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Open Microfluidic Capillary Systems

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Abstract

Open microfluidic capillary systems are a rapidly evolving branch of microfluidics where fluids are manipulated by capillary forces in channels lacking physical walls on all sides. Typical channel geometries include groves, rails or beams, and complex systems with multiple air-liquid interfaces. Removing channel walls allows access for retrieval (fluid sampling) and addition (pipetting reagents or adding objects like tissue scaffolds) at any point in the channel—the entire channel becomes a 'device-to-world' interface, whereas such interfaces are limited to device inlets and outlets in traditional closed-channel microfluidics. Open microfluidic capillary systems are simple to fabricate and reliable to operate. Prototyping methods (e.g., 3D printing) and manufacturing methods (e.g., injection molding) can be used seamlessly, accelerating development. This Perspective highlights fundamentals of open microfluidic capillary systems including unique advantages, design considerations, fabrication methods, and analytical considerations for flow; device features that can be combined to create a 'toolbox' for fluid manipulation; and applications in biology, diagnostics, chemistry, sensing, and biphasic applications.

Graphical Abstract

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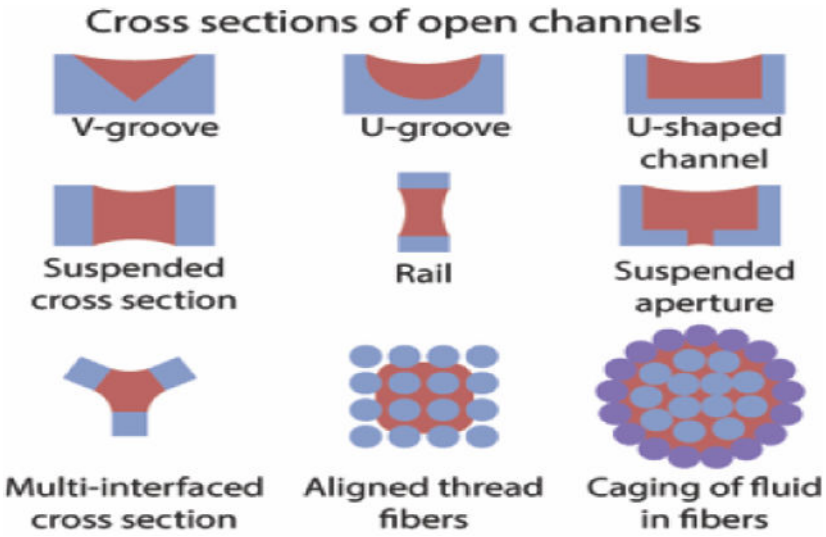

INTRODUCTION

Over the last three decades, the field of microfluidics has evolved toward improved accessibility and ease of fabrication; from the initial revolution of soft lithography[1] to the development of paper microfluidics[2–5] and the current push toward 3D printed and manufacturable devices,[6–8] microfluidics has evolved beyond an academic endeavor to a field that is used for biology, diagnostics, and many commercial applications. One approach toward increasing accessibility that has been gaining traction over the last decade uses open microfluidic capillary systems, which control fluid in microfluidic devices that contain open air-liquid interfaces without requiring external actuation or pumping. This Perspective will focus on open microfluidic capillary systems, navigating their implementation and uniquely enabled applications.

The progression of microscale devices from traditional closed microfluidics to open device embodiments, including open microfluidic capillary systems, is illustrated in Figure 1. Traditional closed devices include a fully enclosed channel, with fluids actively pumped into the channel via tubing that is sealed to the channel inlets (Figure 1A). The move toward semi-open channels, which often include an open inlet (Figure 1B) to a closed channel, allowed fluids to be introduced into the device using a simple pipette, eliminating the need for specialized fluidic pumping equipment.[9] In semi-open channels, fluid can be directed by active pipetting or by passive, surface tension driven methods such as ‘passive pumping’.[10, 11] ‘Open-space’ microscale devices[12, 13] include open microwells and patterned droplets,[9,14,15] as well as microfluidic probes and fluid guiding systems, where part of the fluid path is not bound by a channel—often for applications where the fluid is brought in contact with a biological substrate[16–22] (Figure 1C). ‘Open microfluidic capillary systems’ are an extension of these microfluidic developments that merge the accessibility of open systems with the precision and convenience of capillary driven flow (Figure 1D). In this Perspective we will focus on open microfluidic capillary systems; the fields of semi-open devices,[9]

'open-space' microfluidics,[12, 13] fluidic patterning based on wettability,[9] and digital microfluidics[26] have been reviewed previously.

Open microfluidic capillary systems have emerged as powerful tools with broad applications demonstrated by laboratories around the world in cell culture, sample collection and preparation, metabolite and protein assays, and interfacial chemistry (Figure 2). Different types of open microfluidic capillary configurations are possible, ranging from simple channels devoid of a ceiling (Figure 2C and 2D), to open 'rails' in which fluid flows along two ridges and is exposed to two air-liquid interfaces (Figure 2A), to paper- and thread-based devices in which fluid travels along patterned regions of fibrous materials (Figure 2E and 2F). The conditions for flow in open microfluidic capillary systems can broadly be determined by the 'spontaneous capillary flow' equation (Equation 1; see 'Analytical Considerations'), which relates the ability of a fluid to flow in an open channel with the channel wettability (for a given material and liquid of interest) and channel geometry. Open microfluidic capillary systems are generally simple to manufacture, compatible with a broad range of manufacturing techniques (soft-lithography, 3D printing, micromilling, injection molding, etc.), making them a method of choice for point-of-care diagnostic and consumable applications. This Perspective outlines (1) unique advantages of open microfluidic capillary systems, (2) types of systems, including different channel cross-sections and 'virtual' channels with multiple air-liquid interfaces, (3) analytical considerations for fluid flow in open systems, (4) features of open microfluidic devices that can be combined to create a 'toolbox' for fluid manipulation, (5) applications, and (6) open biphasic systems, a new frontier in open microfluidics.

TYPES OF STRUCTURES

Open microfluidic capillary systems span a large spectrum of geometries and embodiments. The simplest of these are grooves creating a channel without a ceiling, which we refer to in this section as "single air-liquid interface" channels. Creating more complex cross sections containing two or more air-liquid interfaces along the fluid path adds additional functionality and access.

Concus-Finn filaments (or capillary filaments).

Prior to describing open microfluidic structures, we will first examine capillary filaments, which have been studied historically by Concus and Finn and form a fundamental basis for manipulating fluids in open systems. Capillary filaments, also known as Concus-Finn filaments, are surface-tension driven fluid filaments that form in wedges at the intersection of two surfaces.[32, 33] These filaments often precede the bulk capillary flow in rectangular microchannels[33–36] but sometimes extend alone.[37] The formation of these filaments is dependent on the angle of the wedge and contact angle of the fluid, and the equation for this was derived by Concus and Finn.[32] It can be shown that the conditions for formation of Concus-Finn filaments are similar to those for an open-flow in a V-groove,[38] and follow the spontaneous capillary flow (SCF) equation (Equation 1) detailed further in this Perspective. While these types of filaments are similar to open microfluidic flows, their cross-sectional

size can vary over time and be difficult to control, limiting their direct application in microfluidics.

Capillary filaments can be a drawback in the fabrication of microsystems due to their ability to trigger leaks, prevent the intended pinning in capillary valves,[38] or alter flow characteristics.[25] In other cases, capillary filaments provide an advantage due to their fast velocity for aqueous liquids, including for very viscous fluids such as whole blood or alginates.[39, 40] Further, capillary filaments can be utilized to drive capillary flow around obstacles in a channel.[41] The formation of capillary filaments can be controlled or prevented by altering the cross-section of channels and using rounded corners instead of sharp corners.[25]

Single air-liquid interface.

The simplest open microfluidic capillary channel is composed of three walls with a single air-liquid interface (Figure 3A). This type of channel represents a relatively seamless step away from closed microfluidics as most microfluidics start from patterning grooves in a planar material, followed by sealing of the channel for closed systems. In that sense, these types of channels can be simply fabricated using current milling,[25, 42–45] embossing,[29, 46] etching,[47, 48] or injection molding techniques[7, 49, 50] with minimal modifications post-fabrication.

Configurations for open channels that contain a single air-liquid interface include wedges and grooves, where grooves may be V-shaped or U-shaped. The behavior of fluids in both U-grooves[47, 51, 52] and V-grooves[53–55] as well as the shapes of the interfaces in these grooves[35, 56] have been widely investigated. In recent years, rectangular U-grooves have become widely used for microfluidic devices[25, 29, 48, 52, 57–59] due to the ease of fabrication in comparison to V-grooves.

Two air-liquid interfaces.

Channels where there are two air-liquid interfaces are known as rails or suspended channels, as the fluid is held by two opposing faces[8, 27, 28, 41, 60–64] (Figure 3B). One of the first rail microfluidic devices reported in the literature is that of Satoh and coworkers,[62] who used electrowetting to move aqueous fluid from one electrode to the next. Recently, channels known as suspended microfluidics have been developed where the ceiling and floor of the channel are absent.[41]

Two air-liquid interface systems provide advantages over single air-liquid interface devices, but also present some challenges. As mentioned previously, control over aspect ratios will affect generation of SCF and pumping force. In suspended systems, an aspect ratio greater than 1 (i.e., if the width is greater than the height) will prevent SCF.[38, 41] In single air-liquid interface systems, generation of flow is not as constricted. Interestingly, regardless of contact angle, flow in suspended channels will not form capillary filaments;[38, 41] this deviates from closed systems or single air-liquid interface systems, where capillary filaments may form depending on geometry and contact angle. Suspended channels also provide an additional interface for access to the system, such as by pipet or by interaction with another immiscible flowed liquid for liquid-liquid extraction;[41] this may allow for simpler multiplexing

opportunities compared to U-grooves. There are also applications in creating a gel or liquid barrier between two environments for which these types of channels are beneficial.[63]

Multiple air-liquid interfaces.

Microfluidic devices that utilize multiple air-liquid interfaces, as depicted in Figure 3C, have only recently been discussed theoretically.[44, 65] However, devices that utilize fibers, such as paper or thread devices, contain multiple air-liquid interfaces[2–4, 44, 66, 67] and thus will be discussed briefly here. The wicking liquid in these configurations is partially in contact with the surrounding air or vapor on multiple fronts[44] and guided by beams (e.g., fibers), establishing that paper and thread-based microfluidics fit under the broad definition of open microfluidic capillary systems. Microporous matrices made of fibers are very favorable to capillary flows once the fibers are lyophilic due to the large surface area of the fibers.[68, 69]

Flow within paper devices may be one, two, or three-dimensional. Fu et al. determined that flow of a liquid through one-dimensional paper (i.e., paper strips) follows the Lucas-Washburn-Rideal (LWR) equation;[69] for two-dimensional paper channels, an adaptation of the hydraulic diameter on the LWR law has been proposed.[70] Recently, Martinez et al. have layered paper with hydrophobic and hydrophilic sections to generate three-dimensional channels.[30] At the present time, the use of threads for microfluidics[66, 67] is less developed than paper; however, an advantage of thread-based microfluidics is the ability to transport liquids in a 3D geometry without large modifications or layering.[44]

The physics of wicking of threads has recently been the subject of many investigations; [44, 71–73] hydrophilic treatments of polymeric fibers have also been developed.[74] Berthier et al. demonstrated the theoretical ability to ‘cage’ the flow of liquid within a thread-based system using Surface Evolver[75] (redrawn in Figure 3Ciii). By creating an outer layer of hydrophobic fibers while the inner fibers remain hydrophilic, the liquid is effectively caged within the fiber bundle; this could be useful for prevention of contamination.[44] Interestingly, it has been found that while an increase in numbers of fibers will increase the capillary force, with as few as 25–30 fibers SCF can be generated in liquids with a contact angle of up to 75°; thus, it is not necessary to make larger bundles for most applications.[38] That transition point represents the stage at which one can use the SCF equations (for simpler systems) or the generalized LWR equation. Although paper and thread microfluidics are of great interest, detailed reviews already exist for these domains and further discussion on these methods will be limited in this Perspective.[2, 3, 66]

ADVANTAGES OF OPEN MICROFLUIDIC CAPILLARY SYSTEMS

The configuration of open devices, compared to closed or semi-open microfluidic systems, provides numerous advantages including: simplification of manufacturing techniques and surface modification; significant improvement in device reliability through elimination of failures resulting from bubble formation; and the unique ability to access the fluid at any point in the channel in order to input or sample fluid. These advantages are highlighted in Figure 4 and discussed here.

Fabrication.

Traditional closed microfluidic systems necessitate multi-step fabrication in order to generate a closed channel. The channel geometry/features are typically fabricated using soft lithography,[27, 77, 78] micro-milling,[42, 43, 79–81] injection molding[7, 8, 49] (Figure 4A), or hot embossing.[29, 46] The device is then enclosed by bonding a flat layer to the featured layer using heat-based lamination, solvent bonding, ultrasonic or laser welding, or adhesives (Figure 4Aii).[49, 82–84] The bonding step has the potential of altering the channel geometry, can be a source of variability, and may lead to the introduction of contaminants that can affect the channel contents (e.g., solvents or adhesives used for bonding). Further, the bonding process is often a trade secret of microfluidic manufacturing companies, making it difficult to transpose to a different manufacturer and thus leading to a bottle-neck and risk when scaling-up production volumes. Open channel designs streamline fabrication as the device can be used directly after the first fabrication step, without a bonding step. Additionally, open microfluidics simplifies the prototyping of microfluidic devices by allowing simple and direct use of 3D printing for fabrication. While 3D printing has been demonstrated for closed microfluidic systems, complex solutions to drain uncured polymer are required.[6] Open channel designs allow for decreased fabrication time and increased reproducibility across devices, both during prototyping and large-scale manufacturing.[7]

Surface modification.

Surface modification can be essential to the operation of a microfluidic channel. Many surface modification techniques have been developed, including plasma pretreatment and silanization, chemical vapor deposition, UV irradiation, photochemical grafting, nanomaterial deposition, and atomic layer deposition, amongst others.[85, 86] Some key methods of surface preparation require exposure to an environmental treatment, such as plasma treatment to render the surface wettable[37, 41, 46, 60, 61] or chemical vapor deposition to protect the material from solvents[41, 51, 61, 87, 88] (Figure 4B). In closed systems, the surface modification may be performed before bonding, in which case it may affect the bonding efficiency or be affected by the bonding process (e.g., temperature or solvents).[86] Alternatively, if the surface modification is performed after the bonding step it is challenging to ensure homogenous surface modification.[86, 42, 89] It has been demonstrated that the quality or efficiency of surface modifications may decrease as a function of the distance to the inlets, as shown in the graph presented in Figure 4Biii.

In open devices, as every point in the channel is readily accessible, surface modification can be applied homogeneously and reliably, which uniquely positions open devices to receive chemical vapor deposition, a more difficult method to employ for closed devices .[41, 86, 90] Casavant et al. demonstrated chemical vapor deposition of Parylene C on polydimethylsiloxane (PDMS) to prevent absorption of hydrophobic molecules such as cortisol,[41] which Memic et al. noted as a key advance enabled by the Casavant et al. open systems.[90] Further, Barkal et al. demonstrated a chemical vapor deposition of Parylene C on polystyrene to prevent chloroform solvent from degrading polystyrene when using open microfluidics for biphasic metabolite extraction.[39]

Accessibility.

A unique feature of open microfluidics is the ability to access the fluid at any location along the fluidic path. Researchers are able to add or remove components in their open system with common laboratory tools at any point in the experiment (Figure 4C).[25, 91] For example, open microfluidic systems have been developed allowing the formation and retrieval of spheroids using a simple micropipette.[91] Access to channels is not limited to pipets: tweezers can also be used to introduce or remove tissue scaffolds, similar to manipulation of tissue scaffolds in well plates.[91] Recently, Lee et al. pipetted an immiscible aqueous droplet in a flow of organic solvent, followed by addition of a second fluid to the droplet via micropipetting further down the channel.[25]

Bubble formation.

Bubble formation (Figure 4D) has always been a nemesis of microfluidic operation, as bubbles have the potential of affecting flow characteristics[92] or even leading to critical failures. In cell culture experiments, air bubbles may also decrease cell viability.[93] Multiple specific systems or designs have been engineered to prevent bubble formation or trapping in closed systems (Figure 4Diii).[62, 76, 92, 93] In the case of open microfluidics, due to the presence of an air-liquid interface along the fluidic path bubbles are able to escape, and thus special design features are not necessary (Figure 4Di).[38]

Disadvantages.

Evaporation is a challenging factor for microfluidic systems that have any degree of open air-liquid interfaces.[94, 95] In the case of open microfluidic capillary systems, an air-liquid interface is more prominent as it is situated along the entire fluidic path, leading to higher evaporation that must be accounted for or counteracted. This is exacerbated with the use of volatile solvents that evaporate rapidly. However, evaporation in open systems can be mitigated: surrounding a device with sacrificial droplets of water significantly reduces evaporation; [94] further evaporation reduction is achieved when the system is placed in a secondary or tertiary humidified container (such as a dish or tray containing ~10–50 mL of water). An additional consideration is that the increased air-liquid interface increases gas exchange with the air which can lead to further challenges, such as a change in dissolved gases in the fluid being shuttled in the microfluidic device. In some cases, the increased gas exchange can be advantageous (e.g., supplying oxygen to cells in culture). Further, to mitigate both evaporation or gas exchange effects, open microsystems can be placed in confined environments such as a cartridge or transportation box.

Some researchers are concerned that an open channel can result in leaking/loss of fluid. However, the dominance of surface tension forces over gravitational forces confines liquids within the channels, as can be seen in suspended microchannels where both the floor and ceiling are removed.[41, 79] The proper design of open channels, using the spontaneous capillary flow equation detailed further on in the text (Analytical Considerations), can ensure a strong capillary force, maintaining the liquid within the channel even when the device is manipulated and transported. Further, design features can be added to ‘pin’ the fluid, preventing leaking.

Finally, as liquids in open microfluidic capillary systems are driven by surface-tension based forces, there is a physical limitation on the range of pressures that can be generated. While higher pressures can be generated by simply reducing the dimensions of the channel, this also comes with increased fluidic resistance. These limitations extend to general challenges of using electronic actuators in the fluid path, such as valves, pressure sources, etc. However, as the field of open microfluidic capillary systems continues to evolve, advanced methods to control surface tension are demonstrating the potential to recreate many of the traditional closed microfluidics control features, some of which are highlighted later in this Perspective.

ANALYTICAL CONSIDERATIONS

Designing open channels requires careful consideration of channel geometry to enable and control capillary flow. The hydrophilic surfaces along the cross-section of a channel increase the ability to flow aqueous fluids, while the hydrophobic or free-standing air-liquid surfaces prevent the occurrence of flow. Design guidelines and equations have been developed to determine if spontaneous capillary flow is possible in a given channel. In this section, we present a condition for flow in a simple monolithic open microchannel, where all surfaces have the same contact angle with the fluid, as well as a generalized condition for flow in open systems that may have multiple different materials with differing contact angles. Further, we detail some analytical considerations of velocities in open microfluidic systems.

Conditions for capillary flow in open microfluidic channels.

Spontaneous capillary flows are defined as flows with no external pressure at the origin or throughout the path of the fluid, entirely driven by the capillary force of liquid in the channel and neither hindered nor helped by other forces such as hydrostatic pressure, gravity, or other sources. These type of flows are typically used in open microfluidics as the addition of pressure at the inlet can cause fluids to overflow the boundaries of the open channel. Open microfluidic capillary systems are also typically designed to operate on a flat surface where the inlet of fluid is at the same level as the channel itself, making capillary forces the unique forces acting on the fluid.

The condition for SCF has been derived by Casavant et al.[41] and defines the conditions at which it is energetically favorable for a fluid to advance in an open microchannel. If the condition is not met, the fluid will not flow in the channel without any additional input (e.g., hydrostatic pressure, gravity); if the condition is met, flow in the open microfluidic channel occurs. For a monolithic channel (Figure 5A), where every solid surface has the same contact angle, θ, and for which the length of air-liquid interfaces along the perimeter of the cross section is defined as the free perimeter, p_f, while the length of liquid-solid interfaces along the perimeter of the cross section is defined as the wetted perimeter, p_w, the condition for SCF is presented in Equation 1:[41, 65]

$$\cos\theta > \frac{p_f}{p_w} \qquad \text{Equation (1)}$$

The two typical approaches to apply Equation 1 to an experimental design are (1) to determine the minimum aspect ratio possible given a known contact angle or (2) to determine the maximum contact angle that would still enable SCF when given set channel dimensions. Box 1 demonstrates how these approaches can be applied using two different channel cross sections. Further, it is noteworthy that the equation describing the conditions for SCF extends to standard geometries that preceded the development of microfluidics, such as a closed capillary tube and filament flows in a wedge as described by Concus and Finn in 1969.[32]

The condition for SCF has been generalized to channels that may have multiple surfaces, each with different contact angles with the fluid (Figure 5B). This can be the case in rail or suspended microfluidics where a channel is defined between two different materials[63] or in the case of thread microfluidics where different threads can have different coatings.[44] In the general case where a channel is comprised of multiple surfaces with different materials or surface chemistries with unique contact angles, the condition for advancement of a fluid in the channel is given by a condition on the Cassie Angle, $\boldsymbol{\theta^*}$ (Equation 2a), referred to as the Generalized Cassie law (Equation 2b), where $\boldsymbol{p_{w,i}}$ and $\boldsymbol{\theta_i}$ are the cross-sectional lengths and contact angles for each material, p_f is the cross-sectional length of free air-liquid interfaces, and p is the total perimeter of the cross-section of the microfluidic channel.[38] It is convention that the contact angle with air is 180°. In Equation 2, $\boldsymbol{\theta^*}$ defines the Cassie angle. SCF occurs when $\cos \boldsymbol{\theta^*} > 0$.

$$\boldsymbol{\cos}\theta^* = \Sigma_i \boldsymbol{\cos}(\theta_i)\frac{p_{w,i}}{p} + \boldsymbol{\cos}(180°)\frac{p_f}{p} \quad \text{Equation (2a)}$$

$$\boldsymbol{\cos}\theta^* > 0 \quad \text{Equation (2b)}$$

Capillary flows can be enhanced by imposing a pressure at the inlet (e.g., hydrostatic pressure, Laplace pressure)[61] or an increased capillary force on the meniscus (for example electrowetting-on-dielectric, or EWOD).[62] The flow is then called an *enhanced* capillary flow (as opposed to *spontaneous* capillary flow). Importantly, the additional pressure must be smaller than the Laplace pressure at any location in the channel to prevent the fluid from overflowing the boundaries of the open channel.

Velocities in open microfluidic capillary systems.

The equations describing the conditions for SCF and the Generalized Cassie law are useful when designing open channels and determining if capillary flow can occur. These equations also give a qualitative idea of the magnitude of the capillary effects in the channel. However, they do not provide dynamic information on flow in open microchannels.

The Bosanquet equation is used to describe the dynamic behavior of flows in capillaries or porous materials.[96, 97] This equation is based on the balance between inertial, viscous, and capillary forces. In capillary driven systems, at the very beginning of the flow, friction is negligible because the surface area of the wetted walls is small; this is the inertial regime.[98] In the short-lived inertial regime, the travel distance, z, is proportional to time: $z \sim t$.

Subsequently, the flow is governed by the balance between friction and capillary forces[99–101] and can be described by the Lucas-Washburn-Rideal law (LWR) for the viscous regime. In the viscous regime, the travel distance is proportional to the square root of time: $z \sim \sqrt{t}$ (Figure 5C). A generalization of the LWR for arbitrary cross-section closed and open channels has been reported based on the Poiseuille friction of the flow.[37] The generalized LWR expression for the distance the fluid front has travelled, z, as a function of time, is provided by Equation 3,

$$z = \sqrt{\frac{\gamma}{\mu}}\sqrt{cos\theta^*}\sqrt{2\bar{\lambda}t} \quad \text{Equation (3)}$$

where $\bar{\lambda}$ is the average friction length representing the equivalent friction along the walls in a cross section, γ is the surface tension of the fluid in air, and μ is the viscosity of the fluid. The evaluation of the average friction length can be done analytically in closed systems, however in open systems a numerical or experimental approach is often necessary.[25]

FEATURES OF OPEN MICROFLUIDIC CAPILLARY SYSTEMS

Open microfluidic capillary systems are typically passive systems by nature that do not integrate actuation elements, valves, or pumps. Despite this lack of external actuation, a number of passive methods–many of which are carried over from closed capillary systems–enable a high level of control over the fluids. The open aspect of the channels leads to some improvements or advantages over closed systems. We review these features here.

Capillary pumps.

Flow in open microfluidic systems relies on the capillary advance of the fluid in the channel and is intrinsically limited in volume and in duration (Figure 6A). Further, as the length of the channel increases, the flow rate decreases. The duration and stability of the pumping can be increased using capillary pumping techniques. Capillary pumping techniques can be grouped in two categories: the first relies on using a wicking material that can absorb a large volume of fluid (such as a cotton or paper pad), while the second relies on multiplexing a large number of discrete channels to allow more volume of fluid to flow through the system while each channel remains short in length (Figure 6B).[102, 103] An example of this could be the addition of many capillary tubes or a bundle of fibers to the end of an open channel, increasing the capillary force and thus the flow. Capillary pumping has been used in a wide variety of open microfluidic applications,[25, 27, 29, 30, 48, 104, 105] including expansions to generate continuous flow using evaporation,[59] gravity, or an absorbent pad at the end of a microfluidic channel.[105, 106]

Capillary valves.

The development of valves that operate based on surface tension forces, called capillary valves, enabled passive control of a device without the need for complex fabrication techniques or off-chip instrumentation.[103, 107, 108] These autonomous valves rely on the pinning of a liquid within a channel at a location where the geometry expands rapidly, or where the wettability of the surface changes abruptly such that advancement of the fluid is energetically unfavorable. Two types of capillary valves have been designed, known as stop

and trigger valves. Stop valves are created by abruptly enlarging the channel to create a pinning line (Figure 6C),[103] and prevent further flow along that path. Trigger valves connect a second liquid to a stop valve; when the second liquid comes in contact with the stopped fluid, the valve is triggered and flow of both fluids occurs (Figure 6D).[103] While capillary valves have been developed and used in traditional closed-channel systems,[109] these valves have recently been characterized in open and suspended channels[44] and may be used for timed interaction of fluids. Open microfluidics simplifies the creation of robust capillary valves as it is much simpler to create a 'step' valve in which both the width and depth of the geometry changes.[102] Creating such a valve in closed microfluidics would typically require complex fabrication to distance the first section of the valve both from the floor and ceiling of the second section of the valve.

Velocity control.

As flow in open microfluidic systems is driven by the capillary action of the fluid in the channel, regulating the velocity of the flow requires careful control of channel geometry in various areas of the device. Delay valves control the progression of a liquid by introducing the liquid to a widened channel, forcing the fluid front to spread and lowering the velocity (Figure 6Ei).[80, 103] An enlarged channel geometry will reduce fluid velocity; however, once the fluid has advanced beyond the enlarged section, the velocity will return to approximately its original value.[80, 45] Alternatively, constrictions of channels can act as flow resistors by decelerating the fluid front for the whole pathway of the fluid downstream of the constriction.[80, 45] These small changes in dimensions can be used to regulate fluid velocity within a microchannel without the use of auxiliary equipment.[45] Delay valves and delay lines (Figure 6Eii) can thus be fabricated to control interactions of fluids and allow mixing of reagents at specified time points.

APPLICATIONS OF OPEN MICROFLUIDIC CAPILLARY SYSTEMS

Open microfluidic capillary systems offer unique opportunities to directly deliver and access biological and chemical samples at any point in the device using standard tools (e.g., pipettes, tweezers), enabling experimental designs, workflows, and analysis methods that are infeasible with traditional closed microfluidics. Further, device fabrication is simplified, allowing the use of thermoplastics without further bonding which is enabling for cell culture, and low-cost disposable materials like paper and thread which is particularly enabling for diagnostics in low resource settings. This section highlights some of the applications of open microfluidic capillary systems that capitalize on these unique advantages.

Biological applications.

Numerous open microfluidic capillary devices have been developed for biological applications including cell signaling studies,[27, 81, 41, 39, 91, 63, 110, 111] organotypic models,[28, 81, 91, 112] metabolomics,[41, 39] multikingdom studies,[39, 63] biomimetic models,[28, 81] and cell migration studies.[61] Open systems allow direct access to cell cultures for medium changes or treatment with substances[41, 91, 63] or the addition of solid substrates and tissue culture scaffolds using simple tweezers.[81, 91] Additionally, since open microfluidic devices do not require peripheral equipment (e.g., pumps), they can be placed inside traditional

incubators for cell culture experiments and imaged on a standard microscope stage. As discussed previously in the ‘Fabrication’ section, open devices alleviate a bonding step inherent to closed devices. This is particularly important for cell culture applications since devices can be fabricated directly from polystyrene, the material most commonly used for cell culture,[113] using micromilling[42, 43, 81] or injection molding.[7, 8]

More advanced features of open microfluidic capillary systems have also been utilized for biological applications. Ragelle et al. utilize surface tension to create thin windows of cell-laden hydrogel in 3D printed scaffolds.[114] Casavant et al. and Humayun et al. used SCF to create horizontal suspended gel membranes for cell culture, effectively making a microscale version of a transwell membrane with the added advantages of membrane generation on demand, easy membrane ‘fabrication’ with a simple gel pipetting step, and the ability to position membranes anywhere within a device by using the design rules of the SCF equation (Figure 7A and B).[41, 81] Using suspended gel membranes, Casavant et al. developed a microscale cellular invasion assay in a 3-layered microfluidic system in which the suspended gel layer served as a separator between an upper open channel containing cancer cells and a lower open channel containing chemoattractants, where both the upper and lower channels were filled using SCF (Figure 7A).[41] Similarly, Humayun et al. utilized suspended gel membranes to obtain a biomimetic environment composed of collagen I and Matrigel, as opposed to the polymeric membrane present in transwells; additionally, these suspended gels could be removed from the device (after cell fixing) for imaging (Figure 7B).[81] SCF may also be used to pattern channels of cell cultures[27, 60] or vertical hydrogel walls;[8, 27, 63, 61] these tools enable multi-cultures of varying cell types at distances relevant for cell signaling. Lee et al. utilized the creation of spatially defined vertical hydrogel walls to study quorum sensing of *Escherichia coli*.[27] The open nature of these systems allows for imaging and collection of secreted metabolites and proteins at any time point without disrupting the cultures.[81, 41, 39, 91, 63]

Diagnostics.

Many point-of-care devices fall within the definition of open microfluidic capillary systems: paper and thread devices utilize multiple air-liquid interfaces, as discussed in the ‘Types of Structures’ section. Paper and thread devices facilitate wicking of liquids through the device without the need for pumps or complex fabrication methods, simply requiring the user to add liquid to the device *via* a pipet or capillary tube. Additionally, the open aspect of these microfluidic devices often enables direct observation of a qualitative result, enabling quick diagnostic results without the need for an imaging device.[29, 30, 73, 115] Diagnostic open microfluidic devices have been developed for separation and analysis of blood,[40, 73, 105, 106, 116, 117] detection of glucose,[29, 30, 64, 67] enzyme-linked immunosorbent assay (ELISA),[118, 119] gel electrophoresis,[120] and as medical sensors.[67] Figure 7D provides an example of a pH sensor fabricated using thread, utilizing the wicking properties as well as simplified surface modification of threads enabled by the open features of the device.[67] While many diagnostic devices are fabricated using paper and thread, open devices using other materials such as plastics have been developed. Huet et al. developed an injection-molded device to determine blood type *via* blood cell agglutination (Figure 7E); as the device channel is pre-loaded with reagents and only requires loading a drop of blood, human

error is minimized.[50] The open V-groove channel transports undiluted blood, eliminating pretreatment of the blood and resulting in an autonomous assay.[50] Airborne contamination of samples can be a concern with open systems, and the risk of contamination can be mitigated by implementing multiple levels of containment or engineered housings around the open microfluidic device. A common practice includes placing the device in a primary container with a lid and then placing the primary container in a secondary container with a lid, providing two levels of protection from contamination. For more examples of microfluidic point-of-care devices, see reviews by Gervais et al. and Hu et al.[2, 108]

Chemistry, sensing, and other applications.

Open microfluidic capillary devices and principles have been used for applications including microscale chemical reactions, detection of compounds both qualitatively and quantitatively, [62, 48, 57, 58, 121, 104, 122] and utilization in zero gravity environments such as in space.[34, 123] The presence of an open channel and thus at least one air-liquid interface allows for gas exchange, direct visualization of results, and manipulation of fluids that would require complex fabrication methods in closed devices. Piorek et al. developed a microfluidic chip that can detect the explosive small molecule 2,4-dinitrotoluene using surface enhanced raman spectroscopy (SERS) (Figure 7A).[58] This device uses the large surface area of the open air-liquid interface to exchange molecules from the gas phase into the aqueous phase; thus, the inherent properties of an open microfluidic capillary device facilitates trace detection of analyte molecules.[57, 58] Additionally, several sensing devices have been developed that utilize capillary forces for autonomous flow and direct visualization for an optical readout, enabled by the open access to the devices.[48, 121, 122, 104] Similarly, open microfluidic capillary principles have been used to address fluid manipulation in zero gravity[34] and develop bioreactors that rely on air-liquid interfaces.[123]

OPEN BIPHASIC MICROFLUDICS

Liquid-liquid extraction.

Open channel biphasic systems have recently been used for liquid-liquid extraction.[41, 39] In traditional liquid-liquid extraction of metabolites from cell culture, numerous flasks and large volumes of solvent are used; the ability to evaporate solvent from extracted metabolites is also a limiting factor in the workflow.[39] Open biphasic devices have been used to study culture conditions of multiple cell types, including mammalian,[41] fungal,[39] and bacterial cultures.[39] Careful control of immiscible fluids *via* open device features generates a stable biphasic interface, enabling extraction of metabolites by diffusion and direct access to collection of solvent with a pipette or automatic liquid handler (Figure 8A).[41, 39, 124] The open microfluidic devices designed by Barkal et al. and Casavant et al. give researchers the ability to use solvents not commonly used for liquid-liquid extraction, co-culture different cell types that are connected by diffusion, screen for novel metabolites, and reduce experimental time and materials used.[41, 39]

Open biphasic droplets.

Very little work has been performed on the generation of droplets in open microfluidic channels due to difficulty confining liquids with low surface tension within channels.[124]

Recently, Lee et al. designed a device to study the interactions of droplets with an immiscible solvent driven by capillary flow in an open channel (Figure 8B).[25] Theoretical work using the software Surface Evolver[75] predicted three behavioral modes of droplets pipetted into an open system; two of these behaviors were determined experimentally, along with a third behavior that was not predicted by the software. These modes are determined by various aspects, such as velocity of the carrier fluid and surface tension forces between the fluids; this work thus successfully characterized the behavior of droplets in open channels.[25] As more work is done to generate open biphasic systems,[125] direct access to droplets for addition or removal will become feasible, allowing access to chemical reactions or cell culture at any time.

CONCLUSIONS

Open microfluidic capillary systems are on a trajectory of continued growth. The ability to rapidly design and fabricate devices using 3D printing and micromilling facilitates prototyping and development in academic research labs. Open microfluidic capillary devices developed using these methods are then directly injection moldable, allowing scale-up to larger batch sizes with excellent fidelity across replicates, a key consideration when producing devices for biological and clinical research. The advent of rapid injection molding companies brings mold costs down to the $1000–5000 range (in contrast to costs in the tens of thousands of dollars for traditional injection molding), further extending the accessibility of open microfluidic capillary device production.[7, 8] Simple design principles, ease of prototyping, and the ability to ultimately manufacture open devices result in a low barrier to entry for commercial enterprises—both in biomedical startup companies and large scale companies and manufacturers.

There are numerous exciting research directions in the field of open microfluidic capillary systems, and several new publications have come out even in the course of writing this article. Future technological additions to the ‘open microfluidic toolbox’ include developing more advanced valving methods and enhancing capillary flow with actuation and pumping methods. Biphasic open microfluidic droplet platforms have just recently been conceived, and future work will bring many of the advantages and capabilities of closed-channel droplet-based microfluidics to open systems. Open microfluidic capillary devices with more than one air-liquid interface allow direct access to fluids in multiple directions, offering exciting possibilities to integrate pipetting systems and automation based on robotics. Similarly, the ability to create air-liquid interfaces in multiple directions presents new opportunities for dynamic and reconfigurable device assemblies fabricated by advanced manufacturing methods such as 3D printing. Finally, advances in our fundamental understanding of the physics of fluid flow in open systems have the potential to spawn new domains and applications in open microfluidic capillary systems.

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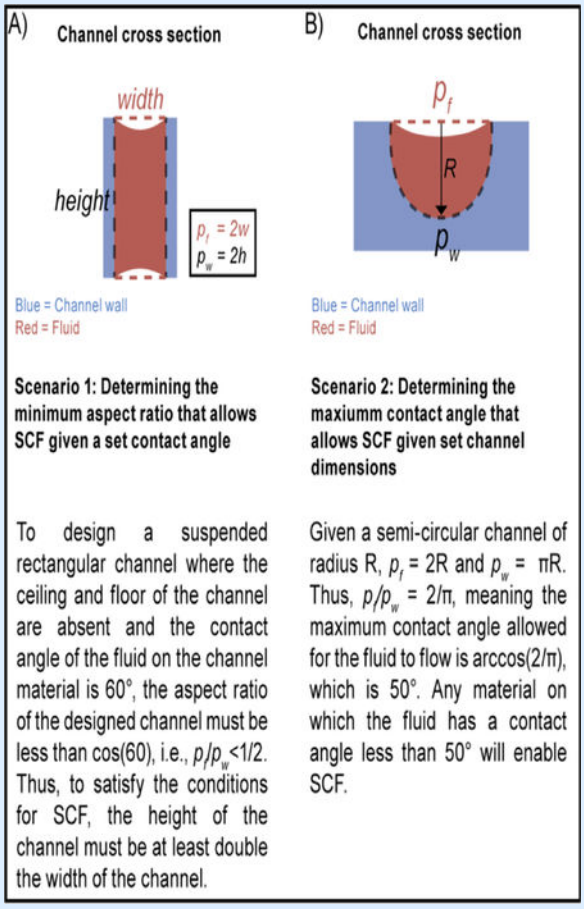
Box 1.

Applying Equation 1 to (A) design channel dimensions or (B) choose device materials. Two different types of channel cross sections are shown; this method holds across all channel cross sections.



Scenario 1: Determining the minimum aspect ratio that allows SCF given a set contact angle

To design a suspended rectangular channel where the ceiling and floor of the channel are absent and the contact angle of the fluid on the channel material is 60°, the aspect ratio of the designed channel must be less than cos(60), i.e., $p_f/p_w<1/2$. Thus, to satisfy the conditions for SCF, the height of the channel must be at least double the width of the channel.

Scenario 2: Determining the maxiumm contact angle that allows SCF given set channel dimensions

Given a semi-circular channel of radius R, $p_f = 2R$ and $p_w = \pi R$. Thus, $p_f/p_w = 2/\pi$, meaning the maximum contact angle allowed for the fluid to flow is arccos(2/π), which is 50°. Any material on which the fluid has a contact angle less than 50° will enable SCF.

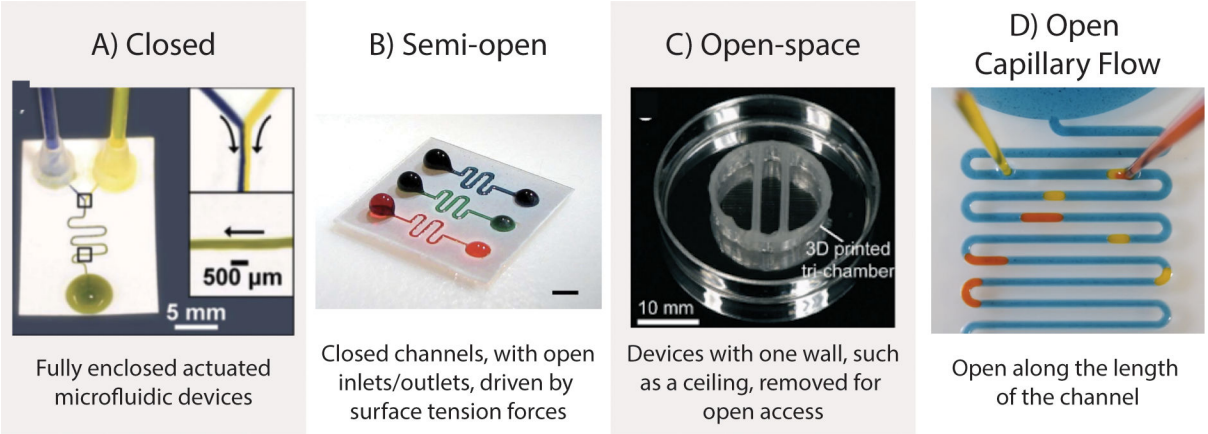


Figure 1.

Examples of different types of microfluidic devices, ranging from closed to open. A) A closed device with inlets connected to off-device syringe pumps to drive fluid through the channel. B) A semi-open device where the inlets and outlets are open and flow is driven by surface tension forces, referred to as ‘passive pumping’. C) An open-space device where cells may be seeded in different chambers and accessed directly by a pipette. D) An open microfluidic capillary system with pipettes adding yellow- or red-tinted droplets to the channel as the blue solvent flows *via* capillary forces. A) Reproduced with permission. Ref. 23. Copyright 2013, Royal Society of Chemistry. B) Reproduced with permission. Ref. 24. Copyright 2011, Royal Society of Chemistry. C) Reproduced with permission. Ref. 15. Copyright 2016, Royal Society of Chemistry. D) Reproduced with permission. Ref. 25. Copyright 2018, American Chemical Society.

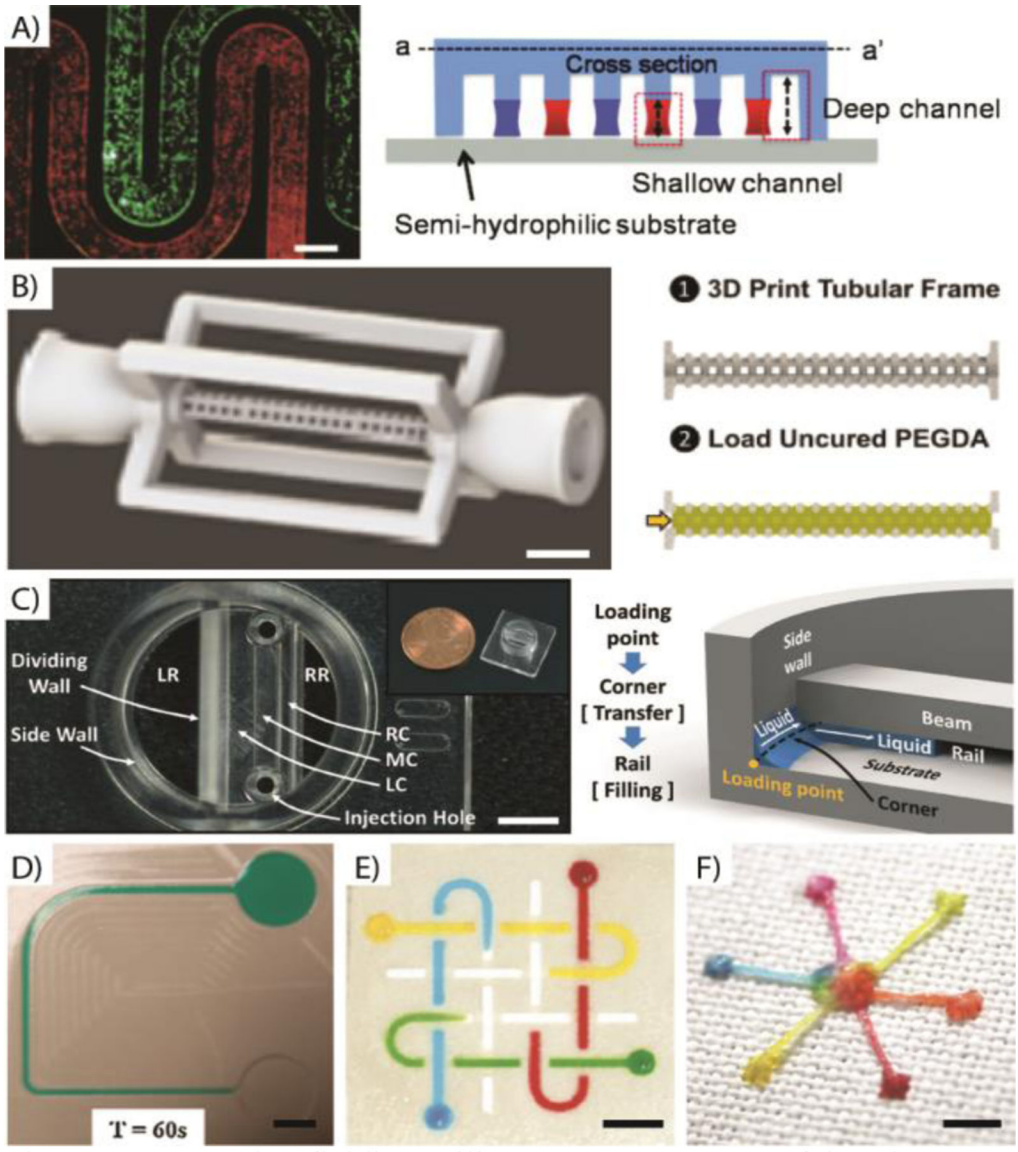


Figure 2.

Open microfluidic capillary systems are powerful tools across a large spectrum of fabrication techniques and embodiments. This figure presents a subset of the broad methods achievable using open microfluidic devices produced in different materials, including: A) Fluorescently labeled cells seeded in channels generated using rails of PDMS over a polystyrene substrate (cells are seeded in the regions labelled “shallow channel” in the cross section schematic). Scale bar is 200 μm. B) A 3D printed device that uses suspended microfluidics to create gels that have been polymerized into a biologically relevant configuration. Uncured gel is loaded through the side ports indicated by a yellow arrow to fill the 3D printed structure and suspend the gel throughout the tubular frame. Scale bar is 2 mm. C) Injection molded polystyrene device for multicell culture. Schematic shows liquid flow between two horizontal surfaces (labeled “beam” and “substrate” in the cross section schematic), a type of open channel. Scale bar is 2 mm. D) Colorimetric glucose

concentration analysis using hot embossed paper channels that are open on the top surface. Scale bar is 5 mm. E) Channels open on the top face designed in paper devices for glucose or protein assays that cross each other in different planes without mixing. Scale bar is 5 mm. F) Thread-based device for removal and collection of biofluids guided on a hydrophillic thread sewn into a hydrophobic fabric. Scale bar is 5 mm. A) Reproduced with permission. Ref. 27. Copyright 2010, American Chemical Society. B) Reproduced with permission. Ref. 28. Copyright 2017, IEEE. C) Reproduced with permission. Ref. 8. Copyright 2018, Royal Society of Chemistry. D) Reproduced with permission. Ref. 29. Copyright 2017, Elsevier. E) Reproduced with permission. Ref. 30. Copyright 2008, National Academy of Sciences. F) Reproduced with permission. Ref. 31. Copyright 2013, Royal Society of Chemistry.

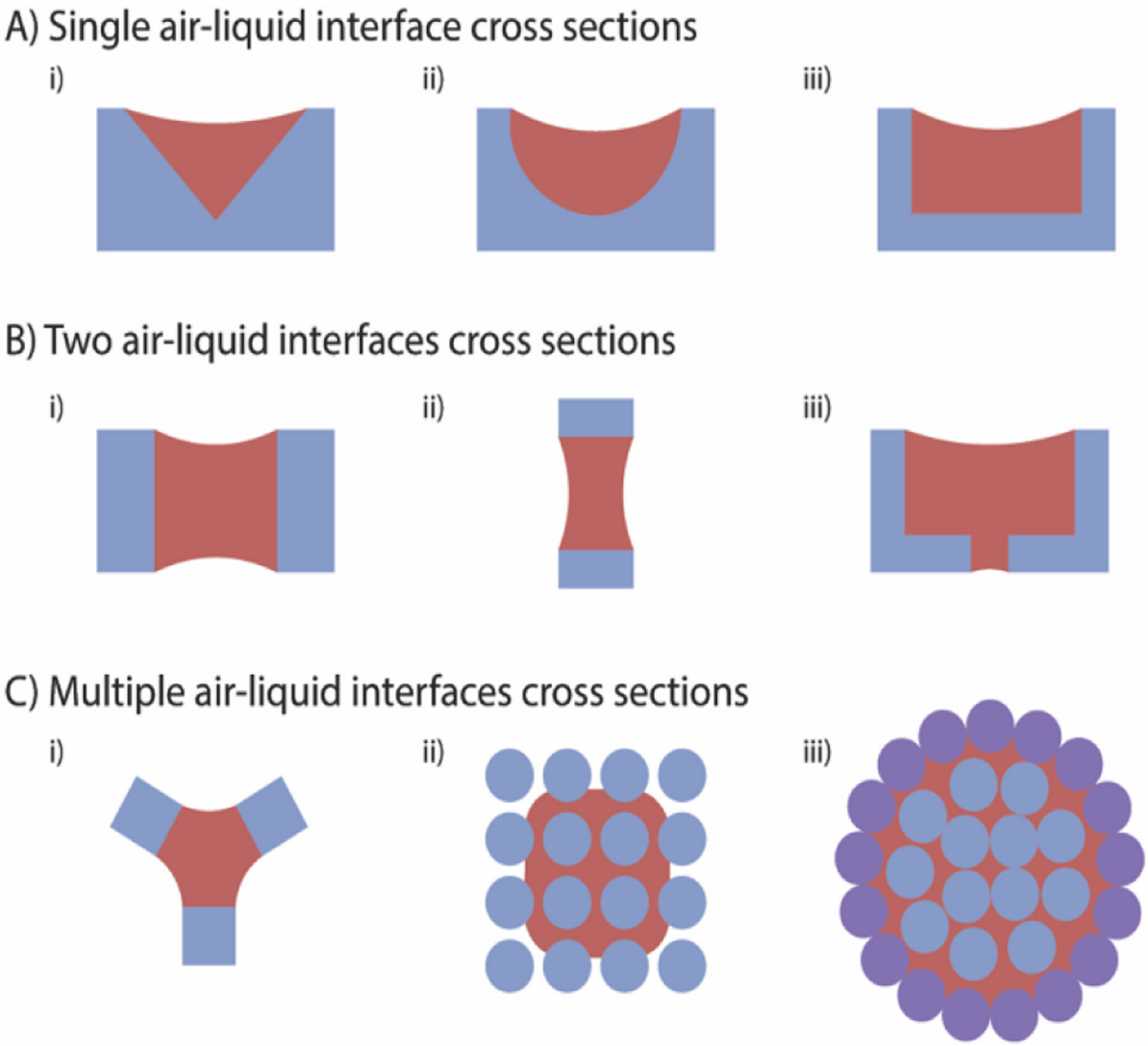


Figure 3.

Cross sections of channels with A) a single air-liquid interface, B) two air-liquid interfaces, and C) multiple air-liquid interfaces. Ai) V-groove, Aii) semi-cylinder, Aiii) U-groove; Bi) suspended, Bii) rail, Biii) suspended aperture; Ci) multi-interfaced cross section, Cii) aligned thread fibers, Ciii) caging of a liquid in fibers. Blue represents the device, red is liquid, and purple represents hydrophobic fibers.

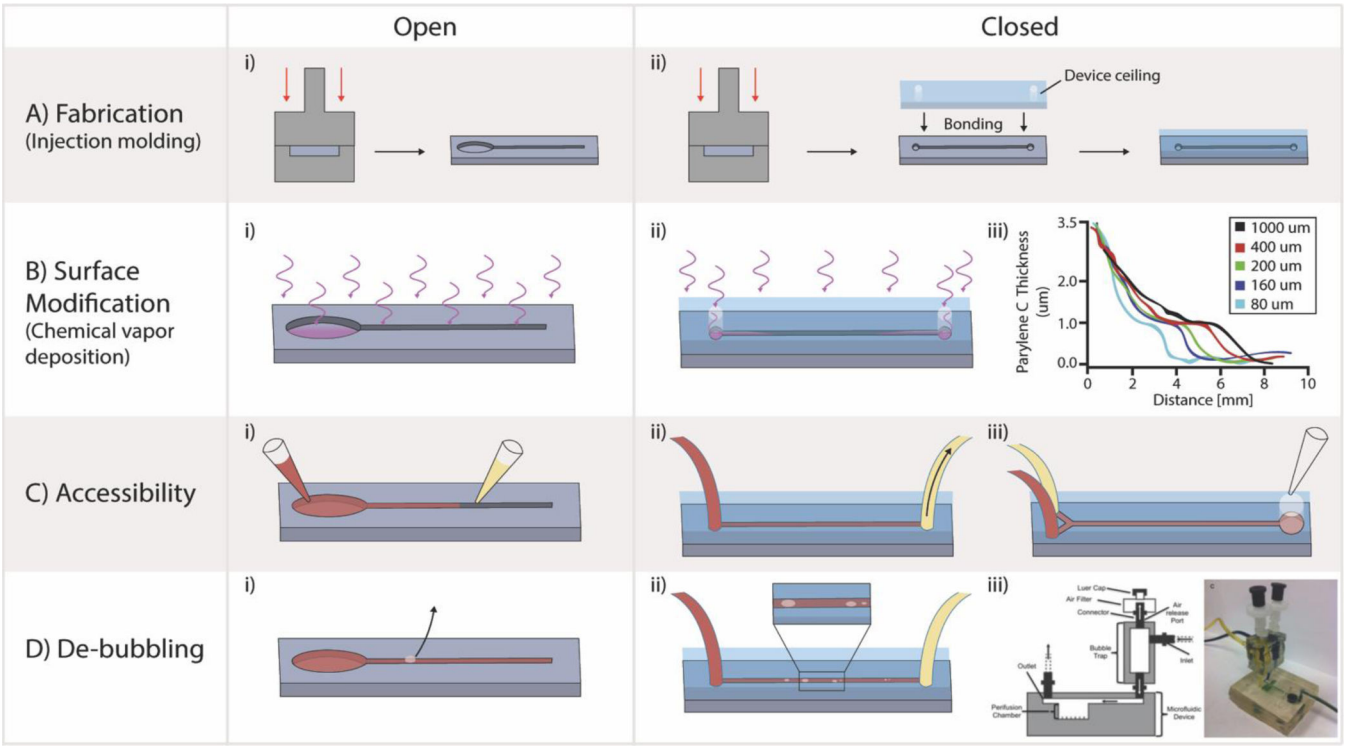


Figure 4.

Comparing key features of microfluidics in open and closed systems. A) In open microfluidics, devices can be directly ready to use after molding or milling, whereas closed microfluidics requires a sensitive bonding step. Bi) Surface treatments in open microfluidics can be applied evenly on all surfaces of the channel. Bii) In closed microfluidics environmentally applied surface treatments decay after a certain penetration distance within the channel, as illustrated by the thickness of Parylene C deposition along the channel length by chemical vapor deposition. Ci) In open microfluidic channels fluids and contents in the channel can be inputted or sampled at any location along the channel. Cii) In closed or semi-open microfluidics, tubing is often required to interface with the system, and contents of the channel have to be shuttled to a specific location for retrieval. Di) In open microfluidics bubbles that form or are inputted in the channel can be evacuated at any point along the channel length. Dii) In closed microfluidics bubbles are a major cause of catastrophic failure, and complex degassing systems are engineered to remove the bubbles in channel. Diii) Reproduced with permission. Ref. 76. Copyright 2012, Springer.

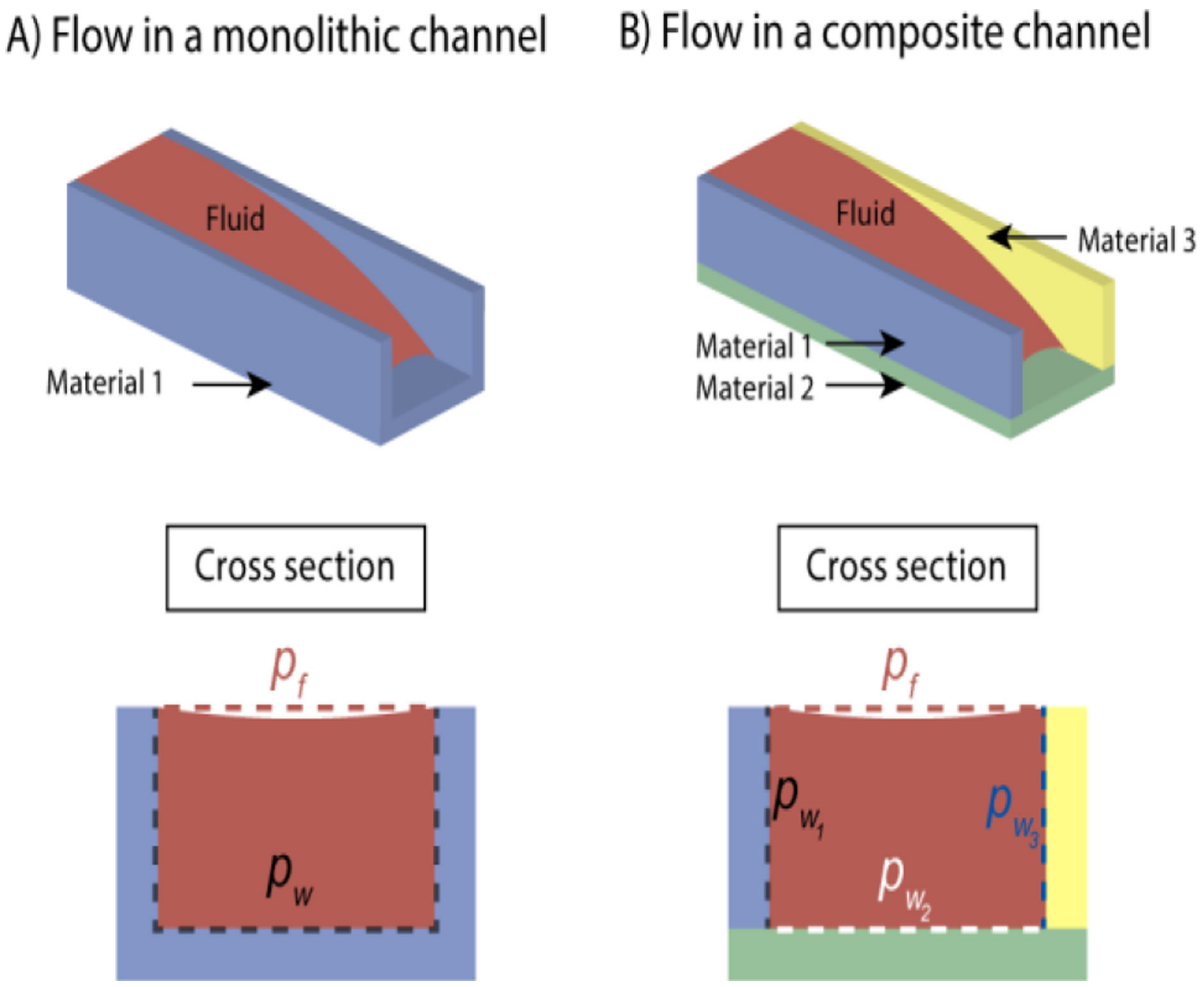


Figure 5.

Flow in monolithic and composite open channels. A) SCF in a monolithic open channel. B) SCF in a composite open channel. The fluid is represented in red, and materials 1, 2, and 3 are represented in blue, green, and yellow, respectively. Conditions determining if flow will occur in monolithic and composite channels are given in Eq (1) and (2), respectively.

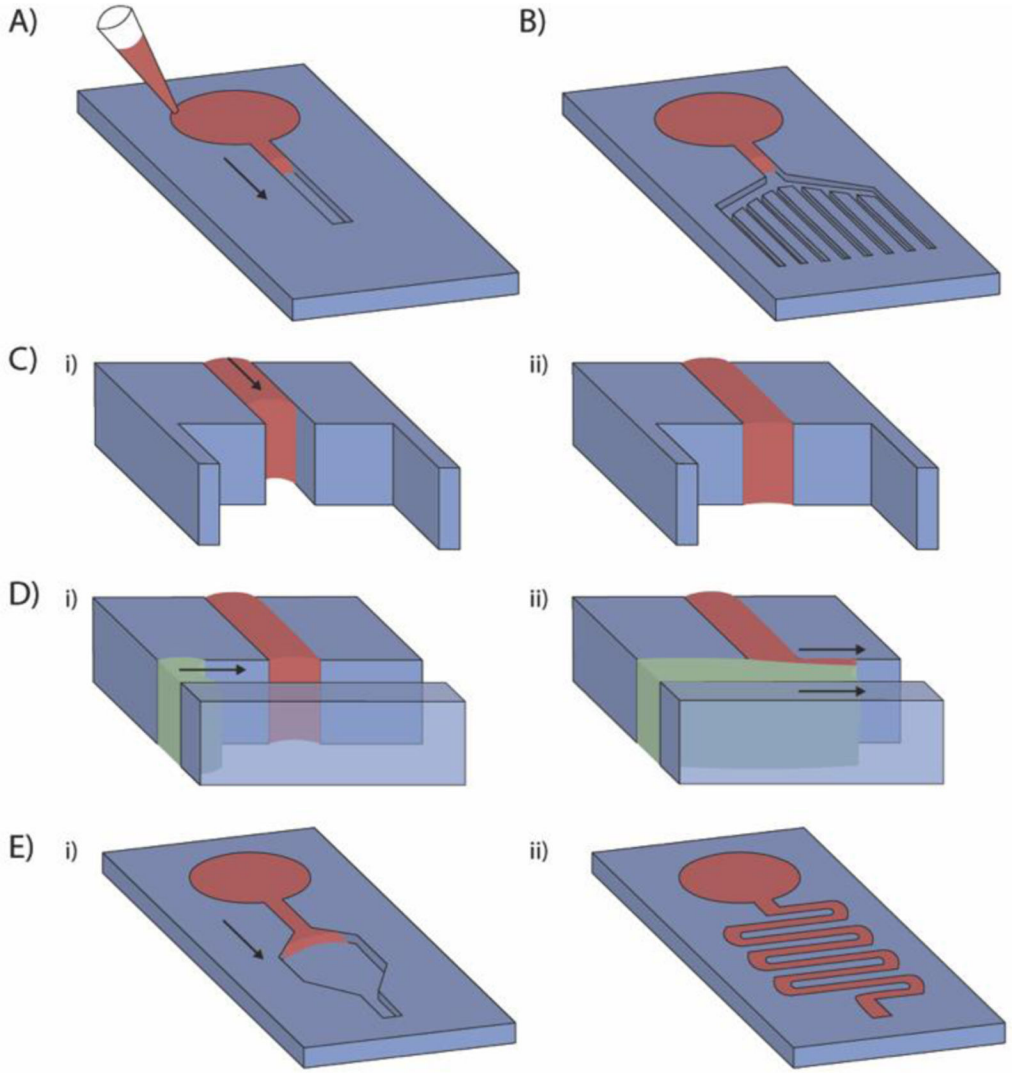


Figure 6.

A) Schematic of capillary flow generated by the pressure difference between the large reservoir and the channel. B) A capillary pump designed by branching a larger channel into multiple smaller channels. C) Schematic of a suspended channel showing Ci) fluid flowing towards a stop valve, with Cii) showing the halting of the fluid front upon a sudden enlargement in the channel. D) A trigger valve, where Di) the red liquid has been stopped and then Dii) merges and flows with the green liquid upon contact. E) Examples of delay features: Ei) uses the widening of a channel to create a delay valve, and Eii) uses a delay line.

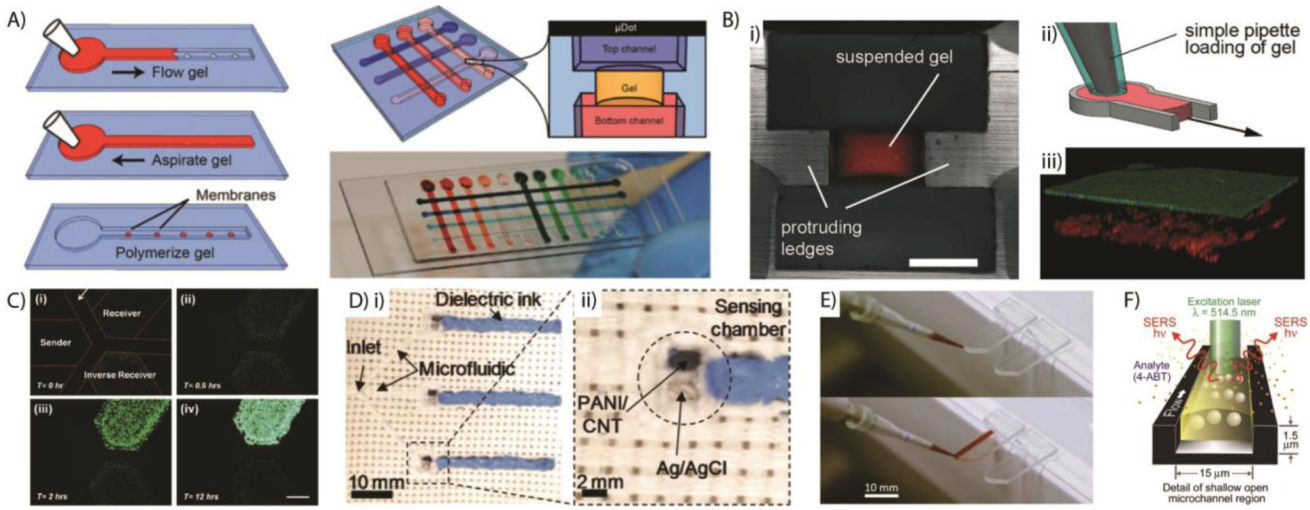


Figure 7.

Biological, diagnostic, chemical and other applications of open microfluidic capillary systems. A) A microfluidic channel with suspended apertures (cross section depicted in Figure 3Biii) open on the top surface and below the gel apertures to suspend hydrogels for 3D cell culture. B) An open device consisting of three layers to generate an air-liquid interface (ALI) in order to differentiate epithelial cells to replicate the lung environment. Bi) A gel (red) is loaded in a suspended channel (cross section depicted in Figure 3Bi). Scale bar is 500 μm. Bii) Schematic of gel loading in a suspended channel. Biii) Confocal image of airway epithelial cells (green) and smooth muscle cells (red) cultured on and in the suspended gel. C) Quorum sensing of *E. coli* separated by hydrogel walls generated by SCF using the device shown in Figure 2A. Scale bar is 200 μm. D) Thread-based (cross section depicted in Figure 3Cii) pH sensor that can be used for point-of-care. E) A plastic device with an open V-groove (cross section depicted in Figure 3Ai) for collecting blood samples and determining blood type *via* red blood cell agglutination. F) Schematic of a U-groove (cross section depicted in Figure 3Aiii) used for surface-enhanced Raman sensing, enabling the detection of airborne particles. A) Reproduced with permission. Ref. 41. Copyright 2013, National Academy of Sciences. B) Reproduced with permission. Ref. 81. Copyright 2018, Royal Society of Chemistry. C) Reproduced with permission. Ref. 27. Copyright 2010, American Chemical Society. D) Reproduced with permission. Ref. 67. Copyright 2016 Springer Nature Publishing AG. E) Reproduced with permission. Ref. 50. Copyright 2018 MDPI. F) Reproduced with permission. Ref. 58. Copyright 2007, National Academy of Sciences.

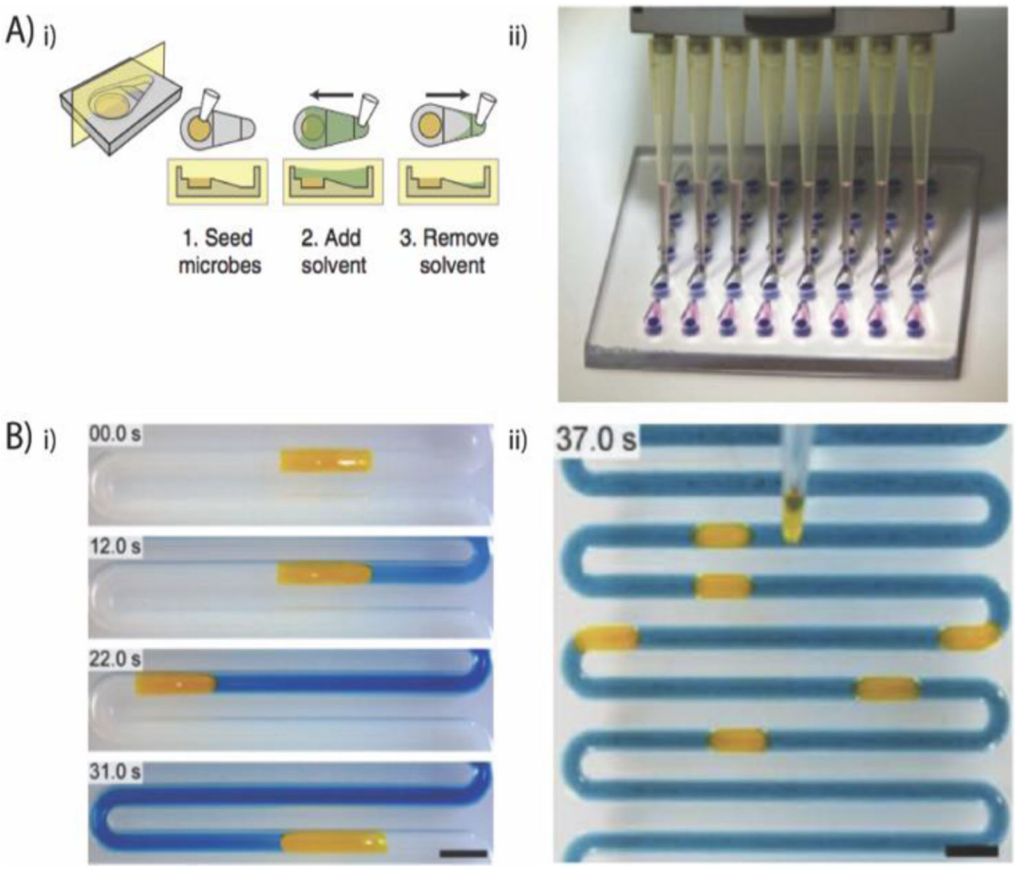


Figure 8.

A) An open liquid-liquid extraction device. i) Workflow of extracting metabolites from a culture, ii) Image of multipipetter adding solvent to device. B) Images of immiscible droplets (colored yellow) in an open channel from a top view, showing both i) shift mode and ii) multiple droplets added into flowing solvent (colored blue) *via* a pipette. A) Reproduced with permission. Ref. 39. Copyright 2016, Springer Nature Publishing AG. B) Reproduced with permission. Ref. 25. Copyright 2018, American Chemical Society.