks, by polymerizing the basic constituents using local illumination[42,43]. This principle was then expanded to achieve self-regulation based on other stimuli , including chemical concentrations[44] and temperature[45]. One of the first implementations of an actively controlled hydrogel valve was demonstrated by Richter *et al.* They used an external heating element to control the temperature of a temperature-sensitive hydrogel (poly(N-isopropylacrylamide)), which expands at room temperature and shrinks at temperatures above ~33°C[46]. The same group showed the utility of this mechanism for controlling individual valves within a preexisting microfluidic network. They further extended this approach in the context of creating artificial skin to a large-scale array of 65 x 65 hydrogel pixels, each with a footprint of 300 μm x 300 μm, that were individually addressed by a temperature field dynamically controlled by a light projection system[47]. However, this particular implementation was never explored in the context of microfluidics. It is foreseeable that it could in fact serve as a significant expansion of the work by D'Eramo *et al.*[31] (see section 3) where, instead of a predefined array of traps that can all be turned on or off at the same time, the structures could be individually controlled and have an arbitrary shape based on the projected light pattern. In this way, the entire channel network could be formed and modified in real time, and a variety of functional elements, beyond traps, could be implemented.

Advances in hydrogels[31,47], which have recently fueled the enormous progress in soft robotics[48,49] and biomaterials[50,51], can contribute significantly to the realization of dynamically controlled physical boundaries. Due to their inherent nano-sized porous structure, using hydrogels as 'walls' can block advective flows while still allowing diffusion of chemical species through them. This represents a unique feature that can be leveraged towards integrating flow routing with applications requiring mass transport with zero net flow; examples include the delivery of reagents to cells without shearing them, separations (e.g. micro-dialysis, chromatography), creation of chemical gradients, and biosensing[52].

Mechanical deformations. As an alternative approach, one could imagine, for example, a device consisting of a rigid ceiling and an elastic floor, suspended on top of an array of actuators, which can deform arbitrarily, thus defining the fluid path. The challenge lies in obtaining a system capable of providing enough displacement, while sustaining large enough pressures and providing a sufficient spatio-temporal resolution. A Digital micromirror device (DMD) is a well-established technology that can provide deformation of individual (~10 μm) pixels over a high-resolution array. However, micromirrors only need enough force to redirect light, and not to push on a fluidic system. Such silicon micro-electro-mechanical-systems (MEMS) were simply not designed to generate enough force to create substantial deformations. At the same time, while there are many technologies for single ~100 μm-scale actuators that can generate the required force[53–58], creating and controlling compact arrays of such actuators remains challenging.

One of the most advanced platforms implementing the concept of mechanical deformations of a membrane to date is by Richter *et al.*[46] (also discussed in the previous section in the context of hydrogels), in which the authors used an array of hydrogel 'pixels', individually addressable by optothermal actuation, to arbitrarily deform a membrane attached to it. However, the work was presented solely in the context of its application to artificial skins. Based on previous work done on hydrogel actuation and its ability to sustain sufficient forces when used as a valve, we believe that this technology has great potential for reconfigurable microfluidics, e.g. where the fluid is placed on top of the membrane and the microfluidic network is modified by actuating the hydrogel array. This demonstration supports our claim that technologies to create high-resolution devices do exist, and will have to be adapted to realize reconfigurable microfluidics.

The actuation of the deformable surface could be achieved not only by using an array of discrete mechanical actuators, but could also be based on creating pressure with an underlying layer of fluid[59]. For example, Boyko *et al.* demonstrated the ability to deform an elastic sheet suspended on top of a thin liquid film by subjecting the liquid to non-uniform electroosmotic flow[60]. However, the pressures that such system can produce are fairly low (tens to hundreds of Pa), and while the use of non-Newtonian fluids could potentially increase the pressure by as much as two orders of magnitude, this has not yet been demonstrated in practice. Many of the fluidic mechanisms that will be discussed in the next section (e.g. acoustic, magnetohydrodynamic) could likely be used to create such pressure distributions resulting in the desired deformations, and they should be further studied in the context of their ability to provide sufficient resolution, force, and displacement.

Virtual boundaries

As discussed in Section 3, hydrodynamic control is likely the most straightforward and clear implementation of the virtual boundaries concept. In this approach, streamlines are shaped by the injection of fluid at multiple locations within a fluidic chamber, resulting in an internal pressure distribution and thus guiding the streamline. The number of degrees of freedom can be increased by having additional actuation sources, however, this approach is not scalable due to the size and cost of pumping systems. Furthermore, hydrodynamic control is based on the injection of momentum together with mass, where the latter is not always desired. Here, we review additional physical mechanisms that allow injection of pure momentum into the flow and are potentially more amenable to scaling.

Electrically driven flows. Electrically driven flows result from the interaction of electric fields with electrolyte solutions, and can be roughly divided into (i) electrokinetic flows, in which charges arise in the diffused electric double layer (EDL) formed at liquid-solid or liquid-liquid interfaces[61], and (ii) electrohydrodynamic flows, in which net charges in the fluid bulk arise due to a gradient of the liquid electric properties, i.e. conductivity and permittivity[62].

The most widely used form of electrokinetic flows is electroosmotic flow. In its simplest form, a dc electric field is applied parallel to a surface and applies a body force to the fluid through its interaction with the net charge in the EDL, dragging the liquid bulk through viscous forces. Non-uniformities in either one of these elements, i.e. EDL or electric field, give rise to pressure gradients which affect the flow field[63]. As discussed in Section 3, dynamically modulating the charge distribution in a microfluidic chamber (e.g. using gate electrodes) allows to achieve a certain level of flow reconfigurability. However, other electroosmosis-based mechanisms that are commonly used to pump fluids could also potentially be implemented for this purpose. A good candidate is induced-charge electroosmosis (ICEO)[64], a phenomenon occurring when an electric field acts on the induced EDL on a polarizable surface, e.g. an electrode. Prior studies have already demonstrated that when using a linear array of electrodes net flow can be generated either by having directional asymmetry of the electrodes (ac electroosmosis – ACEO [65–68]), or by activating the electrodes sequentially (travelling wave electroosmosis - TWEO[69]). We speculate that by having a 2-dimensional array of electrodes that can be individually addressed with a dedicated ac signal, one could shape complex flow patterns in real-time. ACEO and TWEO often use exposed electrodes which are susceptible to degradation over time and might cause faradaic reactions leading to a device failure. However, they require only a few volts and no external electric field along the channel and are thus, in contrast to electroosmotic flow, more suitable for being integrated in solid state platforms.

Electrically driven pumping was also demonstrated by leveraging the interaction of an electric field with induced gradients of conductivity and permittivity in the fluid bulk, also known as induction electrohydrodynamic flows. A convenient way to form such gradients is by an imposed thermal gradient[70], usually produced by strong illumination[71] or Joule heating[72]. Similar to the electrokinetic techniques previously discussed, we believe that such electrothermal flows could also be leveraged to implement reconfigurable flow. For instance, one could create arbitrary conductivity gradients that would drive the desired flow by having localized and individually addressable heat sources at the bottom of a microfluidic chamber, e.g. using patterned resistors or patterned light. In contrast to other electrokinetic techniques, electrothermal flows can generate stronger microflows for fluids with higher conductivities. Therefore, these mechanisms have been proven to work robustly in biological applications that involve high conductivity biofluids (above 0.7 S m^{-1}), such as saliva, blood, and urine[73].

Thermocapillary flows. Marangoni flow is obtained at fluid-fluid interfaces (e.g. between two immiscible liquids or between a liquid and a gas) that are subjected to a non-uniform surface tension. Such non-uniformities give rise to tangential stresses that drive the fluid along the interface, away from lower surface tension regions, and carry the rest of the fluid through viscous interactions. Thermocapillary flows are a subset of Marangoni flows, wherein surface tension variations are driven by temperature gradients. They have been the subject of active study in the fluid mechanics community for the past several decades[6]. In contrast to other Marangoni flow mechanisms, such as chemical gradients, thermocapillary flows can be dynamically controlled because heat can be added and removed from the system relatively easily by using external means, and small temperature gradients (a few degrees over cm scales) can yield significant flows[74]. Furthermore, because at the microscale effects of surface tension become dominant over body forces, such as density gradients and gravitational forces, thermocapillary flow has the potential to serve as an effective method for the control and manipulation of liquids in microfluidic devices.

A major challenge in using thermocapillary flows for large-scale flow patterning lies in the need for an interface between two immiscible fluids, thus limiting its use for configurations containing free surfaces. Consequently, both evaporation and contamination pose difficulties for practical implementation. One option to minimize these undesired effects is to have a microfluidic channel with only few openings exposing a limited free surface region. Frumkin *et al.* showed that when such a free surface region is placed as a segment within a microfluidic channel, the resulting pressure gradient is able to drive the flow through the rest of the microchannel[75]. Another approach is to create air-pockets on one of the microfluidic chamber walls; this would limit the evaporation and create a large area of water-air interface[76]. Baier *et al.* showed theoretically that thermocapillary flows can be achieved on superhydrophobic surfaces[77], wherein liquid-air interfaces are formed between pillars on which the fluid is suspended. This can certainly be a path toward an implementation in closed configurations, however, the introduction of superhydrophobic surfaces introduces new practical challenges. Namely, superhydrophobic surfaces are more susceptible to instability triggered by various factors such as external pressure, condensation, and electrowetting[78], and more work is needed to create stable superhydrophobic structures that allow operation over long periods of time without collapsing.

Similar to the case of electrothermal flows and hydrogel actuation, a substantial challenge is the large-scale control of the temperature field. Potential implementations are local heating of the bulk liquid electrically or optically[79], or heating only the interface, e.g. through the local heating of particles placed

at the interface. Because the process is governed by the interface, the latter would provide both a higher spatial resolution and faster response time compared to heat transfer through the liquid film.

Surface acoustic waves. Acoustic waves result from pressure oscillations that propagate through matter and can move fluids through the transfer of energy into the volume and manipulate particles through acoustic radiation from the surrounding liquid.

The most common implementation of acoustic waves in microfluidics is through surface acoustic waves (SAW). SAW sources can be integrated on the same chip as the fluidic components and are typically made of piezoelectric materials[80]. In addition, SAW is not very sensitive to the composition of the fluid, and could thus be easily adapted to different applications, including those which involve biological samples, spanning a range of pH and ionic strengths values. Up to date, several works have showed the potential of SAW to serve as a pumping element in microfluidic channels. Cecchini *et al.* demonstrated a SAW-driven device capable of pulling liquid from a droplet reservoir into a microchannel, leveraging the liquid-air interface[81]. Massini *et al*. expanded this concept to a microchannel grid in which the liquid is driven by activating multiple transducers located at the entry/exit points of the grid[82]. SAW-driven pumps have also been demonstrated by Fallah *et al.* in an entirely filled closed-loop channel without the need for a liquid-air interface[83], making them a good potential candidate to be used as a driving mechanism for reconfigurable systems. However, in contrast to electrical or thermal forces, which can directly act on the entire area of the fluidic chamber, effective energy coupling in SAW occurs at liquid-air interfaces and therefore SAW actuation would be based on an array of actuators located at the circumference of the chamber. This has some resemblance to hydrodynamic flow manipulation through injection of fluids at the boundaries[33,38], except that here momentum is injected through the forces on the boundaries of the channel, rather than through the injection of mass. Similar to other mechanisms, technological challenges that need to be overcome lie in the scaling and integration of a large array of individual SAW sources, with emphasis on the thermal management of dense high-energy actuators[80].

Magnetohydrodynamics (MHD). MHD describes the motion of a conductive liquid subjected simultaneously to an electric field and a perpendicular magnetic field component, giving rise to a Lorenz body force that acts on the liquid. MHD has been demonstrated as an effective method for fluidic pumping, with the most common implementation making use of a magnetic field produced by a magnet (permanent or electric) external to the chip and an electric field produced by sets of electrodes located on opposite walls of the fluidic channel.

MHD could be implemented using dc or ac fields. Direct current actuation allows the use of permanent magnets with zero power consumption, but has practical challenges related to bubble generation and degradation of the electrodes due to electrolysis. Methods for avoiding or reducing these effects include placing the electrodes in open reservoirs far from the controlled channel[84], or using redox species to minimize faradaic reactions[85]. Alternating current actuation essentially eliminates bubble generation, but requires the use of electromagnets that are synchronized with the electric field, and which require high power to produce significant magnetic fields. Furthermore, alternating magnetic fields induce parasitic currents in the channel electrodes, giving rise to joule heating. Since MHD actuation relies on a volumetric force to drive the fluid, which does not scale favorably as the channel dimensions decrease, most implementations have focused on dimensions larger than 100 μm[86]. A significant step toward reconfigurability was taken by Bau *et al.* who demonstrated the ability to control the flow within a fluidic network, by controlling pairs of electrodes in different branches of the network[29]. At present,

demonstrations have been limited to a relatively small number of controllable channels, but it is foreseeable that, by having a very large number of individually controlled branches, such a platform could be used as a truly reconfigurable system. Furthermore, one could envision the use of an array of electrodes to create localized flows within an unobstructed chamber, thus creating virtual channels. Importantly, MHD electrodes in such a chamber could be operated by voltages in the order of tens of volts or less, which is much less than in other electrokinetic techniques (typically requiring hundreds of volts). Thus, this opens the door to an easier implementation of large arrays using standard microelectronic controllers. A successful implementation of this vision would require overcoming problems associated with joule heating, electrolysis, and individual electrode control in large arrays.

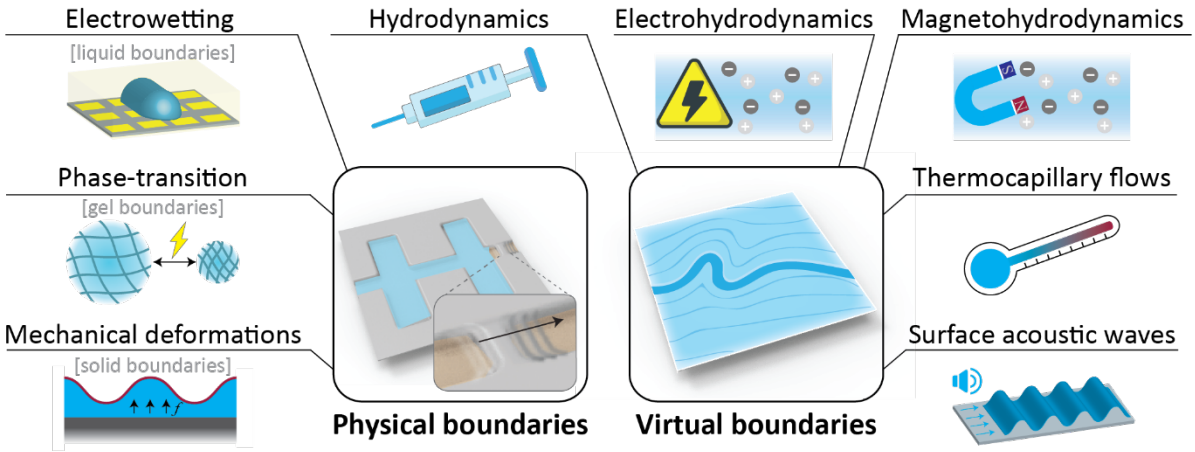


Figure 4 | Potential mechanisms for dynamic manipulation of physical and virtual boundaries. We chose to focus on mechanisms that have been studied extensively and have proven practical feasibility, but have not yet been utilized for reconfigurable microfluidics. The most direct form of reconfiguration is by manipulating physical boundaries. Such boundaries can be solids as in the case of a deformable elastic sheet, gels such as phase-transition hydrogels, or immiscible liquids as in the case of water in oil channels. An alternative form of reconfiguration is by applying surface or body forces to the liquid itself, thus forming virtual boundaries. Such forces can arise through the interaction of ions with electric and/or magnetic fields as in the case of electrohydrodynamics or magnetohydrodynamics, through non-uniform surface tension as in the case of thermocapillary flows, or through transfer of momentum with or without mass as in hydrodynamics and surface acoustic waves. We believe that further research and development of these mechanisms could lead to the creation of advanced systems with unique functionalities.

5. Different mechanisms - common challenges

A common challenge in the implementation of reconfigurable microfluidic platforms, regardless of the physical actuation mechanism, is the ability to achieve high spatial resolution while providing sufficient force within a short actuation time.

The spatial resolution, or number of degrees of freedom, ultimately dictates the functionality of the device. In analogy to displays, the ultimate desire is to achieve a 'high-definition' actuation density, in the order of 1,000,000 actuators per cm^2 (10x10 µm 'pixels'). However, even 10,000 actuators/cm^2 would provide substantial functionality and is yet very difficult to implement and has not been attained to date. One of the greatest challenges is the ability to address each actuator individually. In displays, this is

typically done by scanning over the rows and columns of the display matrix, and using per-pixel circuitry to maintain the pixel active until it is addressed again. Unfortunately, this methodology cannot be directly applied to the majority of microfluidic actuation mechanisms, as those rely on substantially higher power per pixel, which is not supported by standard microelectronics. Thus, in tandem with the development and miniaturization of the actuators, a significant effort of the community is required to integrate specialized high-power CMOS processes with microfluidics. Alternatively, the unique and diverse physical mechanisms that could be used in reconfigurable microfluidics also provide opportunities for other large-scale control approaches. For example, using photosensitive materials on-chip may allow to decouple the control layer from the chip itself and use an external light-projection system, which is inherently high resolution, to project a desired configuration onto the chip. The photosensitive materials could trigger any number of subsequent physical mechanisms, from conductivity changes for implementing switches, through heating for inducing phase changes, to changing mechanical properties to drive direct deformations.

Along with spatial resolution requirements, the ideal reconfigurable microfluidic device should also be able to switch from one configuration to another sufficiently fast. For cellular studies the required time scales are relatively long, posing no particular challenges to the response time. However, applications in separation, sorting, or synthesis, particularly at high throughputs, require fast response times – ideally in the millisecond range. For methods relying on electric or magnetic fields, the response time is typically in the order of tens of milliseconds. However, for methods using phase-change materials or temperature gradients, the response time is significantly longer, in the order of hundreds of milliseconds to seconds. This presents an opportunity for chemists and material scientists to contribute to the development of new types of responsive materials. Such materials should not only have a sufficiently fast response time, but also provide sufficient force to withstand pressures of at least 0.1-1 atmospheres typically found in microfluidic systems.

6. Concluding remarks

The concept of lab-on-a-chip is often presented in analogy to microelectronics, aiming to revolutionize chemical and biological analysis in the same way that microelectronics has revolutionized information technology. However, in contrast to microfluidics, microelectronics evolved with a strong emphasis on reconfigurability and scalability, i.e. a single chip capable of changing its function. One of the most important aspects in reconfigurability is that it allows users to define the functionality of the chip and create novel applications and uses, without having to possess expert knowledge about the underlying hardware or physical mechanism driving it.

Microfluidics that is based on rigid structures has already made a tremendous impact on chemical and biological analysis. However, because the design of novel applications is still in the hands of microfluidic experts, traditional microfluidics did not become a standard tool in the hands of practitioners in other fields. We believe that enabling true reconfigurability is key for the translation of microfluidics from this community to the user community and for the much-anticipated explosion in applications.

In this perspective, we reviewed some of the technologies that we believe can serve as the baseline for reconfigurable platforms. It is by no means an exhaustive list, and we are aware that it is very likely that many other mechanisms, at different stages of development, could be equally relevant. We do not know from what particular field or discipline the ‘solution’ for reconfigurable microfluidics will arise. It is as likely

to come from engineering disciplines - such as micromechanics or microelectronics, from physics - such as fluid mechanics or photonics, or from chemistry - such as stimulus responsive materials or zeta potential manipulation. At the same time, the most significant impact for such a platform is clearly in the biosciences. Regardless of the choice of mechanism, the vision of a reconfigurable microfluidic platform provides ample opportunities for innovation to researchers in a variety of disciplines. We call on the community to join us in this effort.

Acknowledgements

This perspective was greatly influenced by many discussions with Prof. Herbert Shea (EPFL) in the context of a joint research proposal. F.P., V.B., and G.V.K. acknowledge E. Delamarche, and H. Riel for their continuous support. Finally, we thank L. Rudin for proof-reading the manuscript. This project has received funding from the European Research Council under the European Union's Horizon 2020 Research and Innovation Programme, Grant agreement 678734 (MetamorphChip). G.V.K. gratefully acknowledges funding from a SNF grant (CRSK-2_190877). F.P. gratefully acknowledges the BRIDGE Proof-of-Concept program, project number 40B1-0 191549, funded by Innosuisse and the Swiss National Science Foundation.

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