Microfluidics on Standard Petri Dishes for Bioscientists

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Few microfluidic devices are used in biomedical labs, despite the obvious potential; reasons given include the devices are rarely made with cell-friendly materials, and liquids are inaccessibly buried behind solid confining walls. An open microfluidic approach is reviewed in which aqueous circuits with almost any imaginable 2D shape are fabricated in minutes on standard polystyrene Petri dishes by reshaping two liquids (cell-culture media plus an immiscible and bioinert fluorocarbon, FC40). Then, the aqueous phase becomes confined by fluid FC40 walls firmly pinned to the dish by interfacial forces. Such walls can be pierced at any point with pipets and liquids added or removed through them, while flows can be driven actively using external pumps or passively by exploiting local differences in Laplace pressure. As walls are robust, permeable to O_2 plus CO_2 , and transparent, cells are grown in incubators and monitored microscopically as usual. It is hoped that this simple, accessible, and affordable fluid-shaping technology provides bioscientists with an easy entrée into microfluidics.

1. Introduction

Microfluidic approaches aim to increase throughput while minimizing cost and waste. Many microfluidic devices have been made for bioscientists (often out of polydimethylsiloxane, PDMS) using techniques applied successfully to shrink integrated circuits in computer chips,^[1] and some devices are incorporated into the specialized equipment they use (e.g., the

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TapeStation made by Agilent, and DNA sequencers made by Illumina and Oxford Nanopore). However, a recent review states "...most... biotechnologists are still not used to integrate microfluidic systems into their typical experimental procedures in a regular manner."^[2] Many reasons are given for this, with probably the most important being that devices are complex and rarely made with materials familiar to biologists.^[1-3] Moreover, the aqueous phase is usually inaccessibly buried behind solid walls, although open microfluidics improves this (Figure 1A).^[4–5] Clearly, an optimal solution is to construct devices out of the culture media and polystyrene dishes that biologists use daily to grow their cells. But how might one do so? Adaptations of existing approaches are possible, including confining cells in one phase in an aqueous two-phase system^[6]

or within an elastic skin of nanoparticles,^[7] by magnetically manipulating aqueous interfaces,^[8–9] and by modifying dish surfaces.^[10,11] An approach that uses fluid (not solid) walls—an interface between two immiscible liquids—to confine media on untreated dishes provides a simpler answer.

The approach is based on three principles. First, at the microscale, gravity is weak. Consider raindrops stuck to windows; they defy gravity pinned to glass by strong interfacial forces. Therefore, a three-way traverse holding a "pen" can print "letters" of culture medium on a standard 6 cm Petri dish, and air-water interfaces hold the letters in place (Figure 1B). Second, nanoliter volumes in such letters (which have maximum widths and heights of \approx 500 and \approx 150 µm) soon evaporate, but this can be prevented by overlaying an immiscible and lighter-than-water oil. But if gravity-and so buoyancyis irrelevant, denser oils become alternatives. For reasons we will see, the fluorocarbon, FC40, is particularly attractive as <7 ppm water dissolve in it, compared to <200 ppm for the silicone oil often used by biologists.^[12] (It was selected after screening only some of the many fluorocarbons currently available, so others may prove suitable.) Third, medium can be added/removed to/from such letters without change in aqueous footprint. Consider a 500 nL water drop sitting on a dish (Figure 1C). On adding (or removing) water, drop footprint increases (or decreases) only when the advancing contact angle, $\theta_{\rm A}$ (or receding contact angle, $\theta_{\rm R}$) is reached. Between $\theta_{\rm A}$ and $\theta_{\rm R}$, such contact-angle hysteresis ensures that drop footprint remains unchanged despite volume changes.^[13] Incredibly, for media used to culture human cells, θ_A is >70° and θ_R is <3°, so drops can hold a wide range of volumes as fluid walls/ceilings morph above unaltered footprints (Figure 1D).^[14]

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Figure 1. Microfluidics with fluid walls. A) Liquids in traditional and open devices are either buried behind, or confined by, solid walls. B) When medium + blue dye are printed in air on a dish, letters are not confined by solid walls. Reproduced with permission under the terms of the Creative Commons CC BY license.^[14] Copyright 2017, the Authors. Published by Springer Nature. C) Contact-angle hysteresis. In (iii), a 500 nL water drop sits on a dish under FC40 (which prevents evaporation). ii–iv) The water:FC40 interface morphs above an unchanging footprint as water is added/removed between θ_A and θ_R . i,v) Above/below these angles, the footprint expands/contracts. Adapted with permission under the terms of the Creative Commons CC BY license.^[14] Copyright 2017, the Authors. Published by Springer Nature. D) Morphing walls. All chambers contain medium ± red dye under FC40 and have identical square footprints (2.2 × 2.2 mm) despite volume variations. Adapted with permission.^[15] Copyright 2018, the Authors. Published by PNAS. This open access article is distributed under Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND).

2. "Printing" Almost Any 2D Pattern

Fluid walls are built by reshaping media and FC40 with different tools in ways that artists recognize (**Figure 2A**). Often, they paint a pattern with a brush; in "positive printing", a "pen" prints the circuit.^[14] They also cover a canvas in paint, and then remove some to develop the pattern (as in sgraffito); in "negative printing", the bottom of a dish is covered with a thin layer of medium overlaid with FC40, and a "stylus" or "microjet" removes medium locally to replace it with FC40. Thus, a stylus (made of fluorophilic polytetrafluoroethylene, PTFE) or a submerged jet bring FC40 down through the medium into contact with the dish; as FC40 wets polystyrene better than medium, it remains stuck to the dish.^[15,16] In all cases, circuit fabrication depends on wetting sequence and interfacial forces acting on medium, FC40, polystyrene, and a tool.

Building straight fluid walls can yield "grids" with many chambers (Figure 2B) that are used like wells in microplates: liquids are simply added/removed by pipetting through FC40 instead of air. Surprisingly, these chambers accept a wider range of working volumes than those in 96-well microplates with the same interwell spacing (i.e., \approx 30-fold compared to \approx 8-fold for a standard well).^[15] Even more surprisingly, fluid walls are remarkably robust (Figure 2C), and dishes supporting them can be carried around labs like any filled dish. Complex circuits are built in much the same time it takes to draw freehand the plan on a piece of paper (e.g., a "human circulatory system" in \approx 90 min; Figure 2D).

Each printing method has advantages and disadvantages.^[14–16] For example, precision is reduced by changes in tool shape (e.g., as serum proteins in media aggregate on a pen, or a stylus wears when dragged over a dish). Additionally, a pen's outer diameter, and jetting nozzle's inner diameter, are major determinants of the minimum widths of aqueous features and FC40 walls, respectively. Consequently, jetting is often the method of choice, as it is contactless and forgiving. Then, we routinely use a portable "printer" small enough to fit in a biosafety cabinet (Figure 2E) that jets FC40 through a nozzle (internal diameter 70 μ m) at 8 μ L s⁻¹ to build walls ~120 μ m wide—and so sterile grids and circuits. www.advancedsciencenews.com

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Figure 2. Printing fluid walls. A) Three methods. In positive printing, a pen draws the pattern, and overlaying an immiscible liquid (FC40) prevents evaporation. In negative printing, the bottom of a dish is covered with medium and overlaid with FC40; then a PTFE stylus or microjet removes some medium to create the pattern (both tools bring FC40 down to wet polystyrene, where it remains stuck). B) Example grids made using i) a pen (Reproduced with permission under the terms of the Creative Commons CC BY license.^[14] Copyright 2017, the Authors. Published by Springer Nature.) or ii,iii) stylus (Reproduced with permission.^[15] Copyright 2018, the Authors. Published by PNAS. This open access article is distributed under Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND)). C) Fluid walls are robust. Both grids are initially covered with FC40; when the left-hand dish is flipped over, FC40 drains away but the grid remains intact. Reproduced with permission.^[18] Copyright 2019, Society for Laboratory Automation and Screening. D) Circuits made by jetting in ≈90 min. Reproduced with permission.^[16] Copyright 2020, Wiley. E) Printer in biosafety cabinet. The printer consists of a three-way traverse + built-in software; this one has two steel needles—one earlier jetted 2 grids in 6 cm dishes, and the other is dispensing blue dye to successive chambers in the second grid.

3. Benefits of Liquid FC40 Walls

At the microscale, liquid FC40 walls have many advantages over solid ones.^[14–16] Their fabrication in minutes allows rapid prototyping (contrast the days taken to make PDMS devices in specialized clean rooms). Moreover, circuit layouts can even be reconfigured around living cells on the fly during experiments (e.g., flow through conduits can be started/stopped repeatedly by building/removing blocking walls, and new conduits/reservoirs can be added).^[16–17] Significantly, FC40 is as transparent as water with a refractive index close it (i.e., 1.29 vs 1.33), so one can see

through these fluid walls with little diffractive distortion.^[18] Sampling pipets can also be inserted anywhere in circuits, and walls self-heal automatically when they are withdrawn. Additionally, air bubbles causing catastrophic failure in conventional devices^[19] are lost spontaneously to the atmosphere through fluid walls.

FC40 is arguably one of the most bioinert immiscible liquids known.^[12] The CF bond is not found in nature, and it is the strongest in organic chemistry (\approx 485 kJ mol⁻¹, compared to \approx 413 kJ mol⁻¹ for CH). Consequently, fluorocarbons are both bioinert and unreactive. Biologists also think of chemicals as hydrophilic or hydrophobic, but fluorocarbons constitute



another group that is strikingly illustrated by the three-way emulsions formed when water, hydrocarbons, and fluorocarbons are shaken together. As a result, it is likely that most molecules found in cells will be insoluble in FC40. Moreover, FC40 carries approximately tenfold more O2 than water (and approximately twofold more CO₂), as well as binding neither gas, so its close relatives have been used as human blood substitutes and for liquid ventilation of neonatal babies.^[20] In combination, these properties mean that cells under FC40 can be grown in standard CO2 incubators, and viewed on standard microscopes. FC40 walls even provide additional sterility barriers. For example, if every second chamber in a grid is seeded with bacteria, growth occurs only in inoculated chambers as others remain sterile. If now more medium is fed to each chamber by scanning a pipet tip through FC40 just above each chamber, aqueous drops jump from tip to chamber, as uninoculated chambers remain sterile.^[15] Consequently, our printers carry another tool—a dispensing needle that is used repeatedly, often without washing between repeats (as in Figure 2E, inset).

4. Flow with and without External Pumps

Flow through circuits can be driven by external pumps; steel needles connected to pumps are inserted through fluid walls to yield leak-free joints.^[14,16] Flow rates can vary widely (in **Figure 3**A, two inputs merge to flow as laminar streams down one conduit to a sink that automatically self-empties). Note, however, progressively increasing the flow into any fluid-walled conduit inevitably increases θ , and fluid walls move outward once θ_A is reached and burst when θ rises above 90°.

Flow can also be driven without external pumps. Drops with small radii of curvature harbor higher Laplace pressures than those with larger radii (Figure 3B-i; Laplace pressure = $2\gamma/R$, where γ is interfacial tension and R is radius of curvature).^[21] In Figure 3B-ii, all six dumbbell-shaped circuits are initially identical, but when decreasing dye volumes are pipetted successively into drops 6-2, consequential changes in Laplace pressure drive flows rightward at different rates (e.g., 30 s after the last addition, dye in circuit 2 reaches its sink before that added earlier to circuit 6). The circuit in Figure 3B-iii serially dilutes and mixes dyes; pipetting dyes into input drops increases local pressures so chamber a fills only with red dye, f only with blue, and b-e with dilute mixtures. Flow rates in circuits without external pumps depend on many factors (e.g., circuit geometry, density, viscosity, and interfacial tension), but can be predicted,^[22] and-for a fixed footprint-are maximal when the contact angle of the source drop is 90° and the sink drop is completely flat. Geometrical changes can have a large impact: increasing conduit width from 590 to 880 µm in a dumbbellshaped circuit can increase flow rate sixfold.^[14]

5. Examples: Cell Cloning and Feeding

Grids and circuits have now been used for all core cellculture methods (e.g., feeding,^[15] replating,^[15] cloning,^[15,23] and cryopreservation)^[15] with organisms ranging from bacteria^[15] through yeast^[24] and worms^[15] to man,^[14–15,23] as well as for drug



Figure 3. Driving flow (6 cm dishes). A) An external pump (not shown) drives medium + red/blue dyes through needles into the circuit. i) Circuit plan. ii-iv) Operation. With 1 nL s-1, dyes diffuse between laminar streams in the central conduit so both appear purple on reaching the sink. With 1000 nL s⁻¹, there is little time for diffusion, so streams remain blue or red all the way to the sink. The back view illustrates the sink automatically self-emptying (bouyancy detaches part of the sink drop and it floats above denser FC40). B) Without external pump. i) Principle. In this dumbbell circuit (plan, side view), the left-hand drop has the smaller radius of curvature and so a higher Laplace pressure that drives flow to the sink. ii) Six dumbbell circuits. 10, 8, 6, 4, and 2 μ L red dye are pipetted successively into drops 6-2 (giving drop 2 the highest Laplace pressure). After ≈30 s, dye added last to drop 2 reaches its sink first. iii) Circuit serially diluting and mixing dyes. Dyes are pipetted into drops (arrows) and flow autonomously to chambers a-f. Reproduced with permission under the terms of the Creative Commons CC BY license.^[14] Copyright 2017, the Authors. Published by Springer Nature.

screening,^[14–15] chemotaxis^[14] plus cell-wounding assays,^[25] lysis plus RT-PCR,^[14] transfection plus genome editing,^[15] and fixation plus immunolabeling,^[15] Note that although most of these applications are cell-based, the general technology can nevertheless be applied wherever small volumes require manipulation. We now give two example cell-based applications.

Mammalian cells are often cloned by splitting a dilute cell suspension among wells in microplates before clones are picked. However, Poisson statistics ensure most wells get no cells, and a few only one (usually $\ll 10\%$). Anyone who has cloned this way worries that picked colonies may be derived from >1 founder, so they perform another cloning round to increase the chances of achieving monoclonality. Moreover, one can never be sure a colony is truly derived from one progenitor, as edge effects obscure views of the periphery of wells.^[18] Jetting fluid walls (shaped like Voronoi polygons) enables analogs of cloning rings to be built around almost all single cells in a dish (**Figure 4**A); then, after growing clones, pipetting trypsin into polygons, and picking colonies, cloning efficiencies as high as those obtained conventionally can be obtained. This enables

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A Beating the Poisson limit during cloning

B Continuous feeding (7 d) as myoblasts → myotubes dye pumped in



Figure 4. Example applications. A) Beating the Poisson limit during cell cloning. i) Workflow. Single mouse cells (≈100 NM18) are plated (35 mm dish), phase-contrast images collected, single cells located, a Voronoi diagram computed (1 cell per polygon), polygonal walls jetted around cells, and cells grown (8 days) and reimaged. ii-iv) Images of one region of the dish. Rectangles in (ii) contain cells 1–4 (inset bar = 20 μ m), and dotted lines in (iv) show limits of derivative colonies (insets show packed cells). B) Feeding mouse C2C12 myoblasts as they differentiate into myotubes. i) Setup. An external pump drives medium + red dye through a needle ("in") held by a red adapter on the dish, through 48 chambers (1 μ L day⁻¹ per chamber), and out into the dish (no pump withdraws medium from the dish). ii) Workflow. Myoblasts are deposited in drops in a dish, a circuit jetted around cells once they attach, and grown. iii-v) Images (phasecontrast except for fluorescence in (v), right inset) of one part of the dish at different times. Dashed lines: edges of some walls. Myoblasts grow to fill chambers, fuse, and express EGFP-DOK7, a myotube marker. Insets (day 7): Arrows mark fluorescing syncytia each >200 μ m long and containing >20 nuclei. Reproduced with permission.^[16] Copyright 2020, Wiley.

the Poisson limit to be beaten in the sense that >90% polygons contain a single cell. Additionally, the excellent optical clarity afforded by fluid walls gives users confidence which polygons contain only one founder, and so to pick clones after 1 week (instead of \approx 2) and forego second cloning rounds.^[16,23]

In another example, fresh medium is fed continuously to 48 sets of mouse myoblasts as they differentiate into myotubes over 7 days (Figure 4B-i,ii).^[16] Cells are deposited in 48 drops

on a virgin dish and allowed to attach (Figure 4B-iii), a circuit jetted around them (Figure 4B-iv), and fresh medium perfused (1 μ L day⁻¹) through each of 48 chambers; cells fuse to give syncytial myotubes expressing a component of the neuromuscular junction (i.e., DOK7 tagged with EGFP; Figure 4B-v). This circuit can easily be adapted to screen for drugs affecting this developmental pathway (e.g., as syncytia form, each chamber is isolated from others by building new FC40 walls across inputs and outputs, drugs added, and fluorescence monitored).

6. Conclusion

We describe a methodology for constructing and operating microfluidic devices using just a trio of cell-friendly materials (cell culture media, polystyrene Petri dishes, FC40) plus a threeway traverse, three simple tools, syringe pumps, and pipettors. All parts of these circuits are accessible from above, so cells in them can easily be sampled. What are the major shortcomings? First, our devices will never be as robust as solid-walled ones (e.g., they survive careful carriage by bike or car, but not over speed bumps). Second, they cannot support high flow rates that increase contact angles beyond θ_A or 90°, as then fluid walls shift or rupture; therefore, they are unsuited for applications like high-throughput droplet-based microfluidics.^[26] Third, despite the limited solubility of water in FC40, some static media in features $<20 \ \mu m$ wide evaporate, and this limits further miniaturization. Fourth, circuits are currently limited to two dimensions. Fifth, while circuit operation may be simple, circuit design often requires specialized know-how. Nevertheless, we hope the simplicity and robustness of this affordable approach will increase adoption of microfluidics in biolabs.

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Conflict of Interest

Oxford University Innovation—the technology transfer company of The University of Oxford—has filed patent applications for fluid-walled technologies on behalf of P.R.C. and E.J.W. iotaSciences Ltd. is exploiting this technology. P.R.C. and E.J.W. each hold equity in the company and receive salaries or fees from it; the company also provides scholarships for C.D. and F.N., printers, and FC40.

Keywords

cell cloning, fluid walls, fluorocarbon FC40, Laplace pressure, microfluidics, open microfluidics

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