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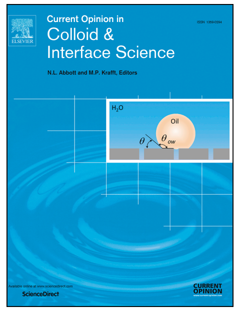

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Droplet manipulation with bioinspired liquid-infused surfaces: a review of recent progress and potential for integrated detection

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Abstract

Point-of-need (PON) diagnostics offer promising methods to gather information relevant to health and safety on-site without the requirement for a fully-equipped laboratory. In this review, we discuss how liquid-infused surfaces offer a promising platform to expand the capabilities of PON devices in the areas of biological sample preparation and system integration, providing new methods of controlling the movement of droplets and facilitating detection of biological and chemical compounds contained therein. Modifications to the underlying surface structure can be used to passively control the direction of droplet movement, while the careful selection of responsive solids substrates and/or overlying liquids can allow active control through induced temperature gradients, electrical stimulation, and exposure to magnetic fields. Recent work leveraging other advantages of liquid-infused systems such as ultra-low friction, non-coalescence of droplets, and liquid-liquid patterning has demonstrated the unique ways in which this approach can be used to both enhance current detection methods as well as enable new ones. Together, these recent developments in the manipulation of droplets on liquid-infused surfaces point to their significant potential for furthering the capacity of PON devices for both biological and environmental samples.

Keywords: Liquid-Infused Surfaces, SLIPS, LIS, Biological Sample Preparation, Droplet Manipulation, Detection Platforms

Abbreviations

CAH: contact angle hysteresis

LIS: lubricant-impregnated surfaces

NIR: near infrared-light irradiation

PCR: polymerase chain reaction

PDMS: polydimethylsiloxane

PON: point-of-need

SERS: surface-enhanced Raman scattering

SLIPS: slippery liquid-infused porous surfaces

1 Introduction

There is a large and growing need for low-cost, portable, and durable devices which can provide information on the presence and composition of biological and chemical materials in our environment [1,2]. Multi-drug resistant bacteria[3,4] in hospital-acquired and secondary infections [5,6] pose a significant threat to human health, as do the inevitable outbreaks of bacterial and viral epidemics such as Ebola, cholera, and Zika [7]. Through the work of many researchers, companies, and communities, these threats have been met with innovation in point-of-need (PON) detection systems which monitor biomarkers or other signs of the presence of infectious diseases. Currently, simple PON devices are widely used as both paper and other disposable assays [8], while advances in synthetic biology [9] and engineering of microfluidic devices [10,11] are showing tremendous promise for expanded capabilities in the future. Yet despite these advancements, there remain several major challenges to realizing the full capability of on-site detection systems.

PON detection platforms are designed to provide information that enables a decision for a course of action at the site of need. However, the results delivered by current widely available platforms suffer from a lack of either specificity or precision, often requiring that samples be sent to brick-and-mortar laboratories for further testing [1,2,12]. At the same time, more specific and precise approaches to detection being developed in laboratories around the world face the challenge of scale-up [1,2,13] and the current lack of established validation protocols [8,13]. In addition, a fully integrated system which combines sample preparation and analysis would likely facilitate the use of PON devices; however, when dealing with heterogeneous biological or environmental materials the complexities associated with handling, mixing, and transport are significant [1,13,14].

Beginning to approach the challenges associated with enabling the next generation of PON testing devices will require technology that is by its nature integrative, adaptive, and versatile. Although multiple solutions will doubtlessly be required, one such approach that has recently generated attention is the use of liquid-infused surfaces, often referred to as either slippery liquid-infused porous surfaces (SLIPS) or lubricant-impregnated surfaces (LIS). Inspired by bio-active and dynamic wet surfaces in nature [15,16], this platform technology is proving to be adaptable to multiple applications, including the control of biological materials [17–19], medical surfaces [16,20,21] and droplet movement [22–24]. Furthermore, liquid-infused surfaces are more often being used as a method of facilitating synergy between multiple functionalities such as anti-adhesion, environmental responsiveness, self-healing capabilities, and surface chemistry control [16]. In this review, we present recent progress in the field of liquid-infused surfaces in the manipulation and control of droplets. We further describe the ways in which these surfaces are beginning to be used in unique ways for sample handling and analysis, but highlight the fact that so far only very few reports of actual applications relevant to diagnostics exist. This points toward a promising gap in the field, which when addressed may enable the development and deployment of new classes of PON detection devices.

2 Droplet Interactions with Liquid-Infused Surfaces

Liquid-infused surfaces are created by trapping a thin layer of liquid on a surface through a combination of physical means, such as capillary action, and chemical means, such as van der Waals forces [25]. When the trapped liquid immiscible with a given contaminant, the resulting liquid layer presents an anti-fouling surface which is pressure stable and even able to self-heal due to its liquid nature [15]. An in-depth discussion of the physics and chemistry behind liquid-infused surface can be found in any one of several recent reviews on the subject [16,26,27]; however, one of the attractive properties of these surfaces is their ability to be created on a wide range of substrates, from polymers to metal to paper, using different types of infusing liquids [16,28,29]. In all cases, droplet interactions with fully-functional liquid-infused surfaces are characterized by a low contact angle hysteresis (CAH $\leq 10°$), or the difference between the receding and advancing contact angles of a droplet sliding along the surface. This measurement can be viewed as proportional to the energy required to shift a droplet from a static to dynamic state, and is generally used to illustrate the ease with which droplets can be translated from one location to another [30].

While immiscibility of the infusing liquid with the sliding droplet is critical for the system to work, the way in which the droplet interacts with the liquid layer is variable. Recent investigations using confocal optical interferometry [31] have revealed three possible equilibrium states for a droplet at rest interacting with a liquid layer: one in which the infusing liquid is fully displaced and the droplet makes full contact with the surface (failure); one in which the liquid is partially displaced and the droplet makes contact with several discrete areas on the surface (partial failure); and a final one in which the liquid layer remains congruent underneath the droplet, allowing the droplet to effectively hydroplane/oleoplane across the surface (functional). Which state a liquid infused surface/droplet pair will produce depends greatly on the composition of the liquid as well as the composition and texture of the solid surface. However, the stability of any given combination of solid substrate, infusing liquid, and impinging fluid under static conditions can be predicted via a spreading parameter, which takes into account the surface and interfacial energies [32]. It has also been demonstrated that putting the droplet into motion can alter a partially-failed state into a fully functional state. In this case, the stability of the liquid-infused surface under dynamic conditions can be predicted by the Landau-Levich-Derjaguin law, where film thickness is related to the capillary number of

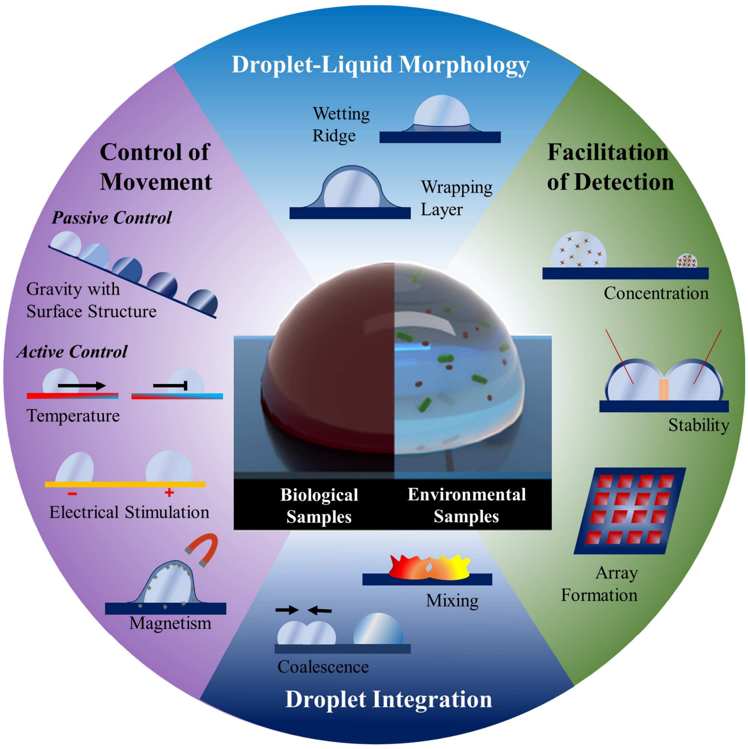

Figure 1. Schematic illustration of the different morphologies, movement control methods, and detection-facilitating properties of droplets on liquid-infused surfaces.

the system [31]. When droplets are in motion across a liquid-infused surface, the speed with which they travel can be tuned by altering the viscosity, with more viscous infusing liquids slowing the rate of motion [33].

Additional studies on liquid layer/droplet interaction have looked into a unique set of phenomena that occur on liquid-infused surfaces: the creation of a wetting ridge (or wetting skirt), the displaced infusing-layer liquid which rises up partially around the droplet; and the wrapping layer, the thin encapsulation film of the infusion liquid around the droplet (**Figure 1**) [34–36]. Both of these phenomena have been shown to affect evaporation rates of the drop [34], and increase the rate of stripping of the infusing liquid from the surface when the droplet falls off of the infused surface, bringing its wetting ridge and wrapping layer with it [35,36]. Whether or not a wrapping layer forms can be tuned by selecting specific infusing-repelling liquid pairs, although this is most achievable when repelling other low-surface-tension liquids [37,38].

In the application of liquid-infused surfaces, particularly in anti-fouling capacities, much attention has been given to the understanding and improvement of their self-healing capabilities and ultimate longevity [16,39]. Attempts at limiting the rate of depletion of the infusing liquid by liquid layer stripping have recently included increasing the viscosity of the infusing layer to slow or prevent wetting ridge and wrapping layer formation [37], creating a system of vascularized channels within the surface substrate that can be filled with the infusing liquid to continually self-replenish the depleted liquid layer [40], building in self-secreting droplet reservoirs [41–43] adding amphiphilic porous cellulose nanofibers to the surface microstructure to act as infusing-layer reservoirs and provide additional capillary force to retain the infusing liquid [44], and adding a brush-like low molecular weight PDMS graft over initial surface and spin coating the infusing layer to increase the robustness of the layer [45]. Other options to address longevity have looked to tuning the crosslinking density of infused polymers, which have been shown to have an effect of longevity in the face of repeated removal of the infusing liquid overlayer [46].

While not yet investigated with individual droplets, there have been several reports of modifying either the repelling liquid or the solid to introduce an additional degree of functionality to the system. For example, work responding to the need for liquid-infused surfaces to not only resist adhesion by contaminating bacteria, but also prevent them from multiplying was addressed by using and infusing liquid doped with bacterial quorum sensing inhibitors [47], the antimicrobial agent triclosan [48] or nitric oxide [49]. The doped liquid was found to release the active molecules slowly over time, producing the desired dual response. Another potential concern with liquid-infused surfaces is the entrainment of organic molecules into the infusion layer. A recently reported method to address this issue is to graft a photocatalyst, like titanium dioxide, onto the solid surface. Upon contamination of the infusing layer, UV illumination of the liquid-infused surface photocatalytically decomposed the organic contaminants [50]. Further advances in controlled release and incorporation of active molecules in the infusing liquid layer may also present an interesting opportunity to achieve multi-faceted responses in the interaction of droplets containing biological or environmental samples with liquid interfaces.

3 Droplet Manipulation on Liquid-Infused Surfaces

One critical issue in the creation of self-contained PON detection platforms is development of methods to incorporate both sample preparation and detection within the same small area. Preparation steps may require sample separation, mixing with buffers or reagents, or concentration, while detection likely requires movement along a path to a detection site, as has been demonstrated for some PCR applications [51,52]. Current research on droplet manipulation on liquid-infused surfaces offers several promising approaches which may prove useful in further achieving this goal.

3.1 Passive Control via Surface Structure Modification

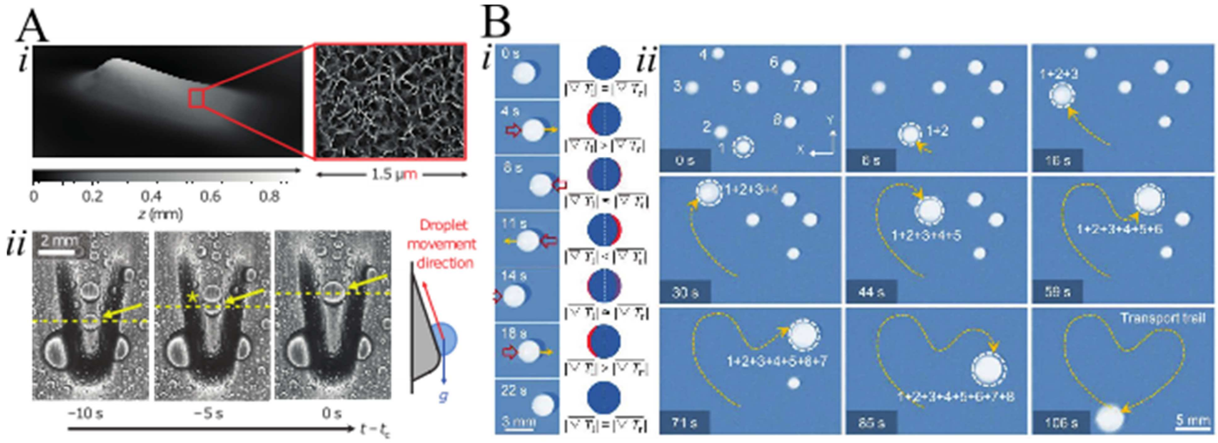

Figure 2. (A) ***i*** A profilometer image (oblique view) showing nanostructure (inset) infused with lubricant, and the tangentially connected bottom slope. ***ii*** Time-lapsed optical images of condensed water droplets on an asymmetric bump rotated 180° relative to gravity. The yellow asterisk indicates coalescence with another drop, while the dotted yellow line tracks the vertical progress of the droplet. Reproduced with permission [45]. Copyright 2016, Macmillan Publishers Limited. (B) ***i*** Time-sequence images (top view) of reversible light-induced motion of a water droplet (≈5 μL) on a horizontal POS. Insets show schematic in top view of ∇T changes within droplet. ***ii*** Time sequence images (top view) of sequentially light-induced coalescence of droplets on POS. There are eight water droplets (numbered with 1–8, volume of each droplet varies between ≈3 and 5 μL). Droplet 1 can be moved to coalesce with droplet 2 and sequentially coalesce with others to form a larger droplet along a designed "heart"-shaped trajectory in 106 s. Yellow dashed lines in each image indicate transport trail of droplet. Reproduced with permission [56]. Copyright 2018, Wiley-VCH.

Surface structure or texture is a crucial element of liquid-infused surfaces, and is one of the most accessible parameters to alter to achieve controlled droplet movement. For example, creating liquid-coated convex asymmetric structures at the millimeter scale, as seen in **Figure 2A**, led to six-fold increase in accumulative droplet growth (coalescence) over flat controls, and could also induce droplet transport that moved opposite the force of gravity [53]. A further liquid-infused surface fabricated on a stretchable elastomer with aligned microscale wrinkles was found to accelerate droplet coalescence in the direction of alignment [54]. Stretching was also used in conjunction with liquid-infused surfaces made with inverse opal patterning as a method of reporting the wetting state of the surface. Upon stretching, the wetting state transitions from one in which the liquid layer is present on top of the surface structure to one in which the surface structure is exposed. At this point the droplet pins to the surface and a color change due to the disruption in transparency of the inverse opal film is visible [55]. Other approaches have made use of structured surface gradients such as V-shaped ramps to influence droplet motion [56]. Mathematical modeling of these systems was used to predict the interfacial tension and therefore the speed with which the droplet was driven along the gradient [57]. A different strategy using gravitational forces was implemented in an omnifluidic device. Using a titanium dioxide nano-textured surface, microchannels were created within the liquid-infused surface via UV exposure in defined patterns. This set-up resulted in solvents with less affinity for the infusing layer than the surface displacing the liquid and entering the microchannel for gravity-driven transport and droplet mixing [58]. In another method of controlling droplet movement, polyelectrolyte films in a layer-by-layer assembly were patterned on an otherwise flat film. When infused and then subjected to mild shear stress, the infusing liquid was depleted from the flat areas while remaining on the textured areas. Droplets moving along the surface would pin on the flat regions, but continue to move over the textured regions, resulting in a guided pathway [59]. A defined-pathway approach using a liquid-infused surface was also described for directing the movement of underwater bubbles [60], an approach which may prove useful in the PON testing of gaseous compounds.

3.2 Active Control via Temperature

Active control of liquid droplets can be achieved using stimulus-response platforms [61], and when combined with liquid-infused surfaces offers a range of possibilities for dynamic and complex droplet-handling systems. Liquid-layer-facilitated droplet manipulation via thermal stimuli was the first method to branch out from the passive structural approach. Exposure to temperatures exceeding 200°C was found to increase droplet velocity by 1,000 times compared to a room-temperature control [62]. A study using a gradient from 70°C to 20°C showed a similarly increased droplet velocity, changing by a factor of five from the cool end to the warm end [63]. Surfaces with temperature-controlled tunable wettability have also been developed using paraffin wax as the infusing "liquid". Transition between the cool, solid wax and the warm liquid wax resulted in a change from pinned to free-moving droplet [64,65]. Tuned light scattering due to the transition in state of the wax was used as a method for self-reporting of wettability transition states with these surfaces [64]. Temperature gradient drivers for droplet motion have also been created using near infrared-light irradiation (NIR) on infused photoresponsive organogels which incorporated Fe_3O_4 in the liquid layer [66]. Illumination with NIR light resulted in localized temperature gradients, which could be used to influence the pathway of the droplet. An advantage of the photoresponsive organogel is that it retains the ability to stimulate droplet movement in a fully reversible manner. This setup allowed for sequential droplet coalescence and real-time droplet guidance (**Figure 2B**).

3.3 Active Control via Electrical Stimulation

In addition to temperature, electrical stimulation has also emerged as a method to manipulate droplet motion on liquid-infused surfaces, When using reduced graphene oxide films as the surface substrate, voltage pinning was achieved below 10 V for water droplets and below 2 V for KCl droplets [67]. Other work used silicone oil as an infusing liquid on a fluorinated membrane coated with a fluorinated silane self-assembled monolayer [68]. In this unique setup in which the surface chemistry was mismatched with the infusing liquid chemistry (in contrast to most other liquid-infused surfaces where the surface and liquid chemistry are similar), the voltage required to change the contact angle of a droplet on the surface was reduced from >100 V to 5 V presumably due to the ease with which the mismatched chemistry allowed dewetting of the surface. Beyond voltage pinning and manipulation of contact angles, liquid-infused surfaces have also been used to facilitate the manipulation of the shape and dynamics of droplets. Liquid-infused dielectric elastomers akin to muscle tissue were used to elongate droplets vertically, cause oscillations within the droplet, induce accelerated multi-droplet collisions and mixing, and even propel of droplets vertically off the surface (**Figure 3A)** by inducing substrate oscillations from 23 to 261 Hz [69]. Further work showed that exposing a liquid-infused surface created on gold to a 275 V electric field could reversibly deform a droplet into a thin film, as seen in **Figure 3B** [70]. The improvement of digital microfluidics represents another potential application of liquid-infused surfaces [71]. Building off of traditional microfluidics, digital

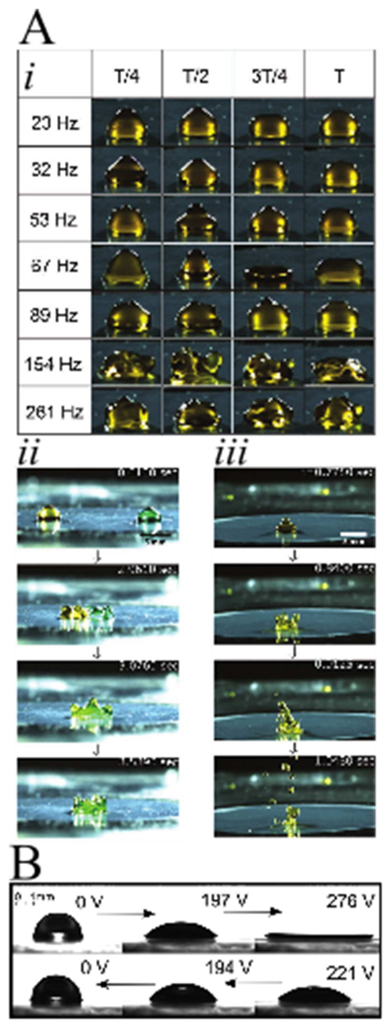

Figure 3. (A) ***i*** Pictures showing the different oscillation modes of a 20 µL water droplet on a horizontally placed dynamically actuated poroelastic film at frequencies ranging from 23-261 Hz with voltage amplitude of 14 kV. Four pictures for each mode of self-oscillation at a time interval of a quarter of the periodicity *T*. ***ii*** Pictures before, during and after the mixing of two 20 µL droplets on the dynamic poroelastic film actuated at 147 Hz frequency and 12 kV voltage. ***iii*** Pictures in time sequence showing jetting of a 20 µL water droplet placed on the dynamic poroelastic film actuated at 154 Hz frequency and 16 kV voltage. Reproduced with permission [59]. Copyright 2018, Wiley-VCH. (B) Side view images of a droplet of glycerol on a spiral dielectrowetting device. Reproduced with permission [60]. Copyright 2017, AIP Publishing.

microfluidics incorporate electrode circuits to manipulate droplets electrostatic forces. Digital microfluidic devices could have their droplet control mechanisms optimized with the integration of a liquid-infused surface. Surface acoustic wave technology combined with liquid-infused surfaces [72] may improve upon the introduction and work-flow of pump-based microfluidic cell sorters, especially in regards to the introduction of a sample into the device [73].

3.4 Active Control via Magnetism

While temperature and electrical control of droplets on liquid-infused surfaces have proven versatile, several recent works have demonstrated the capabilities of magnetically-driven systems as a method to achieve unique outcomes with droplet and even particles. In a magnetically-actuated liquid-infused system, the liquid is infused with magnetic nanoparticles to create a ferrofluid which can be moved and shaped when exposed to a magnetic field. When moving droplets across such a surface, the wrapping layer plays a critical role as its encapsulation of the droplet allows the ferrofluid to act as a vehicle to be manipulated by magnetic fields. Using this approach, even weak magnetic fields are able to vertically elongate droplets, induce droplet coalescence (**Figure 4A**), and guide droplet movement [74]. Using a ferrofluid layer covering a hexagonal nickel array, micro particles could be segregated into discreet groups by magnetically depleting the ferrofluid in the center of each hexagon, as seen in **Figure 4B** [75]. A further study examined the effects of the strength of the magnetic field and the concentration of the ferrofluid on droplet moment, finding that these parameters can be tuned to control the speed of gravity-driven droplets as well the degree of stick-slip movement [76]. This work also found nonlinear friction at work in droplets moving across ferrofluid-infused surfaces due to the presence of the wetting ridge, suggesting an interesting new set of tunable parameters for complex droplet manipulation strategies which may facilitate unique PON detection approaches.

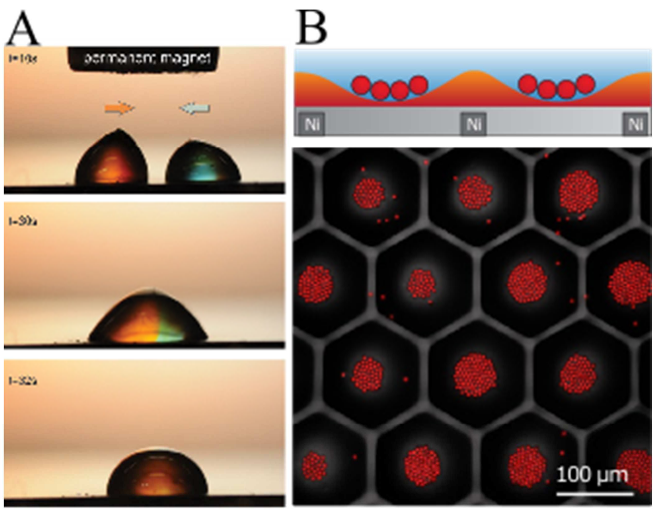

Figure 4. (A) Two water droplets (dye used to color droplets) are placed on ferrofluid-infused surface. A magnet is lowered vertically directly between droplets and causes them to move toward one another and coalesce. Reproduced with permission [62]. Copyright 2014, AIP Publishing. (B) Schematic (top) and confocal fluorescence (bottom, showing top view) images showing the confinement of colloidal particles by the macro-topographical response of a thin layer of ferrofluid alone and the confinement of colloidal particles. Schematics are not shown to scale. Reproduced with permission [63]. Copyright 2018, Macmillan Publishers Limited.

4 Use for Detection Facilitation

The ability of liquid-infused surfaces to facilitate detection has only recently begun to be explored. For this reason, despite the promise of the active control of droplets on liquid-infused surfaces, applications have mainly used passive droplet control. However, the breakthrough potential demonstrated in the use of even passive liquid-infused surfaces in detection applications suggests significant promising for future applications involving active droplet control.

In one of the first reports of the use of liquid-infused surfaces to facilitate detection, sub-femtomolar analyte detection via surface-enhanced Raman scattering (SERS) was made possible due to the ultra-low friction surfaces presented by liquid-infused materials [77]. Droplets containing extremely dilute concentrations of a model analyte were concentrated via evaporation on an infused surface. The low friction of the surface allowed all of the analyte molecules to remain within the shrinking droplet, rather than getting pinned at the edges in a coffee-ring effect. After all the solvent evaporated away, the concentrated point of analyte molecules was able to be detected using surface-enhanced Raman scattering (**Figure 5A)**.

In a second breakthrough, a platform was designed to monitor diffusion across a lipid bilayer formed between non-coalescing droplets [78]. This setup took advantage of an inherent wrapping layer to create two stable droplets on the liquid-infused surface. When the droplets contained phospholipids, it was found that the lipids would migrate toward the interface between the two droplets and replace the wrapping layer, creating a stable bilayer. Importantly, this droplet-supported bilayer was stable in air under ambient temperature and pressure, as opposed to the previous requirement that the entire system be submerged in oil to maintain the integrity of the lipid layer. Initial measurements on these supported bilayers included measuring single-channel gating events across the membrane using standard electrodes (**Figure 5B)**, demonstrating sensitivity in addition to stability that may be useful in future PON detection of aerosols.

The rise of multi-drug-resistant pathogens poses a number of challenges, some of which may be addressed with earlier detection. Toward this goal, a third breakthrough saw the use of liquid-infused surfaces as templates to create liquid-liquid micro-patterns though guided liquid displacement [79]. When exposed to bacteria, discreet biofilm micro-clusters with defined geometries such as those shown in **Figure 5C** could be formed [80]. High-throughput PON antibiotic susceptibility test using this approach could play an important role in speeding effective treatment and controlling the spread of resistant microorganisms.

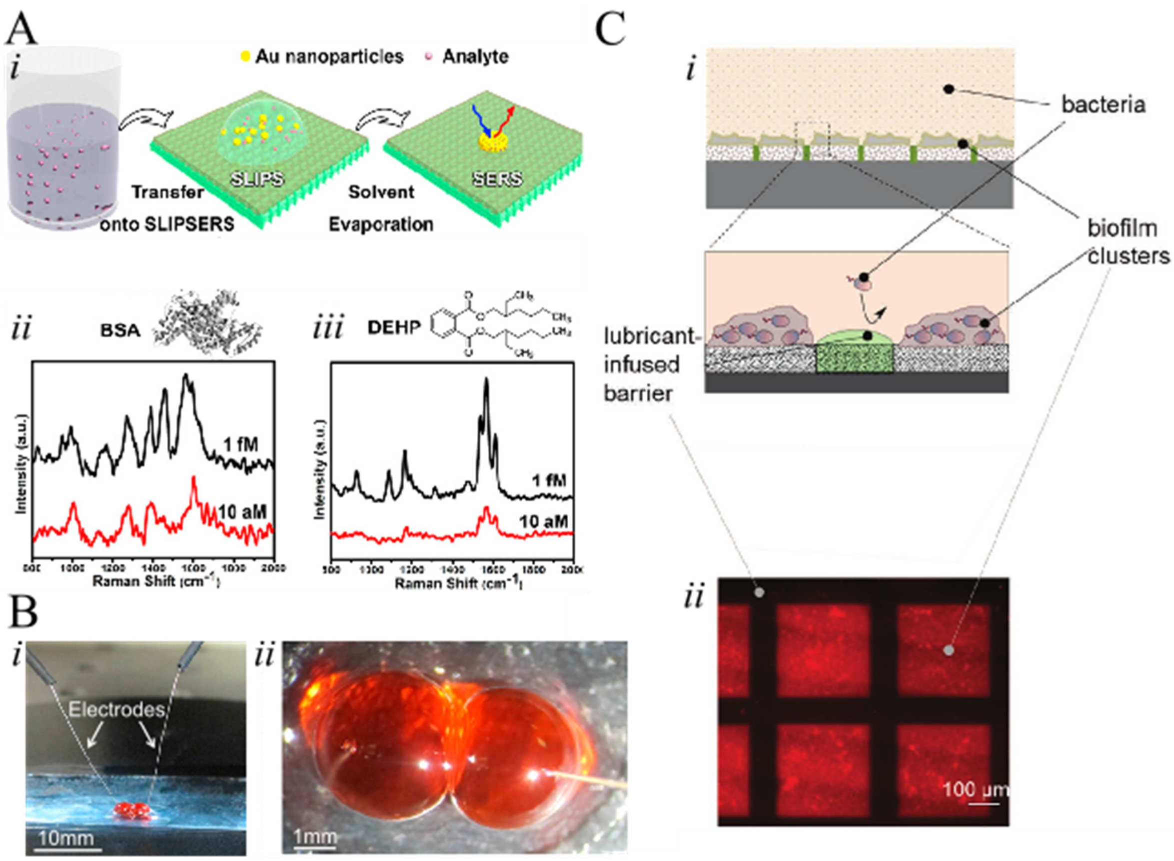

Figure 5. (A) Liquid-phase detection of biological species and environmental pollutants using SLIPS and surface-enhanced Raman spectroscopy (SERS): ***i*** Schematic illustration of the liquid phase detection. ***ii*** BSA in water. ***iii*** DEHP in ethanol. Reproduced with permission [65]. Copyright 2016, the National Academy of Sciences of the United States of America. (B) ***i*** Side-view and ***ii*** top-down photographs of noncoalescing water droplets with inserted electrodes. Reproduced with permission [66]. Copyright 2014, the National Academy of Sciences of the United States of America. (C) Formation of patterned liquid surfaces: ***i*** Bacteria cultured on the substrate adhere to the hydrophilic areas but are repelled by the SLIPS regions. ***ii*** Fluorescence staining and image analysis of *P. aeruginosa* biofilm on hydrophilic squares separated by SLIPS barriers. Reproduced with permission [68]. Copyright 2016, Wiley-VCH.

5 Conclusions and Outlook

With the increasing level of danger posed by antibiotic resistance, environmental contamination, the spread of infectious diseases, and harmful applications of synthetic biology, technologies which provide more efficient and more effective ways of providing information at the point of need will be increasingly in demand. The ability of liquid-infused surfaces to enable the control of droplet movement both passively and actively, as well as facilitate detection through liquid manipulation methods not possible on solid surfaces, provides a new set of tools for enabling efficient and effective PON detection systems and may be useful in improving the performance of existing technologies. Toward this goal, future work on liquid-infused systems should be directed both toward improvements in the accuracy, specificity, durability, and specificity in droplet handling, as well further exploration of how these surfaces can be used to enable and enhance detection.

As liquid-infused surface technology has only recently come to the forefront as an effective and versatile droplet manipulation method, the creative application and adaptation of these systems is an underpopulated area ripe for research. For example, open-channel analyte [81] and gas-exchange [82] detection platforms could benefit from liquid-infused surfaces which limit sample loss via evaporation or surface adhesion, while simultaneously providing a method of sample concentration. The range of molecules being detected, and methods of biological sample analysis conducted by potentiostat-based bandages [83,84] could be expanded due to the ability of liquid-infused surfaces platforms to resist adhesion by complex biological samples. Environmental testing using multi-droplet analysis [85] could benefit from the electrically- and magnetically-controlled liquid-infused platforms to facilitate droplet translation and mixing. And finally, current detection platforms which handle and manipulate microliter sample volumes could be conducted in an open-channel analysis format without risk of rapid evaporation. In these applications and others, liquid-infused surfaces may prove one of the keys necessary to develop the PON detection systems of the future.

Conflict of Interest

The authors have no conflicts to declare.

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