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# Recent advances in surface manipulation using micro-contact printing for biomedical applications

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ABSTRACT

Surface properties are largely responsible for the biological performance of biomedical devices, suggesting the great necessity of surface modification. Micro-contact printing (μCP) is a versatile surface modification technique that is capable of not only producing defined topographical features but also manipulating surface chemical and biological cues through customized inks. Compared to other surface patterning techniques, μCP offers distinct advantages of low cost combined with high reliability and versatility. This review summarizes the principles and characteristics of μCP and presents the latest advances enabled by μCP in the biomedical field, categorized by its applications in constructing cell culture platforms, biosensing platforms, and devices for other biological applications.

## 1. Introduction

The surface properties of biomedical implants have a critical role in supporting implant function. As soon as a biomedical implant is placed in the human body, a cascade of biological reactions immediately takes place on the implant surface and continues to occur in a dynamic state for the entire lifetime of the implant [1,2]. Topographical features, as well as chemical and biological cues presented on the implant surface, have a powerful influence on protein adsorption and cell behavior, which in turn determine the quality of implant integration with surrounding tissues [3]. Therefore, strategies to achieve precise manipulation of the implant surface can be used to realize desired functions. For example, the elongation of macrophages can be achieved through the use of engineered cell culture substrates with specific micro-grooved structures, leading to a pro-regenerative phenotype [4]. On the other hand, spatially confined macrophages have been found to undergo chromatin compaction and epigenetic alterations, resulting in the suppression of late lipopolysaccharide-activated transcriptional programs including IL-6, IL-1β, CXCL9, and iNOS [5]. More potent manipulations on cell behavior can be achieved by combining surface geometry and chemistry, through which micro-tissue constructs or spheroids can be obtained [6]. Other examples include surfaces imprinted with specifically designed geometry to selectively accommodate bacterial growth, which can be used for monitoring *E. coli* in contaminated water or food supplies [7].

A range of surface modification techniques have been developed to achieve precise control of surface properties to endow the implant with advanced functions, and remarkable progress has been made in recent decades in optimizing the precision, controllability, and applicability of these techniques in the biomedical field. Popular techniques include but are not limited to photolithography [8,9], nanoimprint lithography [10–12], femtosecond-laser ablation [13–15], direct laser writing [16–18], and micro-contact printing (μCP) [19–22]. Photolithography is the most commonly used surface technique for fabricating surface pattern, which uses a material capable of polymerization under

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photoirradiation. Patterns are made by selectively exposing the surface coated with the material to visible light, and subsequently removing the un-polymerized areas by washing with appropriate solvents. Photolithography is a cost-effective and high-throughput technique that is suitable for large-area surface patterning with good alignment, controlled topography and a broad range of features. However, it is relatively costly for achieving large-scale manufacturing of patterned surfaces at high resolution. Nanoimprint lithography is a non-conventional and cost-effective lithography technique that shows promise for applications in high-throughput and high-resolution production of patterned polymer nanostructures. In a typical nanoimprint lithography process, an imprint resists (thermo- or UV-curable polymer) is first spin-coated on a substrate surface and then pressed against a rigid mold with topographic features ranging from micro-to nanoscale sizes. In addition to the above two methods, femtosecond-laser ablation and direct laser writing have been widely researched and applied to produce patterned surfaces [15]. Femtosecond-laser ablation is a cost-effective and flexible technique that is suitable for processing a wide range of materials. The surface pattern is produced by altering and removing materials at pre-designed areas using a laser beam focused through an objective lens. Direct laser writing, also known as two-photon laser writing, is a high-resolution technique capable of fabricating nanoscale features on photo-crosslinkable resins with high resolution and high precision [23,24]. Although this technique can produce multiscale and complex structures, it is expensive and time-consuming, and only suitable for processing objects with sub-micrometer sizes. Compared to the four common surface patterning methods described above, μCP is a more convenient technique that can be applied for precisely replicating surface microstructures and/or fabricating surface patterns [24,25]. Besides the precise production of surface geometric structures, μCP is frequently used for chemical group grafting, protein patterning, and biomolecule imprinting, which demonstrate a broad range of applications of this technique in the biomedical field. In recent years, some advanced functions have been realized in biomedical devices through the innovative application of μCP [27–29]. In this review, we present an up-to-date overview of μCP in a diverse range of biomedical applications and illustrate these with representative examples where μCP has been used as a surface patterning technique for manipulating the behavior of cells and for manufacturing materials with a potential biomedical application, as well as for the development of biosensors (Fig. 1), We systematically introduce the diverse capabilities of μCP and its specific advantages in biomedical applications to cover the most recent advances in the field and conclude with a discussion of limitations and future perspectives.

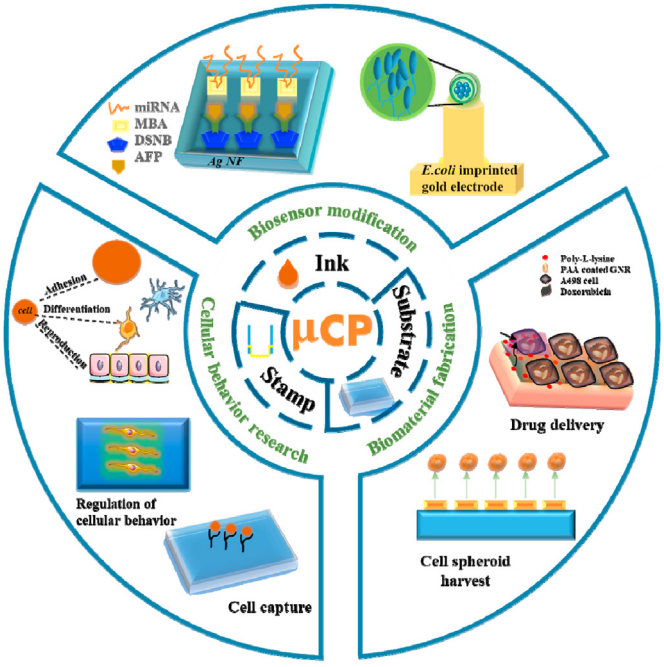


**Fig. 1.** Diverse biomedical applications of μCP.

## 2. μCP and its technical characteristics

μCP was first proposed in 1993 by Lopez [30] as a method for controlling both the concentration and spatial distribution of proteins adsorbed onto patterned self-assembled monolayers (SAMs). It belongs to the family of soft lithography techniques, which is one of the most commonly used categories of surface modification techniques for biomedical applications. The main functions of μCP in surface manipulation include the fabrication of well-defined geometric patterns and 2D surface patterning. The principle of fabricating geometric patterns using μCP is similar to that in nanoimprinted lithography. The main difference is that the stamp used in nanoimprinted lithography comprises surface structured materials that are as-prepared by techniques such as photolithography and femtosecond-laser ablation. In contrast, the stamp used for μCP can be copied from a material with pre-designed geometric patterns. This function is extremely useful for transferring topographic cues from naturally structured materials, such as butterfly wings [31], shark skin [26], and fish scales [15], to the target material and achieve efficient large-scale production. However, the copying of pre-designed geometric patterns from a template inevitably sacrifices the resolution of the topographic features imprinted onto the substrate surface.

The core advantage of μCP over other surface modification techniques is realized through its 2D surface patterning function. This allows chemical functional groups or polymers, proteins, and biological cues to be cast or transferred onto a substrate surface in specifically designed patterns. As shown in Fig. 2A, the principle of protein and chemical molecule patterning using μCP is simple. First, a stamp with pre-defined geometric patterns is produced by replication from a silicon template master. Second, the prepared stamp is soaked in the target protein or chemical molecule solution that is normally termed as the 'ink'. Third, the stamp is fixed to a printing machine, and force is exerted to ensure that the soft stamp has fully contacted and conformed with the substrate surface. Finally, the micropattern of the ink is printed on the substrate surface after the stamp is detached. μCP can also be used to produce topographic features from one material to another, as shown in Fig. 2B. In this process, a thermo- or UV-setting material, such as SU-8 should be spin-coated on the substrate. After material setting and subsequent detachment of the stamp, surface geometric patterns can be produced. Polydimethylsiloxane (PDMS) is the most widely used stamp material. Since it is a soft polymer, PDMS can be easily molded and conformed to make full contact with the substrate surface. In addition, its surface properties can be tuned to accommodate different types of ink through surface treatment, such as ozone and oxygen plasma treatment. For successful transfer of the ink to the substrate surface, the bonding

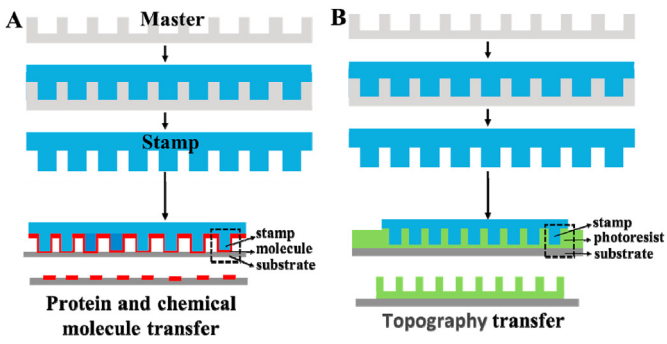


**Fig. 2.** Schematic illustration of the μCP fabrication process, consisting of (A) PDMS stamp preparation and transfer of molecules or (B) PDMS stamp preparation and topography transfer.

strength of the ink with the stamp should be weaker than that with the substrate surface [32]. Therefore, the surface chemistry of the stamp should be adjusted such that the ink can be printed onto a variety of substrate materials. Although the softness of the PDMS stamp makes contact printing more convenient, it also introduces some common drawbacks, such as stamp swelling during inking and stamp deformation, which can lead to distorted patterns or patterns without clearly defined edges [21,33,34]. Fortunately, stamp swelling and deformation can be avoided through the careful optimization of operation methods [35,36] and printing parameters, such as the ratio of PDMS and curing agent [37] and the applied force [38]. Other factors critical for successful patterning of target molecules include the content of the ink immobilized on the stamp, since excessive ink can result in uncontrollable diffusion to areas that should be left bare [39]. By optimizing the critical parameters of bonding strengths among the ink, stamp and substrate, the concentration and content of the ink immobilized on the stamp, and the force applied on the stamp, 2D surface patterning can be realized using μCP with high resolution and efficiency on a wide range of biomedical surfaces.

μCP is a versatile surface modification technique that is capable of not only producing defined topographical features, but also manipulating surface chemical and biological cues through customized inks. Compared to other surface patterning techniques, μCP offers distinct advantages of low cost combined with high reliability and versatility. It also presents the possibility for large-scale customized manufacturing, since the speed of fabrication and sample repeatability are assured by mechanical operation controlled by a preset program. Although the principle of μCP is simple, its operation parameters can be delicately tuned and optimized to obtain ideal surface patterns on a variety of substrates. This technique has been explored and applied in diverse fields, showing high potential for enabling interdisciplinary research in science, engineering and medicine, and its applications are constantly expanding. In the next sections, we present the latest advances enabled by μCP in biomedicine, categorized by its functions in constructing cell culture platforms, biosensing platforms, and devices for other biological applications.

## 3. Applications of μCP in biomedicine

### 3.1. Use of μCP in constructing cell culture platforms

The extracellular matrix (ECM) within which cells reside is a complex 3D microenvironment and constitutes one of the most important extrinsic mechanisms regulating cell behavior [40]. The ECM provides cells with scaffold support in the form of a microscale hierarchical mesh containing topographical and biochemical cues. It has been well-documented that the topographic, chemical and biological cues in the ECM have profound influences on cell activity and fate [41]. Inspired by this, scientists have contemplated the modulation of cell behavior by engineering surface topographical, chemical, and biological features. μCP has been used as a highly versatile method for tailoring surface properties to mimic the functions of the ECM, with the ability to produce precise topographical, chemical and biological patterns that have potent potential in controlling cell behavior.

Contact guidance is a widely reported phenomenon [42,43], which refers to the alignment of cells in the direction of anisotropic topographical or biochemical cues. This alignment induces changes in the cell cytoskeleton that further affect downstream cell behavior. A study investigated the mechanism of contact guidance by fabricating a patterned substrate using μCP, comprising parallel stripes of fibronectin with different widths and inter-stripe spacings [29]. When human myofibroblasts were seeded on these substrates (Fig. 3A), they were found to respond to the anisotropic geometrical cues on the substrate ranging from 2 to 200 μm. The experimental and computational results both suggested that when cell alignment occurred at such length scales, the cells tended to elongate and maximize actin polymerization while avoiding the formation of cellular adhesions on non-adhesive gaps without fibronectin.

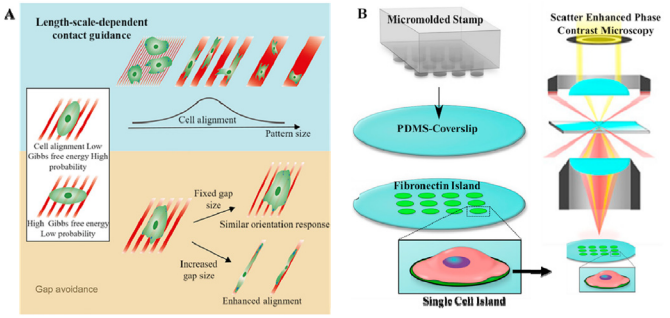


**Fig. 3.** Use of μCP to construct cell culture platform for (A) uncovering the underlying mechanisms of cellular contact guidance [29], (B) discriminating mechanisms of active nanoparticle transport in living cells [47].

In another study involving fibronectin patterning, comet-shaped topographic patterns of fibronectin with four corners were fabricated to study the mechanism of cell extrusion [44]. This is a process through which epithelial tissues remove unnecessary or pathological cells, and is intimately linked to developmental, homeostatic and pathological processes. In this study, epithelial cells were cultured on micropatterned substrates coated with fibronectin using μCP, and their measured strain rate and stress were compared to numerical simulations. The results indicated that comet-shaped topological defects in epithelia could mechanically induce cell apoptosis and extrusion, which could potentially inform tissue regeneration or the suppression of metastasis. This and the above example point out the capability of μCP in fabricating useful platforms for specific studies of cell behavior, and its potential in achieving flexible control of protein patterns at precisely defined spacing arrangements.

μCP has also been used to construct cell culture platforms to study mechanosensation, a process that requires mechanical signals to be integrated and interpreted by cells in the context of chemical cues. In a study focusing on a commonly expressed receptor, ovarian cancer G protein coupled receptor 1 (OGR1), μCP was used to produce a patterned fibronectin surface for cell attachment that delivered both physical and chemical signals [27]. By subjecting cells to a variety of cues including membrane stretch, different substrate stiffness, and exposure to extracellular $H^+$, it was found that OGR1 in different cell types only responded to extracellular acidification under conditions of membrane stretch and vice versa. This example demonstrated the application of μCP in producing cell attachment substrates that could integrate chemical and physical stimuli, and enable mechanistic studies to be performed at the receptor level.

Other than producing patterns to direct cell attachment, μCP can be used to fabricate platforms that enable the controllable modulation of cell migration. An example of this was the use of μCP to produce a surface-engineered near infrared (NIR) light-responsive actuator [45]. A thermoresponsive copolymer hydrogel containing gold nanorods was first grafted onto the substrate surface, where the cell adhesive peptide ligands were then patterned. Upon NIR light irradiation, contraction of the hydrogel led to an increase in Young's modulus of the surface, which induced and accelerated migration of the attached cells along a fixed direction guided by the peptide ligand pattern. This optical modulation of cellular events may enable a range of interesting applications in the study of specific cell behavior. Besides patterning proteins or peptides directly onto surfaces, μCP can also be used to pattern micro- or nano-sized particles grafted with single-stranded DNA oligonucleotides, resulting in the production of creatively functionalized surfaces that can be used for cellular uptake and guidance studies [46].

In addition to using μCP for producing surfaces that directly affect cell behavior, the patterned proteins can be used to produce single cell arrays that achieve real-time monitoring of cell behavior through the combination of analytical techniques. For instance, scatter enhanced phase-

contrast microscopy (SEPC) has been combined with surfaces patterned using μCP to investigate the cellular uptake of $TiO_2$ nanoparticles [47] (Fig. 3B). This method was found to allow effective monitoring of cellular uptake of nanoparticles with sizes down to 35 nm by simultaneously tracking the movement of nanoparticles and the cell membrane. This study demonstrated an expanded application of μCP in studying the dynamics of cellular uptake of nanoparticles or other agents.

A challenge that can be encountered in studies involving surfaces with printed proteins is the geometric shape of patterned proteins can have variable long-term stability. To solve this problem, a study used poly(acrylamide) (PAAm) brushes during μCP to passivate the area surrounding the protein pattern on the substrate surface [48] (Fig. 4A). The PAAm brushes were first patterned on transparent gold using a stamp with square hollow structures, and the un-patterned areas were then immobilized with fibronectin, generating fibronectin squares fenced with PAAm brushes. These micropatterns showed long-term stability (up to 10 days) in culture and a long shelf life of at least 6 months without losing their ability to direct cell function. Different sizes and geometries of PAAm brush-based micropatterns were found to directly influence the morphology of pancreatic tumor and fibroblast cells. This stable cell culture platform, which can be simply and conveniently manufactured using μCP has great potential to be applied in studies on the geometrical regulation of cell differentiation behavior.

Besides 2D surface structures, μCP can be used to create 3D surface modifications for studying the control of cell behavior. A prime example is the use of μCP to produce a 3D constrained cell culture platform [49] (Fig. 4B). PDMS wells with varying anisotropy were prepared by soft lithography, and the surfaces between wells were printed with bovine serum albumin using μCP to prevent cell adhesion. Human fetal lung fibroblasts cultured in these 3D microenvironments showed significant changes in anisotropic alignment depending on the aspect ratio of the rectangular wells used to induce cell confinement, which influenced cell behavior through cytoskeletal changes. This work used a combination of soft lithography and μCP to provide an interesting 3D cell culture platform, which constrained cell migration to allow the study of biophysical cues on directing cell behavior. This platform could be a step forward in translating the biophysics of cell-matrix interactions towards establishing functional 3D tissue constructs in regenerative medicine. In another example, different types of proteins were printed onto a slide to create a platelet capture region in the construction of a flow chamber system for studying blood-implant interactions [28]. By perfusing whole blood through the flow chamber, this system was used to quantify platelet adhesion at the capture region after the platelets were exposed to high shear stress. This is an example of a 3D model system for aiding biomedical device design enabled by μCP.

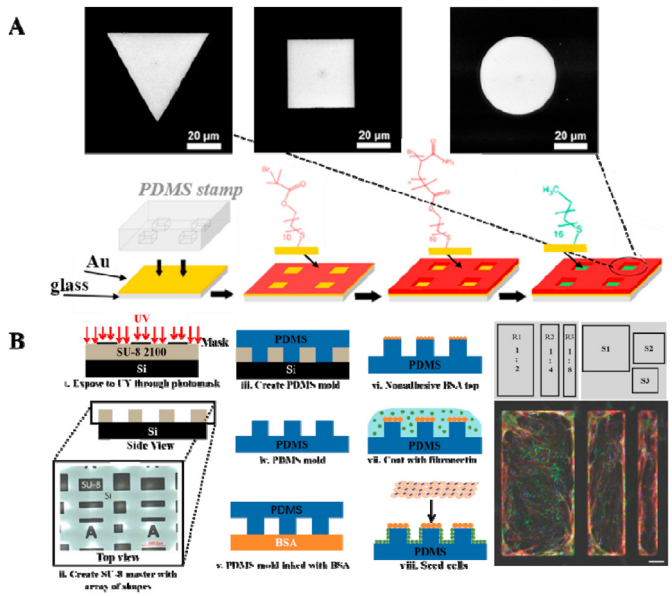


**Fig. 4.** Use of μCP to (A) fabricate micropatterns based on PAAm brushes [48], and (B) construct a 3D constrained cell culture platform [49].

### 3.2. *Use of μCP in constructing biosensing platforms*

In recent years, biosensors as analytical devices have gained great importance in the detection of chemicals and molecules in biological systems. A biosensor consists of two basic units: a bio-receptor for the detection of specific biological elements and a signal converter for translating the findings into a useful signal for analysis and interpretation. Biosensing as a detection method is widely used for the diagnosis of various health problems, including diabetes and obesity [50,51]. Since glucose was first detected by Clark and Lyons in 1962 [52], the applicability of biosensors has expanded to bio-recognition of nucleic acids, antibodies, and cells [53–55]. Biosensors have broad applications in wearable biomedical devices due to their high specificity, speed, portability, low cost, and low power consumption requirements [56]. The detection of biomolecules by biosensors requires that signal receivers have the characteristics of high sensitivity and specificity and multi-functional detection. For these reasons, μCP is often used in the design and preparation of biosensors to improve their performance, since it allows the transfer and grafting of specific molecules with high accuracy and flexibility. Some studies have used μCP to realize the simultaneous detection of multiple specific receptors for a certain disease to improve the sensitivity of molecular detection, while others have achieved multi-functional detection using μCP by combining different types of receiver arrays.

Capacitive biosensors have the advantages of being label-free, having high selectivity and low detection limit, and allowing the rapid and real-time detection of biological molecules [57]. Using μCP, cell or molecular imprinting can be achieved to allow the selective detection of target cells or molecules which are similar in size and shape, or have a matching chemical functionality to that of the template. μCP has been combined with a capacitive biosensor to allow whole cell sensing of *E. coli* with high selectivity and low detection limit [7] (Fig. 5A). In this study, gold electrodes were coated with amino acid-based UV-curable polymers, and *E. coli* were immobilized on a slide as the printing stamp. The gold electrodes were then printed with the stamp and the polymer was cured with UV. Finally, the *E. coli* were wiped off but specific recognition cavities were conserved. This created a whole cell biosensor that was able to distinguish *E. coli* with high specificity, even when presented together with competing for bacterial strains with a similar shape.

In addition to whole cell imprinting, protein molecules can be printed on a substrate surface for biosensor development to create platforms for biomarker-based disease diagnosis. Prostate specific antigen (PSA) is an important biomarker for the diagnosis and prognosis of prostate cancer. To achieve sensitive and real-time detection of PSA, μCP was used to create a PSA-imprinted surface plasmon resonance (SPR) sensor chip [58] (Fig. 5B). SPR biosensors provide optical sensing based on surface refractive index changes when an analyte interacts with the bio-recognition molecule, offering real-time and fast measurement with high sensitivity and specificity. The PSA-imprinted sensor chip is produced by first preparing a protein stamp with immobilized PSA, and then printing the PSA onto the SPR chip coated with a layer of the photo-polymerization monomer solution. During printing, polymerization of the monomer solution is initiated under UV light, resulting in a PSA-imprinted SPR chip. When used for the analysis of clinical serum samples, the developed system showed up to 98% agreement when compared to the results obtained using the commercial enzyme-linked immunosorbent assay (ELISA) method. This novel biosensing system enabled by μCP avoids the drawbacks of traditional PSA detection using ELISA, such as high costs, long preparation steps, long analysis time, and a requirement for labeling agents, making it more suitable for real-time

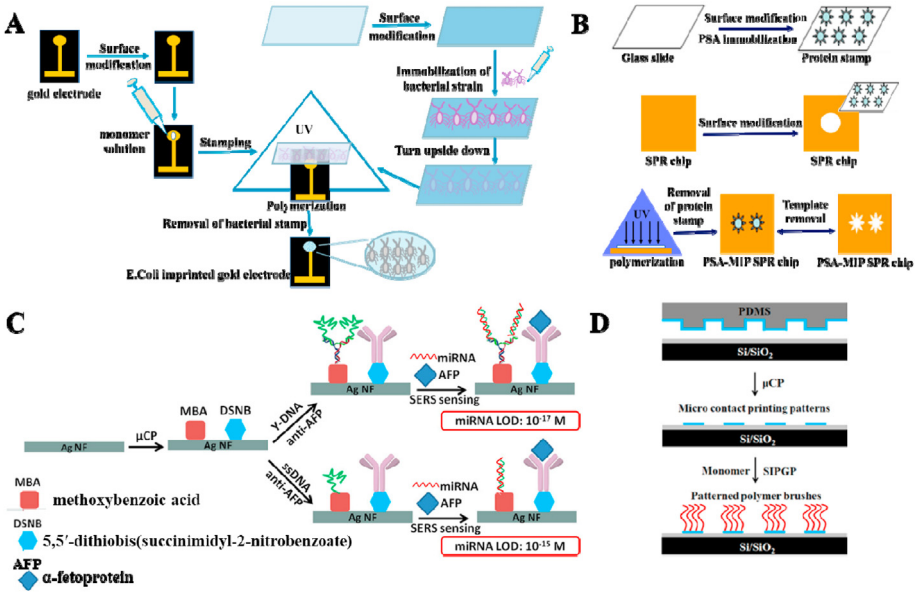


**Fig. 5.** Use of μCP to construct biosensors for (A) *E. coli* [7], (B) PSA [58], and SERS biosensing platforms for (C) multiplex biosensing of miRNA and protein [59], and (D) pollutant monitoring [61].

detection.

In an advanced application of μCP, an ultrasensitive detection platform with the capability for multiplex sensing was developed, allowing both microRNA (miRNA) and protein to be detected simultaneously as liver cancer biomarkers [59]. This work made use of surface-enhanced Raman scattering (SERS), an efficient method for the direct detection of miRNA [60]. Silver nanoparticle films were used as SERS substrates, onto which different domains of Raman reporters were fabricated using μCP (Fig. 5C). These multifunctional domains contained delicately designed branched DNA to increase the sensitivity of detection for miRNA, as well as an antibody for the detection of a specific protein biomarker. The detection limit in this system was as low as $10^{-17}$ M for miRNA, and $10^{-12}$ M for protein. When tested using serum samples, the results of protein biomarker detection were found to be in good agreement with the current gold standard method. Due to its ability to achieve multiplex sensing at ultra-high sensitivity, this system could have great potential for application in the early diagnosis of primary liver cancers, or other diseases with a similar need to simultaneously detect miRNA and protein biomarkers.

Another SERS detection platform was produced using μCP by attaching polymer brushes onto graphitic carbon nitride and then incorporating silver nanoparticles [61] (Fig. 5D). The graphitic carbon nitride polymer was first printed onto a $Si/SiO_2$ substrate using μCP, onto which polymer brushes were patterned and finally silver nanoparticles were incorporated into the polymer brushes. This platform could be used as a multi-functional recyclable active sensing layer for SERS detection and photocatalysis, with example applications in the *in situ* monitoring of pollutants.

Cytotoxicity assays have broad applications in drug screening and therapeutic development. However, one of the challenges is to develop a high-throughput system that is cost-effective and simple to use, while enabling rapid detection of both cell detachment due to death and the toxic effects of compounds that promote cell adhesion. To solve this problem, μCP was used to create a 'single cell adhesion dot array' [62] (Fig. 6A). Dots of fibronectin to allow the attachment of single cells were printed onto the surface of culture plate wells, creating a protein pattern comprised of 20,000 dots of 20 μm in diameter separated from each other by 50μm. Bovine serum albumin was then added to each patterned well to block the spaces between dots and prevent cell adhesion in these areas. During cytotoxicity testing, the dynamic response of cells was digitally

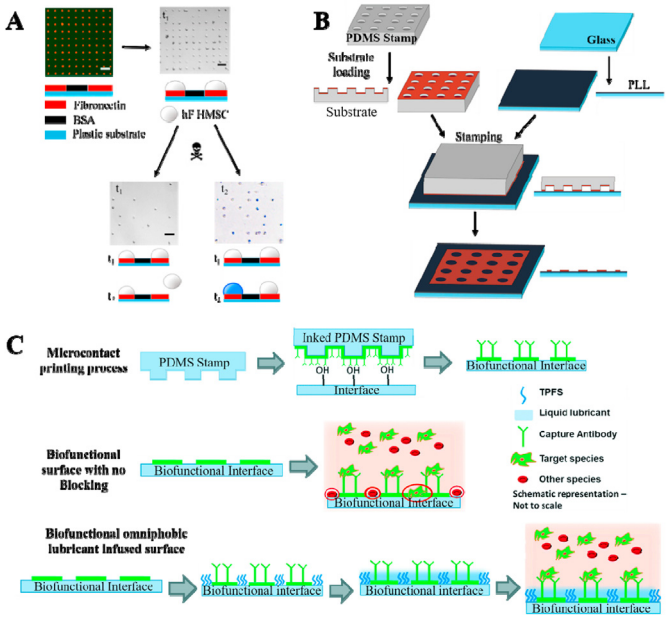


**Fig. 6.** Use of μCP to construct (A) a real-time cytotoxicity assay [62], (B) a synapse compartmentalization culture system [64], and (C) a biofunctional lubricant-infused surface [65].

quantified using bright field microscopy, by monitoring for cell death both through cell detachment (unoccupied dots) and trypan blue live/-dead assay (stained dots). Compared to other currently available cytotoxicity tests based on analogical signals or flow cytometry, this biosensing platform provides single cell resolution due to digital counting, as well as dynamic and real time measurements. This system is also simple and cost-effective, since only optical evaluation needs to be performed rather than relying on sophisticated equipment, which could enable high-throughput cytotoxicity measurements at the point of need. Other designs of single cell adhesion dot arrays created using μCP can be used as high throughput sub-cellular toxicity assays [63].

The application of biosensors can be extended to the assessment of neuronal synapses. The functions of a neuronal circuit are determined by

the quality and quantity of its synapses. However, efficient and cost-effective synapse assessment using conventional culture systems is a challenge. To solve this problem, μCP was used to produce a patterned surface as part of a 'synapse compartmentalization' culture system to concentrate the synapses at controlled locations [64]. A glass slide was first coated with poly-l-lysine (PLL) to induce synapse assembly, after which stamps with a negative dot array were immersed in an anti-adhesive protein and printed onto the PLL-coated surface using μCP, to prevent synapse adhesion at defined locations (Fig. 6B). This created a bio-chip platform that could be used as part of a high-throughput assay to efficiently assess synapse morphology and function.

In addition to the above applications of μCP in the construction of biosensor platforms, this technology can also be used to produce specifically patterned surfaces that may have applications in biosensing. For instance, μCP has been used to create a lubricant-infused surface where biofunctional domains were micropatterned within an omniphobic layer [65]. This surface was shown to promote both localized and directed binding of desired targets, as well as repel undesired species in human whole blood (Fig. 6C). In other examples, μCP was used to create carbohydrate patterns which could enable a range of analytical and diagnostic applications [66], and platelet-repellent polyphenolic surfaces which could be used in platelet adhesion detection [67]. In all of these examples, μCP was used to pattern surfaces with various types of molecules to enhance functionality, targeted bonding, and to prevent non-specific adhesion.

### 3.3. Use of μCP in constructing devices for other biological applications

In addition to the applications of μCP in constructing cell culture and biosensing platforms, this technology has been combined with a range of other approaches to develop new biomedical device designs for various applications, such as drug delivery, biofuel cells, implant coatings, and tissue engineering. All of these applications stem from the ability to use μCP for the selective immobilization of cells, biomolecules, and even liquids with special properties onto a variety of substrates.

In the development of a new drug delivery platform, μCP was used to fabricate plasmonic nanostructures, which use photothermal conversion to manipulate the local temperature in the control of cellular behavior and biologics delivery. In this study, a plasmonic interface with a lattice pattern of surface features was produced through μCP, consisting of gold nanorods with photothermal conversion properties and poly-L-lysine (PLL) as cell adhesion molecules [68] (Fig. 7A). The PLL allowed directed cell positioning on the patterned surface, followed by the addition of doxorubicin into the culture medium as a model drug. Under focused laser irradiation on individual surface features with the attached cells, local heat generation from the photothermal effect of gold nanorods enhanced drug delivery into the cells. This method allowed highly selective and efficient light-induced drug delivery that could be temporally and spatially targeted. This method of using μCP to produce precise micro-to nano-scale surface chemical patterns could be highly useful for enabling targeted molecular delivery to single cells, and subsequent study of single cell behavior. Nevertheless, local temperature changes do not influence the specificity of uptake of chemical factors by cells, and additional recognition factors need to be introduced to allow controlled delivery of multiple types of molecules to cells using this method.

μCP has been applied in the production of new biofuel cells. Compared to other energy sources, the conversion of hydrogen generated by microorganisms such as bacteria and algae into electricity may be more efficient and environmentally friendly. However, effective immobilization of microorganisms or enzymes on the anode of biofuel cells is a common challenge. One study used μCP to imprint algae onto biofuel electrodes [69] (Fig. 7B). Algae were first adsorbed onto a glass slide to form an algal stamp, which was cast using poly(ethylene-co-vinyl alcohol) (EVAL). A platinum-coated poly(ethylene terephthalate) (PET) film was then printed onto the EVAL-coated algae stamp, which when peeled off forms an algae-imprinted EVAL Pt-PET electrode. The algae-imprinted cavities allowed the readsorption of algal cells with high recognition capability, providing great potential for the use of this system as a modified biofuel cell with improved efficiency.

Although μCP has been used in many biomedical platforms to promote cell adhesion, reduced adhesion is desired in certain scenarios. For surgical instruments, the adhesion of blood, bacteria and soft tissues constitutes a significant challenge in maintaining surgical efficiency [70]. To address this challenge, a liquid-infused surface has been developed for reducing the adhesion force of tissues to surgical instruments [71] (Fig. 7C). A photoresist well-texture was first created using μCP, which was transferred onto the instrument surface through electrochemical etching. When the instrument is subsequently immersed in a saline solution of octadecyl trichlorosilane (OTS), a monomolecular layer self-assembles on the well-textured surface that allows liquid infusing. Surgical instruments treated using this process demonstrated significantly reduced adhesion force between the tissue and the instrument tip, together with smaller damage to the operated tissue and greater durability, providing practical value for instrument design.

In tissue engineering applications, μCP has been used to produce cell sheets and spheroids by patterning hydrogel platforms. For instance, thermosensitive hydrogels with patterned polydopamine (PDA) have been constructed using μCP [72] (Fig. 8A). In this system, a PDMS stamp with different widths (50, 100, and 200μm) was coated with PDA and then printed onto a thermosensitive hydrogel. Human dermal fibroblasts

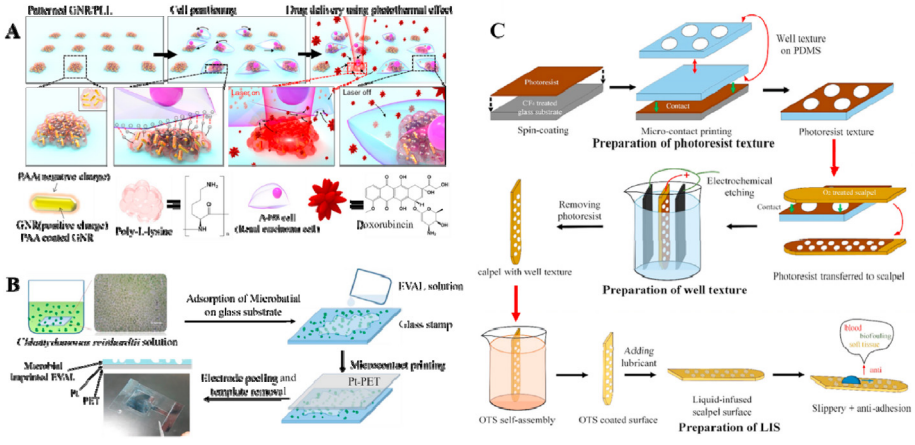


**Fig. 7.** Use of μCP in the development of (A) a light-induced drug delivery system [68], (B) an algae-imprinted biofuel electrode [69], and (C) a liquid-infused anti-adhesion surface for surgical instruments [71].

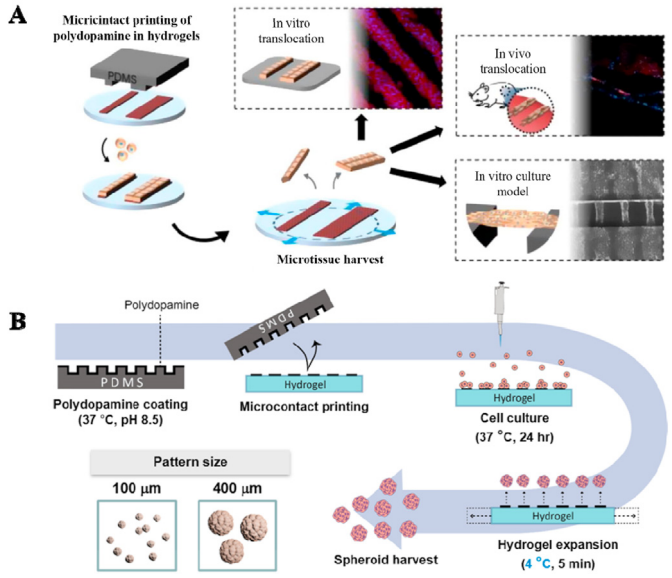


**Fig. 8.** Use of μCP and thermosensitive hydrogels to create (A) a cell sheet harvesting system [72], and (B) size-controlled stromal cell spheroids [6].

were cultured on these printed hydrogels, which were released as cell sheets when the hydrogel responded to a change in temperature from 37 to 4 °C. The harvested cell sheets were found to have similar widths to the original pattern sizes, while maintaining cell viability and the expression of ECM proteins both after *in vitro* translocation and *in vivo* transplantation.

In a similar approach of incorporating thermosensitive hydrogels in the printing process, μCP was used to produce surface patterns for inducing the formation of self-assembled stromal cell spheroids [6] (Fig. 8B). These spheroids have many applications in tissue engineering since they can reproduce the 3D physiological microenvironment of natural tissues. Through the upregulation of hypoxia-induced angiogenic factors such as vascular endothelial growth factor (VEGF), the gradient of oxygen and metabolites in the spheroids accelerates the angiogenic potential of stromal cells. Furthermore, the spheroids allow a greater degree of cell-cell and cell-matrix interactions compared to 2D culture, which can improve the stability of the spheroid and survival rate of cells during delivery or cryopreservation. By printing squares of PDA on a thermosensitive hydrogel using μCP, stromal cells could adhere selectively to the squares and form cell sheets according to the size of the square (100 or 400 μm diameter). When the temperature was changed, hydrogel expansion caused the cell sheets to be released and self-assemble into spheroids. The size of spheroids was determined by the initial dimensions of the cell sheet, and was found to be maintained after injection, cryopreservation and 7 days of suspension culture with high viability. This novel system of creating size-controlled spheroids using μCP could have a wide range of applications in regenerative medicine.

Instead of fixing the printed patterns on the substrate surface as in the above examples, other interesting biological functions can be achieved using μCP by releasing the printed patterns from a sacrificial layer. In one example, injectable and crosslinkable PLGA-based micro-ribbons were prepared by μCP to form a 3D macroporous stem cell niche [73] (Fig. 9A). PLGA micro-ribbons were first printed onto a sacrificial poly(vinyl alcohol) (PVA)-coated glass substrate and subsequently released. After being subjected to surface modification in fibrinogen solution, the PLGA micro-ribbons were freeze-dried to maintain their 3D shape and placed in contact with thrombin to induce crosslinking. This process resulted in the formation of 3D macroporous scaffolds displaying excellent strength and stability, which could be loaded with cells to create a stem cell niche or cell delivery vehicle.

To achieve efficient transportation in targeted drug or cell delivery, self-propelled 'microrockets' have been prepared through innovative use of μCP [74] (Fig. 9B). A PDMS stamp patterned with a micropillar array was first fabricated, after which positively charged chitosan and negatively charged sodium alginate were alternately deposited layer-by-layer onto the patterned stamp to form a polyelectrolyte multilayer (PEM) film. The PEM film serves as the ink and is printed onto a glass slide coated with PVA through μCP, resulting in a well-defined array of PEM microplates. When the sacrificial PVA layer was immersed in pure water and heated to approximately 45 °C, the microplates underwent immediate curling and release from the PVA. The self-rolled PEM membranes were thus transformed into well-defined microtubes. When coupled with platinum nanoparticles, which could decompose hydrogen peroxide to provide a driving force, these microtubes could act as bubble-propelled microrockets with ultrafast speed and a high towing force. This interesting device could be used as an efficient delivery vehicle for single or multiple cells or drugs. In a similar self-actuating system produced using μCP, microtube and single spermatozoon were combined to form a 'spermbot' [75]. The power of these spermbots was found to be correlated with microtube size, and the chemistry of biomolecules on the surface of the inner tube was found to affect the bonding between the microtube and sperm. Both of these parameters could be controlled using μCP to produce more efficient micromotors in this system.

In an integrated approach aimed at developing an improved delivery system for cell therapy, μCP was used to create disk-shaped

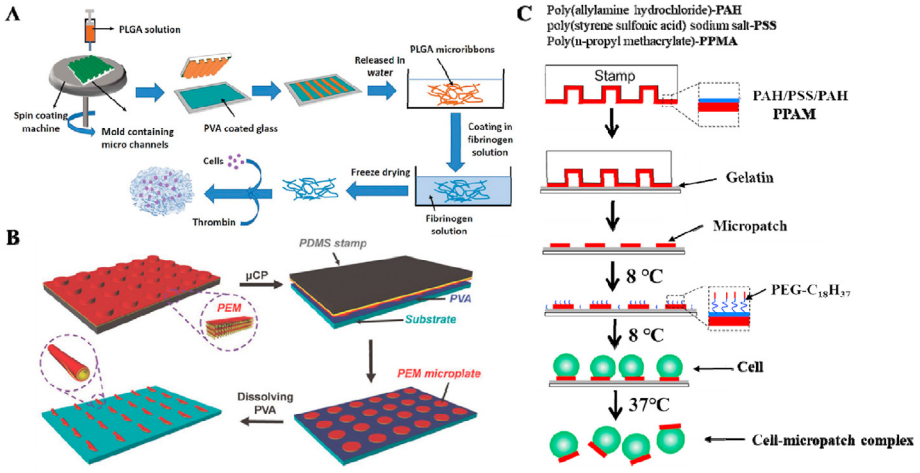


**Fig. 9.** Use of μCP to produce (A) 3D macroporous PLGA scaffolds as a stem cell niche [73], (B) 'microrockets' for efficient cell and drug delivery [74], and (C) cell-micropatch complexes for cell delivery [76].

microparticles, or 'micropatches', that were then conjugated to cells to form cell-particle complexes [76] (Fig. 9C). Patterns of micropatches comprising a specific combination of chemicals were first printed onto a sacrificial gelatin layer coated onto the substrate. The printed micropatches were then functionalized with linear molecules of octadecyl chain and poly(ethylene glycol), which enabled cells to be coupled to the micropatches through membrane intercalation. The gelatin sacrificial layer dissolved when the temperature was increased to 37°C (simulating body conditions), resulting in release of the cell-micropatch complexes. Complexes composed of a range of cell types, such as mouse neuroblastoma cells were found to be stable *in vitro* despite the absence of chemical bonds, and the micropatch-bound cells maintained the ability to remain viable, proliferate, and differentiate. In this example, μCP played a key role in forming a living cell-microparticle conjugated system that could be prepared with low cost and high efficiency, with potential applications in the development of new cell delivery systems.

## 4. Concluding remarks

μCP is a versatile surface modification technique that uses elastomeric PDMS stamps with a topographically patterned surface to print a customized ink onto a variety of substrates. Different from other commonly used surface patterning methods for biomedical applications, μCP offers the ability to produce precisely patterned topographic, chemical and biological cues on the surface for the targeted control of cell or bacterial behavior. μCP is an interdisciplinary surface modification technique, requiring delicate design of the ink-stamp and ink-substrate interfacial bonding to achieve high-quality patterning, as well as micromachining techniques to produce a well-defined surface topographic pattern on the stamp. The incorporation of these physical and chemical fabrication aspects allows μCP to be flexibly applied for producing customizable and precisely controlled surface patterns in many innovative applications.

In this review, we have provided an up-to-date summary of the potent biomedical applications of μCP in constructing novel platforms for cell culture, biosensing and drug delivery. All of the presented examples involve the utilization of multidisciplinary knowledge to precisely measure or control biological behavior. As the field of biomedical engineering continues to evolve rapidly, there is a greater need to understand the mechanisms underlying cell or bacterial behavior in bioengineered systems, for which the use of μCP to create customized research platforms will become more advantageous. From the studies included in this review, it is apparent that topographic features are of great importance in controlling biological behavior. Controlling surface topography has several advantages compared to chemical and biological modification of the surface, such as cost-effectiveness, lower complexity of processing, long shelf life and/or low demand for storage conditions, and relative ease to convert into large-scale manufacturing, all of which are important for practical applications. Surface micro- and nano-topography have been widely used to improve implant-tissue interactions and interfacial integration. For example, our previous study reported the fabrication of nanostructured ceramic coatings on titanium alloy implants, which was found to significantly enhance implant osseointegration [77]. In this case, both bioactive ions released from the coating and the surface nanostructure could have contributed to the enhancement of biological response. However, as is the case with many other studies, it is difficult to effectively decouple the multiple physicals, chemical, or other factors influencing surface-mediated biological reactions and to understand the respective contributions of these factors in regulating cell behavior. There is hence a great need for fabrication techniques that can precisely engineer and control substrate surface properties. μCP can potentially meet this need by providing the ability to adapt its properties for replicating and then fabricating the micro- and nano-scale features of research objects on a new substrate. The patterned surfaces produced by μCP can then be used for mechanistic studies to understand the contribution of specific types of surface features in controlling cell behavior or to construct new platforms for practical applications such as assays, biosensors, drug delivery, and bacterial control. Recent advances in the development of μCP have enabled pattern printing with high resolution down to 100 nm [78].

The role of μCP in enabling new biomedical applications will be sure to expand and diversify in years to come, and its capabilities in this field will become more powerful through the increasing convergence of knowledge across disciplines.

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## Declaration of competing interestCOI

All authors declare no competing financial interests.

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