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Countercurrent liquid–liquid extraction on paper†

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Proof-of-concept is shown for two-phase countercurrent flow on paper. The device consists of two paper layers, one of which has been modified with a sizing agent to be hydrophobic. The layers exhibit different wetting behavior for water and octanol. Both phases dominate wetting in one of the layers and can be made to move in different directions along the interface to achieve liquid–liquid extraction.

Paper has always been a multipurpose material of interest from both scientific and societal views.[1] Recent years have seen its use for the development of cheap analytical tools.[2–6] Early examples of these so-called paper microfluidic devices mainly exploited capillary pressure to drive fluid wicking.[7,8] More complex devices and functionalities are being developed as the field matures,[9] involving the transposition of flow control elements from conventional microfluidics to the paper format.[9–15] This work describes one such development, namely a method to generate two-phase countercurrent flow driven by capillary action in paper. Solving this intrinsically difficult challenge generates new possibilities for on-paper liquid–liquid extractions, which are more efficient in counter than parallel flow configuration. Moreover, this example serves as a reminder that higher levels of functional complexity remain to be developed in paper-based analytics.

Side-by-side flows of the same or different phases, in the same or opposite direction, have been demonstrated in coated or uncoated microchannels under laminar-flow conditions and directionally applied pressures in specific geometries.[16–18] Paper is fundamentally different from closed microchannels, as it consists of an open porous network of fluid microconduits in which solutions exhibit laminar flow, yet cannot be controlled on the microscopic level.[19–21] The realization of countercurrent flows on paper is thus characterized by a number of challenges, illustrated in Fig. 1. The devices consist essentially of paper strips cut into the desired shape (channels) and affixed onto the sticky side of adhesive tape (2 cm wide). The experimental setup is described in the ESI.†

The first challenge resides in the fact that capillary pressure, the passive pump in paper fluidics, does not distinguish between different streams and directions. Parallel flows can be combined into a unidirectional side-by-side flow over limited length (Fig. 1A), yet this system cannot be switched to counter-current flow (Fig. 1B). Secondly, the same capillary network (with average pore size 'r') creates the applied pressure (Young–Laplace, see eqn (1)) for all streams. Different phases, having different surface energies (γ) and contact angles (θ) with the solid surface, experience different pressures (Fig. 1C and D), leading to the domination of one phase over the other. Even when two phases are first applied to different pieces of paper (*i.e.* using pre-wetted channels, Fig. 1E) and then interfaced, the aqueous phase (yellow) quickly replaces the organic phase (blue) (Fig. 1F). The dominance of the aqueous phase over the organic phase is dictated by the higher capillary pressure of the aqueous phase (see Fig. 2A).

$$P_c = \frac{2\gamma\cos\theta}{r} \quad (1)$$

Our solution to this problem is to make sure that there is a geometrically defined border, (i) around which the two phases are confined on opposite sides, whilst (ii) keeping an unhindered liquid–liquid interface. This can be achieved by modification of the surface energy of the porous network, which means a change in contact angle for a given phase, altering the capillary pressure (see eqn (1)). If by doing so, we obtain a higher capillary pressure for phase A on one side of the interface, and a higher capillary pressure for phase B on the other side, we achieve steady state. We can then start to move both phases in opposite directions in a plane parallel to the water–oil interface.

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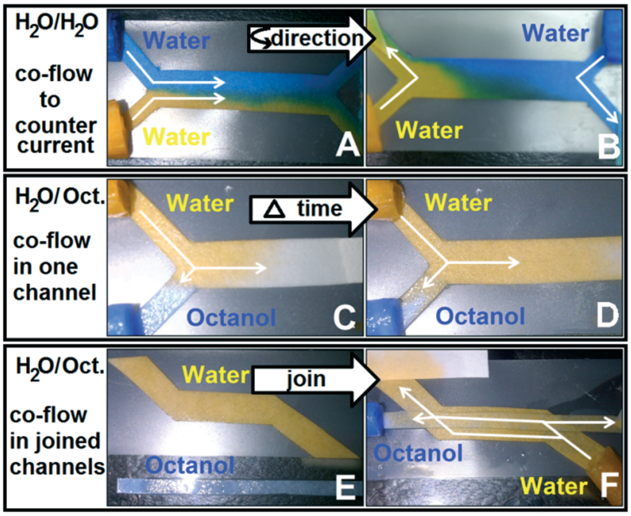

Fig. 1 Challenges in the realization of two-phase (countercurrent) flows on paper. (A) Unidirectional flow of two streams of the same phase (water with either hydrophilic yellow or hydrophilic blue dye) allows side-by-side flow over a certain distance, until diffusion-induced mixing dominates lateral distribution. (B) Opposing the two flows leads to disruption of the side-by-side flow. The porous network does not recognize direction, and liquid will preferentially flow towards regions exerting the strongest fluidic pull (in this case to the nearest outlet). (C and D) Due to differences in fluidic properties, different, immiscible phases experience different capillary pressures, impairing the formation of a side-by-side flow. The water phase contains a hydrophilic yellow dye, while the 1-octanol phase has been tinted with a hydrophobic blue dye (different from the one in panels A and B). (E) Pre-wetting of separate, detachable paper structures is also not a solution for the formation of a stable two-phase system (again 1-octanol with hydrophobic blue dye and water with hydrophilic yellow dye), because (F) upon bringing the two wetted structures into contact, flow will be disrupted due to differences in capillary pressure.

Alkyl ketene dimer (AKD) is a class of molecules used in the paper-making industry to increase the hydrophobicity of paper. It can covalently bind the hydroxyl groups on cellulose, and has two hydrophobic tails (varying in length between C-14 and C-22). AKD can thus be used to change the surface properties of cellulose fibers[22–24] (Fig. 2). This has been used in our previous work to create solvent-dependent valves based on the selective permeability of AKD structures on paper.[25] In this work, we coated a strip of paper with AKD (see ESI† for the procedure), which led to contact angles with water of over 90 degrees, (*i.e.* non-wetting).[25] AKD-treated paper could still be wetted by solvents with lower surface energy, such as 1-octanol. On untreated paper, which can be wetted by water and 1-octanol, the difference in surface tension (72.88 mN m^{-1} *versus* 27.50 mN m^{-1} at 20 °C, respectively[26]) determines the capillary pressure over the interface (Fig. 2A), leading to the expulsion of octanol from the pores. If we have both AKD-treated and untreated regions on paper, a different pressure dominance is exhibited in these regions, allowing the fluidic interface to remain in place. In that case, however, the interface will be formed inside the paper, and the contact area between phases will be relatively small (Fig. 2B). If each region is defined by a separate piece of paper, they can be overlaid, leading to a greater contact interface formed not in but between the pieces of paper (Fig. 2C).

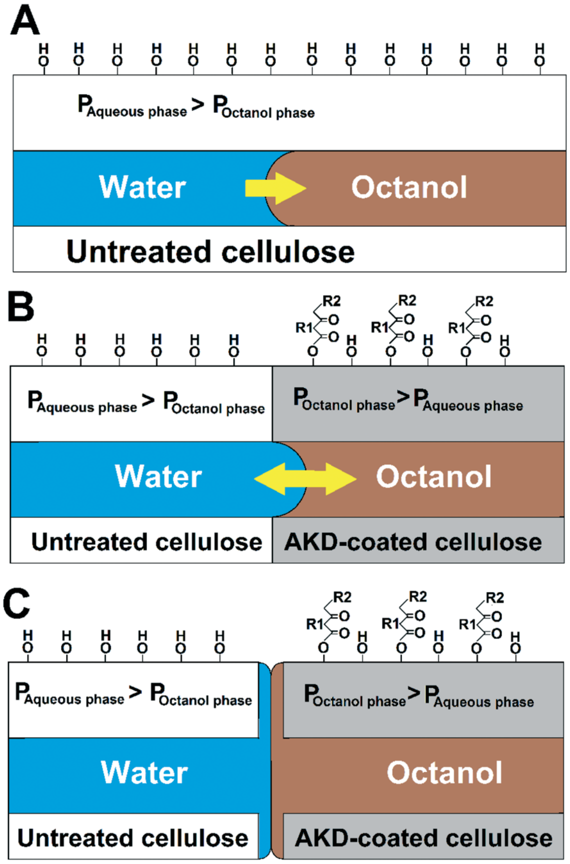

Fig. 2 Schematic representation of the interface between immiscible aqueous and organic (1-octanol) phases in (A) untreated paper and (B and C) untreated paper and alkyl ketene dimer (AKD)-coated paper combined. (A) On untreated paper, the cellulose fibers carry hydroxyl residues, which yield a relatively high surface energy. Both water and octanol can wet this material, and the greater surface tension of water leads to larger capillary pressure for water than for octanol. (B) In this example, one region of a single piece of paper has been treated with AKD. On AKD-coated fibers, the hydroxyl groups have been (partially) covered by molecules with hydrophobic tails, decreasing the surface energy. The resulting contact angle with water is so great that a non-wetting situation is obtained. Therefore, the capillary pressure for octanol, which still can wet the coated paper, is greater than for water. A steady state arises, in which octanol will stay on the AKD side of the interface, and water on the untreated cellulose side. (C) In this situation, an untreated piece of paper wetted with water is brought into contact with a second AKD-treated piece of paper wetted with 1-octanol. Each region is now covered by a thin film of one of the two phases, and a liquid–liquid interface arises between these thin films.

Experiments were performed (see ESI† for procedures) to verify that we can (i) obtain a two-phase system with a geometrically fixed interface, (ii) separately move the individual phases in any desired direction, and (iii) maintain an open interface between the two phases for transport of dissolved species from one phase to the other. Note: all experiments with octanol were carried out in a fume hood.

The first experiment is shown in Fig. 3. A straight, AKD-coated channel was placed on top of a zig-zag, untreated

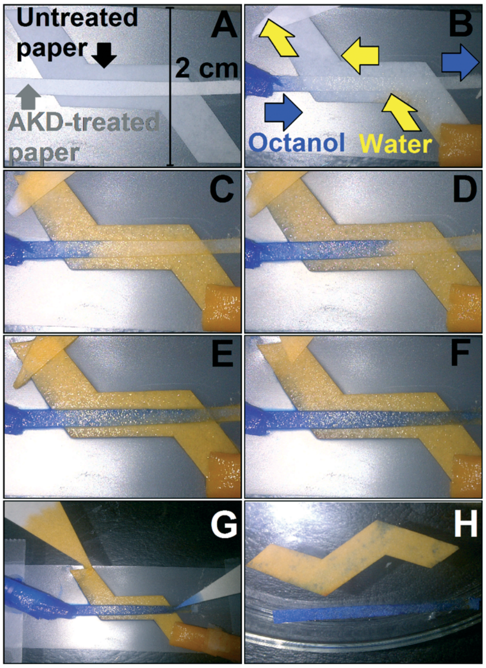

Fig. 3 Demonstration of two-phase countercurrent flow. (A) An untreated paper channel (zig-zag, bottom) and an AKD-coated channel (straight, top) are overlaid and fixed on adhesive tape. The untreated channel is first wetted with water, the coated channel is wetted next with octanol. (B) Source pads for the water and octanol channels are connected to the channels, containing hydrophilic yellow and hydrophobic blue dye, respectively. Arrows indicate the direction of flows. (C–G) The colored solutions replace the colorless solvents. Water stays confined to the untreated channel, octanol to the AKD-coated channel. (H) After separation of the channels, we see that the phases did not switch channels, as evidenced by the fact that no significant amount of hydrophobic blue dye can be found in the hydrophilic yellow channel, and *vice versa*.

channel, with both channels being affixed to adhesive tape. Then, water was applied to the untreated paper (Fig. 3A), which did not move into the AKD-coated channel. Next, octanol was applied to the AKD-coated channel, which would not move into the water channel, due to hydrophilic exclusion. Then, a pad soaked with octanol (with hydrophobic blue dye), was placed on the left entry of the octanol channel, and a pad soaked with water (with hydrophilic yellow dye) was placed on the lower right entry of the water channel (Fig. 3B). Off-paper partitioning in a two-phase system was performed to ensure that the dyes did not partition substantially into the other phase (see ESI,† Fig. S3). On both exits, pieces of paper were placed to serve as outlet wicks; these were replaced regularly to drain effluent and thereby keep drawing the solutions through the paper. The water travelled relatively fast through the untreated channel, whereas the octanol wicked more slowly through the AKD-coated channel. Still, it is clear that both solutions travelled from their source pad to the other end of their respective channels, and did not cross the liquid–liquid interphase between the two regions (Fig. 3C–G). Afterwards, the two strips of paper were separated to further demonstrate that the phases stayed on their own "sides of the fence" (Fig. 3H).

Next, we demonstrate that this system also allows for molecular partition between the two phases. Octanol was saturated with basic fuchsin. Basic fuchsin imparts a purple color to the octanol solution, whereas it is red/pink in water and yellow in acidic water (see ESI,† Fig. S4).[16] The same setup was used as for the previous experiment, but now, after wetting the channels, the aqueous phase pad was just filled with water, and the organic phase pad contained octanol with basic fuchsin (Fig. 4). As the water flowed past the basic fuchsin solution (Fig. 4A), the dye partitioned between the water and oil phases. However, since it does not dissolve well in pure water, most of the basic fuchsin stayed in the octanol (Fig. 4B). The water was then replaced by a 1 M hydrochloric acid (HCl) solution. Since the basic fuchsin dissolves readily in acidic water, the dye partitioned substantially from the octanol to the aqueous phase, losing its purple color due the change of solvent (Fig. 4C). When basic fuchsin was being visibly extracted from the octanol (Fig. 4D), the HCl solution was replaced by water. As the pH in the aqueous channel rose, fuchsin partitioned less readily into this channel (Fig. 4E), and the octanol channel regained more of its original color, as new fuchsin in octanol was infused into it (Fig. 4F). This experiment thus demonstrated molecular transport between the two phases. It also again visualized the countercurrent flow, as the purple dye entered *via* the octanol (left to right), and was extracted with HCl solution (right to left). Furthermore, this paper format allows for easy switching of phases, as demonstrated by the different aqueous phases used in a single experiment (Fig. 4).

We have shown that a two-phase countercurrent flow with extraction interface can be obtained by the above-described

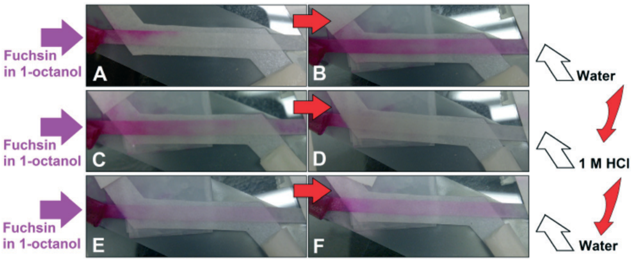

Fig. 4 On-paper extraction by employing a two-phase countercurrent. Basic fuchsin (purple in octanol) enters *via* the octanol phase. (A and B) Water is transported in the opposite direction. Basic fuchsin partitions between the two phases at the fluidic interface, but mainly remains in the organic phase. In figure B, it appears as if dye entered the water channel at the left. However, this was caused by some excess octanol moving over the tape. (C and D) When water is replaced by a 1 M HCl solution, the situation changes. Now basic fuchsin favors the acidic aqueous phase and partitions into it. Due to the low pH, the color changes to light yellow, which is difficult to see due to the paper background (though the disappearance of purple is abundantly clear). (E and F) When the acidic aqueous phase is replaced by water, the pH in the channel rises. The purple color is slowly restored to the central channel, as new basic fuchsin flows in with the octanol and no longer exchanges that quickly into the aqueous domain.

approach. This was demonstrated with cellulose, as the AKD binds covalently to the hydroxyl residues. However, the broader applicability of this work relies on the use of porous materials with different surface energies. It would therefore be of interest to experiment with different materials, coatings and solvents to leverage this approach more generically. Furthermore, we have demonstrated the applicability of a paper-based, two-phase countercurrent flow to liquid–liquid extraction, which can for instance potentially be used for extraction of lipophilic substances from plants or blood. However, further development of the system is required to transcend its rudimentary nature for its adaptation in easy-to-operate devices. Inexpensive, paper-based systems could then be developed for the in-flow determination of partition coefficients,[27,28] or combined with electrokinetics to transfer molecules or particles from one phase into another. In such systems, device configurations will need to be adapted or further developed, but the flexibility of paper-based microfluidics should facilitate the development process. Other future work will focus on sandwich-flow approaches (treated paper in between two pieces of untreated paper or *vice versa*) to increase the contact area and maximize solute exchange.

Conflicts of interest

There are no conflicts to declare.

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