TOPICAL REVIEW

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Topical Review

MEMS-based platforms for mechanical manipulation and characterization of cells

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Abstract

Mechanical manipulation and characterization of single cells are important experimental techniques in biological and medical research. Because of the microscale sizes and highly fragile structures of cells, conventional cell manipulation and characterization techniques are not accurate and/or efficient enough or even cannot meet the more and more demanding needs in different types of cell-based studies. To this end, novel microelectromechanical systems (MEMS)-based technologies have been developed to improve the accuracy, efficiency, and consistency of various cell manipulation and characterization tasks, and enable new types of cell research. This article summarizes existing MEMS-based platforms developed for cell mechanical manipulation and characterization, highlights their specific design considerations making them suitable for their designated tasks, and discuss their advantages and limitations. In closing, an outlook into future trends is also provided.

(Some figures may appear in colour only in the online journal)

1. Introduction

In the past few decades, manipulation and characterization of biological cells have been a popular research topic at the boundaries of several disciplines such as micro and nanotechnology, biomedical engineering, biology, and medicine [1]. Mechanical cell manipulation techniques, such as cell transfer, isolation, immobilization, and injection, have been widely used in many biological and medical applications such as single cell analysis [2], cell-based drug screening [3], *in vitro* fertilization [4], and transgenic animal production [5]. As cells

are fragile, high-resolution force sensors are needed in certain cell manipulation tasks to quantify micro- to nanonewton-level cellular forces and avoid any damage to the cells [6]. In addition, the measurement of cellular forces has also enabled mechanical characterization of the cells [7]. Other types of sensors could also be involved to measure the physical properties of single cells such as mass, density, and traction force [8, 9]. These cellular characteristics can provide us with useful insights into the signalling and function of the cells [10, 11].

Microelectromechanical systems (MEMS) have been regarded as ideal tools for cell manipulation and characterization, because of their unique features such as size matching to single cells and capability of generating/measuring microscale

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motions and forces. MEMS sensors and actuators have characteristic feature sizes ranging from sub-micrometers to hundreds of micrometers, which are at the same level of the sizes of single cells. This perfect size matching makes it straightforward and convenient to adopt MEMS devices for cell manipulation and characterization. MEMS displacement and force sensors possess high resolution down to sub-nanometer and sub-nanonewton levels, respectively; thus, the small cell deformation and low cellular force can be accurately detected by on-chip sensors of MEMS-based platforms.

Despite its compact structure, a MEMS device may realize multiple functions (e.g. micrograsping, cellular force sensing, and cell deformation measurement) required in cell manipulation and characterization. In addition, materials commonly used for constructing MEMS devices (e.g. silicon, silicon dioxide/nitride, and polymers) are biocompatible and thus impose little adverse biological effect on cells being manipulated. Moreover, the amenability of MEMS devices to batch fabrication methods allows for manipulation and characterization of many cells in parallel, improving the manipulation/characterization throughput and resulting in robust statistical data.

A variety of MEMS-based platforms have been developed for mechanical cell manipulation and characterization. Several review articles have been published focusing on MEMS-based devices for cellular force measurement and cell mechanobiology [8, 12–14]; however, there is no comprehensive review summarizing the application of MEMS-based platforms to all kinds of mechanical cell manipulation and characterization tasks. This article is aimed to bridge this gap to review the existing MEMS-based platforms for mechanical cell manipulation and characterization, and discuss their unique features suitable for certain types of cell manipulation/characterization tasks. We will not review microfluidic platforms for cell manipulation and characterization, which represent another category of widely used technologies. One can find several excellent reviews on this topic [15–18]. The following MEMS-based platforms will be discussed: (i) MEMS microgrippers for cell grasping, transfer and mechanical characterization; (ii) MEMS physical sensors for cellular force and mass/density measurement; (iii) MEMS-based devices for cell immobilization and patterning; and (iv) MEMS-based cell injectors. In closing, an outlook into future trends along this direction is provided.

2. MEMS microgrippers for cell grasping, transfer, and mechanical characterization

As one of the earliest developed MEMS end-effectors [19], MEMS microgrippers have been a popular tool for manipulating micro-objects [20–22]. A MEMS microgripper can pick, transport, and place a cell in its culture medium; it can also integrate on-chip force sensors for quantifying and controlling the grasping force, thus avoid damage to the cell, and even characterize its mechanical property during manipulation. As biological cells are fragile and usually need to be manipulated in its aqueous culture medium, special considerations in the microgripper design are needed. In this section, we summarize

the existing MEMS microgrippers that have been applied to mechanical cell manipulation and characterization, and discuss their specific designs and experimental conditions.

Based on the actuation method of their gripping arms, existing MEMS microgrippers for cell manipulation can be largely grouped into five categories. (i) *Electrostatic microgrippers*. Electrostatic microgrippers are the first type of MEMS microgrippers reported in the literature [19], which involve electrostatic forces for driving their gripping arms and open/close their jaws. Electrostatic microgrippers share many advantages with electrostatic actuators such as high positioning resolution, fast response, low power consumption, and good compatibility with silicon microfabrication. For cell manipulation, the gripping jaws of an electrostatic microgripper do not have temperature elevation, and could, if properly configured, remain at zero electric potential during actuation; these features make it particularly suitable for interacting with cells. (ii) *Electrothermal microgrippers*. Electrothermal microgrippers rely on the thermal expansion of microstructures to produce motions and actuate their gripping arms [21, 23]. The heat is usually generated by the Joule effect on conductive microstructures. Compared with electrostatic microgrippers, electrothermal microgrippers require smaller footprints for actuation, provide larger gripping forces, but have slower responses. Electrothermal microgrippers usually have one or two 'hot' gripping arms caused by heat transfer from their electrothermal actuators, and may induce thermal damage to cells during manipulation. Special management of the temperature elevation of the gripping arms is needed.

(iii) *Magnetic microgrippers*. Magnetic forces have been recently used for actuating MEMS microgrippers [26–28]. Different from electrothermal actuation, magnetic actuation does not produce heat and thus does not impose thermal impact on biological cells being manipulated. It produces relatively large actuation forces, and allows both on- and off-chip magnetic sources (e.g. an electromagnet) to apply actuation. It can be used to manipulate cells in ionic liquids without special consideration of the device electrical design. (iv) *Self-Folding Thermobiochemical Microgrippers*. This type of microgrippers integrate multiple self-folding gripping arms and are driven by the differential stress or material swallowing in bilayer thin-film structures [25, 29, 30]. Their operations are typically triggered by changes in temperature or chemical environment, and thus called thermobiochemical microgrippers [30]. These are untethered and integrated with magnetic materials, allowing them to be controlled by an external magnetic field for cell transfer. (v) *Pneumatic microgrippers*. Pneumatic actuation has also been implemented in MEMS microgripper designs, in which deformable structures are actuated by pneumatic forces to open and close gripping arms [31, 32]. Pneumatic actuation can provide larger output forces (i.e. at the level of 10's to 100's mN) than other actuation mechanisms, and thus allow large displacements of the gripping arm tips. Table 1 summarizes the working principle, advantages, and disadvantages of the aforementioned five types of microgrippers.

All the five types of MEMS microgrippers have been applied to cell manipulation and characterization. We will review the previous work by categories, and will also discuss

Table 1. Summary of the five types of MEMS microgrippers.

| Microgripper type	Actuation principle	Advantages	Disadvantages
Electrostatic microgripper	Electrostatic force	High positioning resolution; fast response; low power consumption; good compatibility with silicon microfabrication	Long gripping arms; large footprint for actuation; low gripping force; challenging
Electrothermal microgripper	Thermal expansion of microstructures	Small footprint for actuation; large gripping force; large displacement	Slow response elevation at gripping arms
Magnetic microgripper	Magnetic force	No temperature elevation; relatively large gripping force; no limitation in liquid environment	Hysteresis
Self-folding thermobiochemical microgripper	Stress mismatch or material swallowing induced deformation of microstructures	Untethered; movable by magnetic field; parallel operation of many microgrippers	Inability to control grasping force and displacement
Pneumatic microgrippers	Pneumatic force	Large gripping force and output displacement	Relatively complicated fabrication
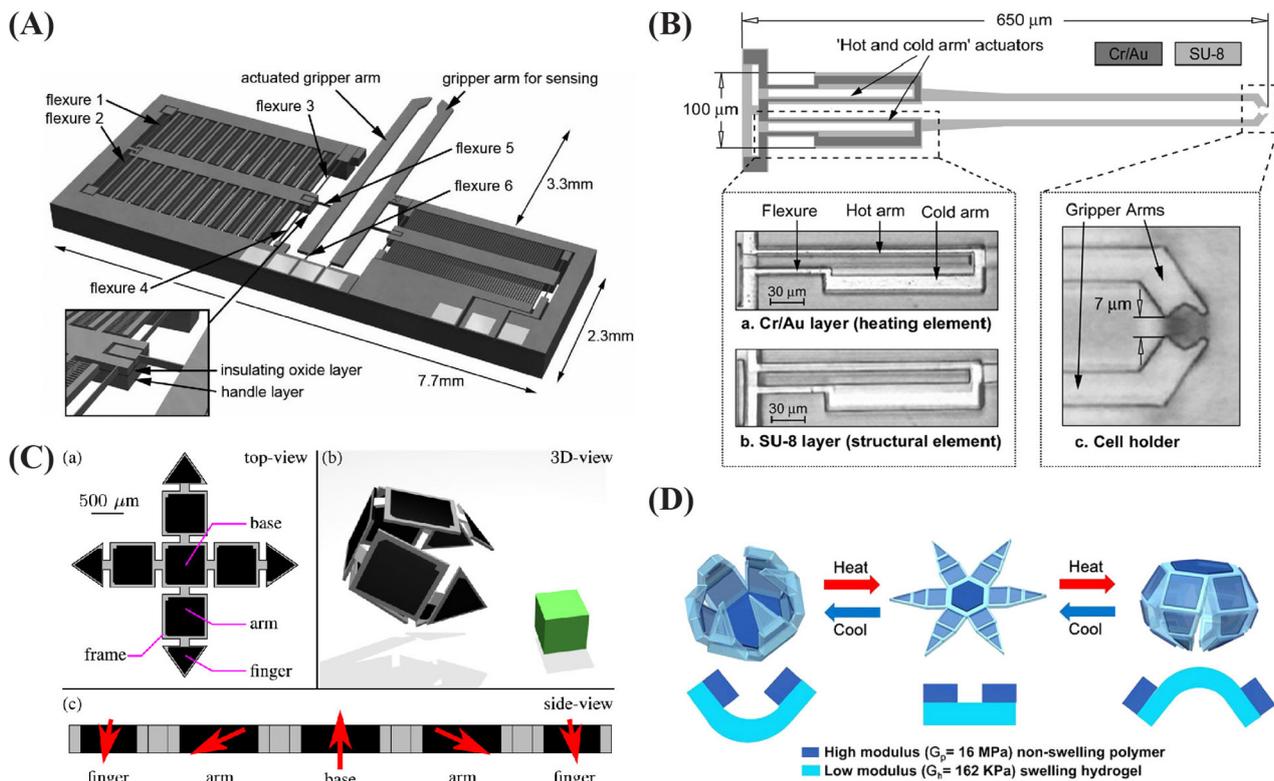
Figure 1. MEMS microgrippers with different actuation mechanisms for cell manipulation and characterization. (A) An electrostatic microgripper with a comb-drive actuator and transverse-comb differential capacitive force sensor. © [2007] IEEE. Reprinted, with permission, from [20]. (B) An electrothermal microgripper fabricated from SU-8 photoresist with the areas of U-beam electrothermal actuators coated with thin-film metal heaters. © [2005] IEEE. Reprinted, with permission, from [23]. (C) An untethered microgripper actuated by magnetically programmable composite materials patterned on its gripping arms. © [2017] IEEE. Reprinted, with permission, from [24]. (D) An untethered microgripper actuated by a swellable polymer layer sensitive to temperature change or chemical. Reprinted with permission from [25]. Copyright (2015) American Chemical Society.

the device design considerations specific for applications in cell manipulation and characterization. For more details of the actuation and sensing mechanisms in MEMS microgrippers, please refer to a recent review article [33].

2.1. Electrostatic microgrippers

Many electrostatic microgrippers have been developed to manipulate micro-objects [19, 20, 34–43], among which several have been applied to cell manipulation. Kim *et al* [19] developed the first electrostatic microgripper with overhanging gripping arms through a surface micromachining process,

and an etch-stop technique was used to create the overhanging gripping arm structures. The device was demonstrated for grasping of red blood cells (RBCs) and micro-organisms. To measure the grasping force during cell manipulation, Beyeler *et al* [20] designed an electrostatic microgripper (figure 1(A)) with an on-chip integrated capacitive force sensor. A lateral comb-drive microactuator was used to drive the active arm, and an transverse-comb differential capacitive force sensor was attached to the passive arm for grasping force measurement. The device was fabricated through a customized silicon-on-insulator (SOI) microfabrication process. To allow this microgripper to operate in aqueous solutions, the active

and passive gripping tips were electrically isolated with the comb-drive actuator and the capacitive force sensor, respectively, by etching through the device layer of the gripping arms with electrical-isolation trenches while using the handle layer of the SOI wafer underneath the trenches for mechanical connection. This microgripper can grasp micro-objects with sizes up to 100 μm with a force measurement resolution down to 70 nN. Glass micro-beads and HeLa cells were picked and placed using this gripper, and the measured grasping force could be monitored to avoid cell damage during manipulation. An updated version of the microgripper design was later reported by Muntwyler *et al* [44], which was used to characterize the mechanical properties of plant cells. Although the on-chip force sensors of these microgrippers could enable force-controlled micrograsping, no such experiment was demonstrated in [20, 44].

Apart from linear electrostatic actuators, rotary electrostatic actuators have also been used to actuate MEMS microgrippers for cells manipulation [45]. In this work, each rotary electrostatic actuator includes two sets of curved, interdigitated fingers, one of which are fixed and the other are suspended by flexures. A novel electrothermal force sensor was developed and integrated with this microgripper. This microgripper can achieve a stroke of 90 μm between two gripping tips and a gripping force measurement range of 17 μN. This microgripper was used to manipulate Lilium pollen cells and measure the cell's bursting point of gripping force to be 8.7 μN. Although the electrothermal force sensor provides a relatively high sensitivity, the heater it involves operates at 786 °C, which could induce a hot passive gripping tip and thus cause adverse impact on a cell being grasped. This work did not measure the temperature of the passive tip during operation.

One should note that the sensors and actuators in the electrostatic microgrippers usually cannot operate in aqueous solutions. Therefore, to make an electrostatic microgripper capable of manipulating cells in solutions, its gripping arms are usually designed long enough to be immersed into a solution while keeping its base with the microactuator and force sensor outside. However, long gripping arms could lead to low loading capability and obvious out-of-plane motions of the gripping tips [23].

2.2. Electrothermal microgrippers

Electrothermal microgrippers represent another popular type of microgripper designs [21, 23, 46–58]. In terms of actuator design, four types of electrothermal actuators have been used.

2.2.1. Microgrippers with U-beam electrothermal actuators.
A U-beam actuator includes a 'hot' arm and a 'cold' arm connected in a U shape [23, 50–52]. These two arms will have different levels of thermal expansion once electric current passes through them, because their different resistance levels cause different levels of Joule heating and thermal expansion in the two arms. This eventually induces a bending

motion of the U-beam actuator. Chronis *et al* [23] developed a polymeric microgripper with two active gripping arms driven by U-beam electrothermal actuators (figure 1(B)). The device was fabricated from SU-8 photoresist and thin-film metals (Cr/Au) through surface micromachining. The Cr/Au layer was embedded in the SU-8 U-beam actuators to form heating resistors. As SU-8 has a higher coefficient of thermal expansion (552 ppm °C^{-1}) than silicon and metals, the device can be operated under low actuation voltages (1–2 V) and at relatively low temperatures (⩽32 °C). In addition, the SU-8 gripping arms are insulative, and thus can be directly immersed into aqueous ionic solutions for cell manipulation. This device can grasp cells with a diameter up to 10 μm, and was used to pick and place Hela cells in solution. Using a similar microfabrication process, a bidirectional electrothermal microgripper was developed by Solano *et al* [50]. By arranging the heating elements asymmetrically, the device can realize bidirectional motions of one gripping tip to open and close the gripper tips. The device was applied for manipulation of mouse oocytes.

2.2.2. Microgrippers with V-beam electrothermal actuators.
Although U-beam actuators can provide sufficient actuation performance for microgrippers, they are usually limited to small operation strokes at the gripping tips. To get large operation displacements, many MEMS microgrippers have involved V-beam electrothermal actuators and motion amplification mechanisms [21, 53, 54]. Colinjivadi *et al* [53] developed a MEMS microgripper with a V-beam actuator and a lever mechanism for motion amplification, which is capable of grasping cells with a size range of 15–50 μm. It was demonstrated for manipulation of rat kidney cells in solution. The long gripping arms of this device limit the temperature elevation at its gripping tips and thus reduce the thermal impact on the target cell. Finite element simulation was used to predict the temperature elevation of the gripping tips, but no experimental measurement was performed to validate the prediction. In another microgripper design [52], a jointless compliant mechanism was used to amplify output motions of a V-beam actuator to achieve a large stroke of gripping tips. The device was used to manipulate bacterial cells.

Kim *et al* [21] proposed a microgripper design involving a V-beam actuator and two-axis differential capacitive force sensors, which was used to perform force-controlled grasping of interstitial cells. The two-axis force sensors, attached to the passive gripping arm, can detect the contact force, along the gripping arm direction, between the passive gripping tip and the target cell or device substrate (resolution: 38.5 nN), and thus avoid damage of the cell or the microgripper; it can also be used to measure the grasping force (resolution: 19.9 nN). A closed-loop force controller was established to regulate the grasping force with a resolution of 20 nN. Using a fine-gauge thermocouple, the temperature of the 'hot' active gripping tip was characterized to be within 29 °C during cell manipulation.

2.2.3. Microgrippers with Z-beam electrothermal actuators.
Due to their inclined beams, V-beam electrothermal

actuators provide limited output displacements. To obtain larger output motions, Zhu *et al* [59] developed a new type of electrothermal actuator called Z-beam electrothermal actuator. This design is similar to the V-beam actuator except using Z-shaped beams instead of V-shaped beams. The Z-beam actuator has smaller stiffness along its output motion direction, and, thus can act as a simultaneous load sensor [60]. Based on this low-stiffness characteristic, a new bidirectional electrothermal actuator was developed, in which two flexible Z-shaped beams are connected back to back to actuate the device bidirectionally [61]. The dynamic range of this new Z-beam actuator is experimentally demonstrated to be more than 20 μm. Yang and Xu [62] proposed a conceptual design of a MEMS microgripper consisting of a Z-beam electrothermal actuator and an electrothermal force sensor. Simulations were performed to show that this microgripper can provide a large grasping range of 80 μm at a low input voltage of 6 V. Microgrippers with Z-beam electrothermal actuators have not been applied to cell manipulation.

2.2.4. Microgrippers with out-of-plane electrothermal actuators. Besides U-beam and V-beam actuators that generate in-plane motions, out-of-plane electrothermal actuators have also been used for microgripper actuation. Li and Xi developed a tri-layer electrothermal actuator using Parylene C and thin-film metal to generate out-of-plane motions, and constructed a six-finger microgripper actuated by electrical current or temperature [56, 63]. Because of the excellent thermal insulation property and high coefficient of thermal expansion of Parylene C, the tri-layer electrothermal actuator requires a low actuation power and produces large out-of-plane displacements. The microgripper was applied to grasping crab eggs with a diameter of ~1 mm.

A critical issue of using electrothermal microgrippers for cell manipulation is the thermal management of electrothermal actuators. It is always desired to minimize the temperature elevation at the active gripping tips and thus avoid any adverse impact on cells. Common practices are to add heat sinks to the electrothermal actuator [21, 64], and create thermal isolation trenches in the 'hot' gripping arm(s) when a SOI microfabrication process is used [21]. For the method of adding heat sinks, Qin and Zhu [65] conducted a combined experimental and modelling study on the effect of heat sink beams on the temperature distribution of a V-beam actuator, providing useful guidelines on the design of heat-sink beams to achieve both low temperature elevation and large output displacement of the actuator.

2.3. Magnetic microgrippers

Some researchers have utilized magnetic force to actuate a microgripper [24, 28, 66]. Ger *et al* developed a microfabricated magnetic microgripper for on-chip cell manipulation [28]. Each of the two gripping arms of this device consists of a zigzag structure with tapered anisotropic magnetic films deposited on them. When an external magnetic field is applied by an electromagnet, the zigzag structures experience in-plane torques and drive two the gripping tips to change their gap. This microgripper can manipulate micro-objects of 22–42

μm, and was employed for grasping single human neural progenitor cells [28]. The device allows for off-chip, remote magnetic actuation; however, it suffers hysteresis in actuation because of magnetization reversal of the zigzag structures.

Zhang *et al* [24, 67] developed the first untethered magnetic microgripper (figure 1(C)) with four gripping arms made from a magnetically programmable composite material, which can be directly actuated and controlled by magnetic forces and torques. The four gripping arms can be reversibly controlled to grasp and release a micro-object, and the entire microgripper can also be moved and rotated in an aqueous solution by applying a magnetic gradient and a rotating magnetic field, respectively. Simple control strategies were proposed to demonstrate autonomous three-dimensional (3D) cell grasping and transfer [24].

2.4. Self-folding thermobiochemical microgrippers

Gracias and co-workers developed a new type of untethered self-folding microgrippers [25, 29, 30, 68], which are actuated by stress mismatch or material swelling in bilayer thin-films of their gripping arms and triggered by signals such as temperature change and chemical treatment. A review on this type of self-folding devices can be found in [69].

The simplest design in this type of microgrippers was proposed by Malachowski *et al* [29] to capture single cells, which has the potential for both *in vitro* and *in vivo* applications. This microgripper is composed of four differentially-stressed SiO/SiO$_2$ bilayer arms with rigid segments (patterned on their surfaces), serving as arm joints. Its operation is initiated by the release of the planar gripping arms from their substrate, during which single cells (fibroblast and RBC) on top of the device are captured. The size and folding radius of the gripping arm are tailored to match the size of the target cell type. The SiO/SiO$_2$ arms are transparent, and the cell encapsulated within the microgripper can be observed under a microscope.

Leong *et al* [30] proposed a more complex design that includes a differentially-stressed metallic bilayer (Cr/Cu) for device actuation, a patterned rigid Ni layer for forming self-folding joints of the gripping arms, and patterned polymer segments on the folding joints for triggering the self-folding. When heated or treated with a chemical, the polymer segments become less rigid and thus allow the gripping arm to fold and release the stresses in the Cr/Cu bilayer. The Ni layer also permits the microgripper to be guided to designated positions by a mobile magnet. Capture and transfer of a living cell mass were demonstrated, and the cell viability after manipulation were verified. The closed form of this microgripper is ~5–20 times larger than typical mammalian cells [30], and thus cannot capture single cells. Another drawback of this design is that the microgripper, once closed, cannot re-open for cargo release. Using a swellable hydrogel (pNIPAM-AAc) as both actuation and triggering material, Breger *et al* [25] developed a self-folding microgripper capable of reversibly folding and unfolding. The device is responsible to a change in temperature around body temperature (~36 °C), promising potential *in vivo* applications.

Compared with other kinds of microgrippers, untethered microgrippers can capture cells in many places where

it is hard to reach by conventional microgrippers. This kind of microgrippers can also manipulate cells or tissues *in vivo* and be controlled by a magnetic resonance imaging facility. In terms of the triggering signal, the body temperature (36–37 °C) could be a turning point for the device to operate, and other types of signals such as pH and physiologically-relevant chemicals are also possible options as a variety of stimuli-responsive materials are available [70]. As an untethered microgripper fabricated with ferromagnetic material can be simultaneously imaged and controlled by a magnetic resonance imaging facility, it can be also loaded with live cells (e.g. through encapsulation in hydrogels) and serve as a vehicle for *in vivo* tissue repairing and/or drug delivery. Due to their unique capability of remote grasping and manoeuvering, the self-folding thermobiochemical microgrippers hold great potential in biological and medical research and practices.

2.5. Pneumatic microgrippers

Bütefisch *et al* [32, 71] reports the first pneumatic MEMS microgripper. The device operation is based on two pneumatic microactuators, each of which includes a flexure-tethered piston actuated by pressurization. The two pneumatic microactuators are connected to the gripping tips through flexure-hinged beams, and are configured open and close the gripping tips, respectively. The microgripper structures were fabricated from either silicon or SU-8 photoresist. It was demonstrated that the SU-8 structures provide lower compliance and thus higher output displacements at the gripping tips, and can be fabricated using a relatively straightforward photolithography process [71]. The microgripper was applied to grasp micrometer-sized gears, but no cell manipulation was demonstrated.

Kim and co-workers developed a pneumatically actuated MEMS microcage [31]. The microcage is a spherical microcontainer formed by curved aluminum cantilevers (i.e. microgripper fingers), and is normally closed without pneumatic actuation. The anchors of the curved cantilevers are arranged on top of a suspended thin membrane of SiO_2/Si_3N_4, which can be bulged through pressurization of the pneumatic chamber underneath it. The bulging of the thin membrane tilts the curved cantilevers and open up the microcage for grasping. This device was used for grasping of live microbes with a size of ~400 μm. The microcage is ~900 μm in diameter, and thus cannot be directly applied to manipulate small mammalian cells (5–20 μm in diameter). Further miniaturizing the microcage design is possible, but challenges in microfabrication may arise.

3. MEMS physical sensors for cell manipulation and characterization

In cell manipulation, a variety of physical signals, such as cellular force, mass, and density, can be measured. This section will discuss existing MEMS physical sensors applied to cell manipulation and characterization, and will be organized by the type of physical measurement conducted by the MEMS devices. Table 2.

3.1. Measuring interaction forces during cell injection

Mechanical cell injection is a typical technique widely used in biological and medical research such as genetics, development, drug discovery, and assisted reproductive technology (ART). In this technique, a glass micropipette is used to penetrate an adhesive or suspended cell and deliever foreign materials into a desired location inside the cell. As cells are fragile and prone to damage, it is highly desired to monitor the injection process through various feedback modalities. Besides the most straightforward visual feedback from a microscope, the interaction force between the micropiette and the target cell could provide critical information of the injection process and potentially avoid unnecessary mechanical impact on the cell.

Due to their high accuracy and sensitivity, many MEMS force sensors have been developed for quantifying interaction forces during cell injection. Micro force sensors based on a piezoelectric polymer, polyvinylidene fluoride (PVDF), have been developed and applied to injection force measurement [56, 72, 73]. This type of device was integrated into robotic cell injection systems for prediction of the cell membrane pentration and closed-loop control of the injection force [74, 75]. The resolution of PVDF-based force sensors can reach sub-micronewton level. Because of the inherent characteristic of piezoelectric sensing, these sensors are more suitable for dynamic force sensing than static measurement.

Zhang *et al* [76] proposed an uniaxial MEMS force sensor based on diffractive optical encoders fabricated from Si_3N_4. This force sensor consists of a pair of transmission phase microgratings (index and scale gratings) with the same constant pitch, and a cell injection probe linked to the index grating. An injection force exerted to the probe tip will lead to a relative displacement between the index and scale gratings and thus a change in the diffraction efficiency of the phase gratings, from which the relative displacement between the two gratings (thus the injection force) can be calculated by the intensities in the diffraction orders. This sensor was used to quantify injection forces of *Drosophila* embryos. This sensor requires a relatively sophisticated and bulky optical setup for signal readout. Liu *et al* [6, 77] employed microfabricated polydimethylsiloxane (PDMS) posts for real-time measurement of injection forces during robotic injection of zebrafish embryos and mouse oocytes. The key idea is to visually track deflections of PDMS posts supporting an embryo being injected, from which the injection force can be calculated through a mechanical model describing the injection force transmission and induced post deflection. The stiffness of the post determines the force measurement range and resolution, and can be tuned by adjusting the post's dimensions (diameter and height) and Young's modulus.

Multi-axis MEMS force sensors are useful for measuring both the normal injection force and the tangential force between the injection probe and the cell. Sun *et al* developed a two-axis transverse-comb differential capacitive force sensor [80]. The high aspect ratio of the comb fingers results in high resolution and sensitivity of the sensor. This device (figure 2(A)) was used

Table 2. Summary of MEMS physical sensors.

Sensor type	Working principle	Range	Resolution	Applications	Examples	Notes
PVDF based force sensor	Piezoelectric effect	μN–mN	sub-μN	Measuring cell injection force	[54, 70, 72]	Suitable for dynamic force sensing; high linearity; high signal-to-noise (S/N) ratio; cannot work in high temperature environment
Micrograting based force sensor	Diffraction efficiency change	μN	N/A	Measuring cell injection force	[73]	High resonant frequency; difficult to fabricate; sophisticated and bulky optical setup
PDMS posts based force sensor	Deflection of PDMS posts	μN–mN	nN	Measuring cell injection force	[6, 74]	Easy to manufacture; can be used to investigate characteristics of different types of cells
Capacitive force sensor	Capacitance change	μN	nN–μN	Measuring cell injection force and characterizing cell mechanics	[7, 77]	High resolution and sensitivity; large dimension; complicated circuit
Piezoresistive force sensor	Resistance change	mN–N	nN–μN	Measuring cell injection and palpation force	[78]	High resolution and sensitivity; simple material; high bandwidth; Sensitive to temperature
Cantilever based force sensor	Deflection of beam	nN–μN	nN	Measuring cell traction force	[98, 99]	Easy to manufacture; relying on visual measurement of structural deformation;
PDMS micropost array based force sensor	Deflection of micropost array	nN	nN	Measuring local cell traction force along arbitrary in-plane directions	[75]	Simple mechanical model; popular in cell studies
Cantilever based force sensor with indentation probe	Deflection of beam	μN	nN–pN	Probing cellular response to extracellular forces	[76, 115–117]	Simple structure; high resolution; capable of studying force responses of cells under large deformation
Cantilever based force sensor with two suspended semi-circular plates	Deflection of beam	μN	N/A	Probing cellular response to extracellular forces	[120]	Semi-transparent cell culture plates enabling simultaneous cell stretching and fluorescence imaging
Cantilever based MEMS resonator	Shift in the resonant frequency of cantilever	N/A	sub-femtogram	Measuring mass and density of single cells	[129]	Able to weigh a single cell mass; mass resolution relies on quality factor
Four tethering beams based MEMS resonator	Shift in the resonant frequency of cantilever	Picogram	N/A	Measuring mass of adherent cells	[124]	Uniform mass sensitivity irrespective of the cell position on the sensor

to measure the injection force of mouse embryos and thus characterize the mechanical properties of the embryo membrane (zona pellucida) [7]. The tangential force measured during embryo injection can also be quantified by the sensor for alignment of the injection probe with the embryo center. Sieber *et al* [81] designed a three-axis piezoresistive force sensor. The sensor was mounted on a three-degree-of-freedom (3-DOF) nanomanipulator with a haptic interface, thus allowing bilateral cell manipulation with triaxial force feedback. The experimental setup was demonstrated for interaction force measurements during palpation and injection of salmon fish eggs.

3.2. Studying cell mechanics and mechanotransduction

Forces generated by cells during interactions with their surrounding extracellular matrix (ECM) affect the cells' functions such as signalling, migration, proliferation, and differentiation [10, 82, 83]. On the other hand, when external forces are exerted on cells, their behaviours will also change [8]. Therefore, it is important to precisely measure forces generated by cells and understand how cells respond to external forces. In addition, it is well accepted that the cell mechanical properties could serve as useful indicators for conditions of the cells. Abnormal or diseased cells, such as cancer cells or red blood cells infected with malaria parasites, are mechanically different from their normal counterparts [84–86]; cells at different developmental stages also reveal different elastic or viscoelastic properties [87]. Correlating a cell's mechanical properties with its biological conditions could shed light onto cell development and provide new diagnostic tools. Due to the small sizes of cells, conventional large-sized force sensors are not suitable for cellular force measurement and cell mechancial chracterization. In contrast, MEMS force sensors have been widely adopted for these studies.
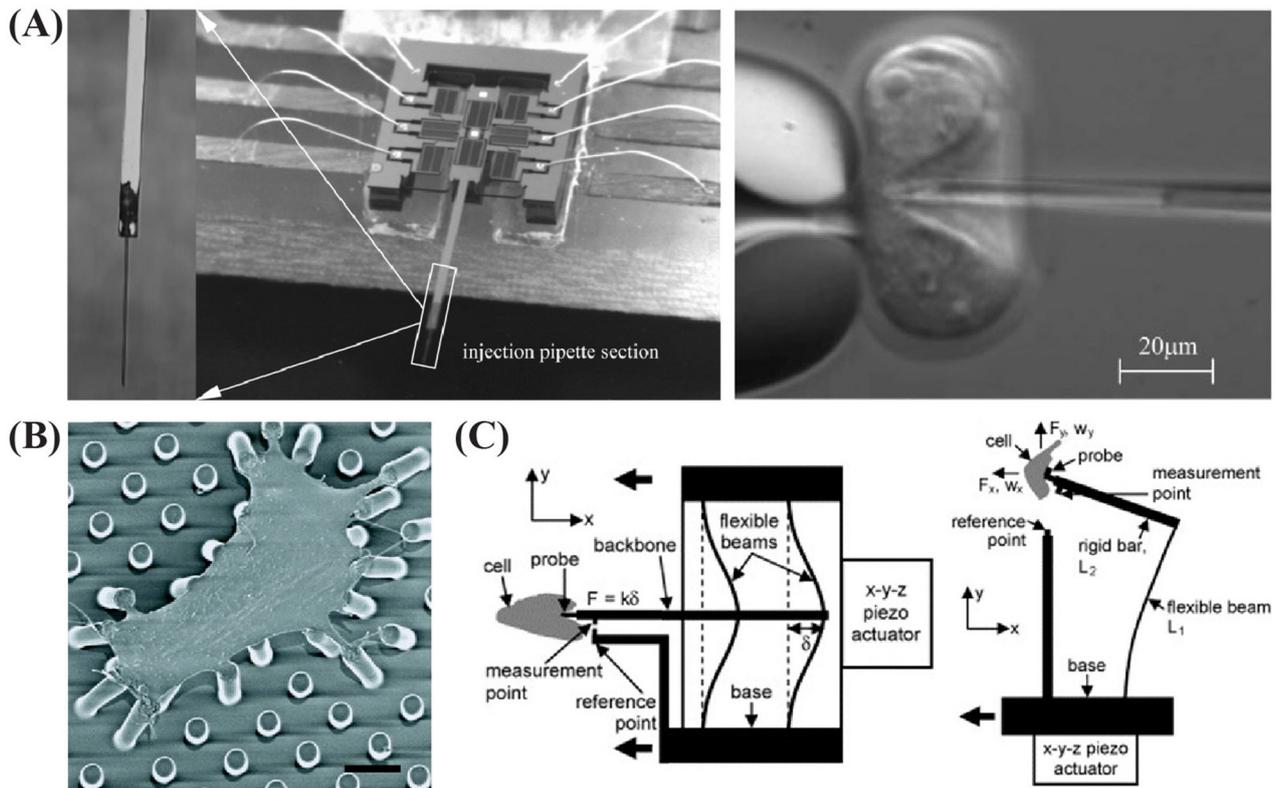
Figure 2. MEMS force sensors for cellular force measurement. (A) A two-axis capacitive force sensor used for measuring injection forces during robotic cell injection. © [2003] IEEE. Reprinted, with permission, from [7]. (B) A PDMS micropost device for measuring the traction force distribution of an adherent cell cultured on top of the microposts. Reproduced with permission from [78]. [Copyright (2003) National Academy]. (C) One-axis (left) and two-axis (right) MEMS force sensors for studying the response of adherent cells to extracellular forces. Reprinted from [79], Copyright (2007), with permission from Elsevier.

3.2.1. Characterizing cell mechanical properties. To characterize mechanical properties of a single cell, the cell needs to be deformed and the force-deformation data need to be accurately measured. Many of the force sensors we reviewed for injection force measurement (section 3.1) have also been used to quantify the mechanical properties of various cell types such as zebrafish embryos [73], mouse embryos [7] and oocytes [88, 89]. There are also other types of MEMS force sensors solely developed for characterizing cell mechanical properties. For instance, a surface-micromachined cell squeezer was recently developed for characterize the stiffness and rupture mechanics of different strains of baker yeast cells [90]. A two-axis capacitive force sensor was also developed and integrated into a micromanipulation system for quantifying mechanical properties of plant cells [91].

Besides MEMS force sensor development, there are also two additional key components required for mechanical characterization of single cells. First, the cell deformation induced by a MEMS force sensor needs to be accurately measured to establish force-deformation curves. Under high-magnification optical microscopy, the cell deformation can be measured with a resolution down to the sub-micrometer level. Computer vision algorithms have also been developed for tracking the deformed membrane contour of a mouse embryo during MEMS-based mechanical characterization [92]. Secondly, based on the loading condition of the target cell, a specific mechanical model needs to be developed to extract the desired mechanical properties

from the measured force-deformation data. Researchers have developed cell mechanics models suitable for different loading conductions such as parallel-plate compression [55] and point loading [7, 88]. Most of the existing cell mechanics models treat a cell as a homogenous solid [55, 88]; when the cell membrane property is of the major concern, mouse embryos can also be modelled as a spherical elastic shell (membrane) enclosing liquid (cytoplasm) [7]. To handle large cell deformations, a semi-analytical-numerical model was developed to describe the mechanics of mouse oocytes under point loading, and its effectiveness was confirmed experimentally [88].

3.2.2. Quantifying traction and contractile forces of adherent cells. When an adherent cell is cultured on a substrate, it will exert traction forces to the substrate through its adhesion sites [93]. It has been demonstrated that the mechanical properties of cell culture substrates affect cells' ability to generate traction forces, and also their morphology, migration, and cytoskeletal structure [10]. Thus, measuring traction forces of cells under culture will help us not only understand behaviours of cells, but also study the relationship between the mechanical properties of ECM and the cells' signalling and functions. With the advent of MEMS technologies, substrate-cell interaction forces can be accurately quantified with high special resolution, which has led to an entire category of microfabricated force sensors for cellular traction/contractile force measurement. An comprehensive review on this topic

was recently published by Polacheck and Chen [94], and we will discuss some typical device designs here.

The first platform for measuring cellular traction forces is developed by Harris *et al* [95]. A thin layer of silicone elastomer was used to culture cells, and local deformations (wrinkles) of the silicone layer was used to indicate the distribution of cellular traction forces. To facilitate the measurement of the local deformations, fluorescent microbeads were embedded into the silicone substrate [96–98], and semi-infinite-space elasticity models were developed to calculate the traction force distribution from the measured substrate deformations [99]. Further improvements were made by Balaban *et al* [100] by introducing regular micropatterns into the elastomer substrate through soft lithography. This micropatterned substrate simplifies the calculation of the cellular traction forces.

Along a different path of technology development, MEMS force sensors were developed for measuring cellular traction forces [101, 102]. Using surface micromachining, Galbraith and Sheetz [101] fabricated an array of horizontally arranged cantilever beams serving as traction force sensors. Lin *et al* [102] also developed a micromachined force sensor for quantifying traction forces of rat heart cells. Both designs [101, 102] rely on visual measurement of structural deformations to determine the traction force exerted by a cell, and can only measure forces generated at one location of the cell and along one direction. Researchers also cultured multiple cardiac myocytes on the surface of a PDMS cantilever, which will be bent up when the myocytes contract [103, 104]. The average stress exerted by the cells on the cantilever surface was determined by mechanical analysis of the cell-PMDS bilayer cantilever using Stoney's equation and finite element modelling. It was found that the stress exerted by the cardiac myocytes on a flat cantilever surface is less than that on a grooved cantilever surface [103].

To replicate the capability of deformable substrates for mapping the traction force distribution from a cell, Chen and co-workers [78] developed an PDMS micropost array made by soft lithography (figure 2(B)), on which cells can be cultured. Two-step replica moulding was used to replicate high-aspect-ratio microposts from a SU-8 template onto a PDMS substrate. The vertically aligned microposts serve as individual force sensors to quantify local traction forces along arbitrary in-plane directions, which were generated at different locations of a cell. To spatially pattern cellular adhesion sites, top surfaces of selected microposts were coated with fluorescently-labelled fibronectin through microcontact printing, and the remaining unprinted areas of the micropost array were coated with a protein-repellent polymer (Pluronics F127). When a cell spreads across and attach to the microposts, its local traction forces will deflect the microposts whose top surfaces are attached to the cell. The deflection of each post can be tracked through fluorescence imaging to generate a traction force vector map of the cell. As the deflection of each micropost is independent of those of its neighbouring microposts, the calculation of local traction forces is straightforward.

Due to the simplicity and versatility of Chen's micropost device, it was rapidly popularized for a variety of cell studies, and different versions of the micropost devices were proposed [105–108]. Petronis *et al* [106] fabricated ultrahigh-aspect-ratio silicon microposts by deep reactive ion etching (DRIE), and achieved high accuracy and spatial resolution of the traction force measurement. Zhao and Zhang [105, 109] employed DRIE-fabricated silicon templates for one-step replica molding of micropost arrays, and applied the device to simultaneous traction force measurement and orientation alignment of cardiac myocytes. Zhang and co-workers [110, 111] also investigated the viscoelastic modeling and material characterization of PDMS microposts with low aspect ratios, which improved the calculation accuracy of traction forces.

Ganz *et al* [107] coated the top surface of microposts with selective adhesion molecules to mimic cell-cell interactions. Some researchers demonstrated that different stiffness and density levels of microposts affect the adhesion and traction of cells cultured on them [112–115]. To study forces exerted by cells cultured in three-dimensional (3D) environments, Ghibaudo *et al* [116] cultured cells within a micropost array. Sniadecki *et al* [117] embedded magnetic cobalt nanowires into selected microposts to make them reponsive to an external magnetic field. Controllable forces were then applied to a cell cultured on the microposts through a magetic field, and the traction force response of the cell was quantified. This design adds to the micropost device the capability of simultaneous mechanical stimulation and traction force measurement on cells.

3.2.3. Probing cellular response to extracellular forces. Uncovering a cell's response to extracellular forces are important for us to better understand the cellular functions and mechanotransduction mechanisms. To this end, many MEMS devices have been developed for this type of studies.

Saif and co-workers [79, 118–120] have developed a series of one- and two-axis MEMS force sensors for studying cellular responses to external forces. These sensors (figure 2(C)) usually consist of a probe for cell indentation/stretching, and low-stiffness force sensing beams attached to the probe for detecting force responses of the cell under indentation and stretching. For cell stretching tests, the probe was coated with fibronectin to create adhesion sites with cells. The total stiffness of the sensing beams was pre-calibrated, and the cellular force experienced by the probe was then determined by quantifying the beam deflection underneath a microscope. The force measurement range is tunable by changing the beam stiffness, and the force resolution could be as low as 0.5 nN [118]. Another advantage of these sensors is their capability of studying force responses of cells under large deformation, which could be as high as 50 μm [119]. These force sensors have been used to examine the force responses of monkey kidney fibroblasts and their corresponding changes in cytoskeletal structures [79, 119, 121].

In order to measure cellular force response under large deformation with high resolution, Saif and co-workers [120] also proposed an improved sensor design with force sensing beams connected in series. With a measurement range of 1 μN, the resolution of this force sensor can reach down to 50 pN. To avoid damage of the ultra-compliant force sensing
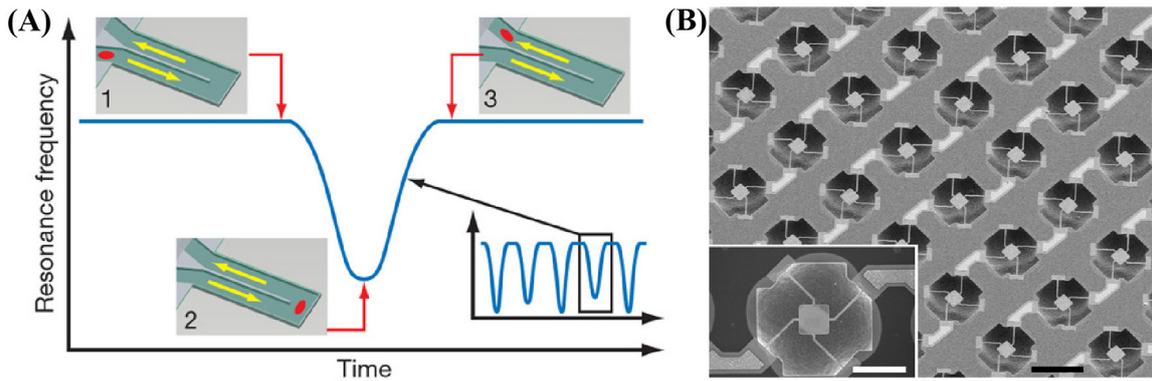
Figure 3. MEMS-based resonators for mass and density measurements of single cells. (A) A cantilever resonator embedded with a microfluidic channel through which a cell is passed for mass measurement. Reprinted by permission from Macmillan Publishers Ltd: [NATURE] [132], Copyright (2007). (B) A MEMS resonator with four tethering beams that has uniform mass sensitivity on the central weighing platform. Reproduced with permission from[127].

beams caused by capillary forces during microfabrication and device use, this sensor was always immersed in liquids (etchants in microfabrication, water in storage, and cell culture medium in use). This sensor was applied to an *in vivo* study on the effect of mechanical tension on vesicle clustering in the presynaptic terminal of the neuromuscular junction in *Drosophila* embryos [122].

Recently, Serrell *et al* [123] designed a surface-micromachined MEMS tensometer for uniaxial stretching and force-deformation measurement of fibroblasts. The device cultures a cell bridging two suspended semi-circular plates, one of which is attached to an actuator and the other of which is connected with force sensing tethering beams. The actuator is driven by an off-chip micromanipulator to stretch the cell, and the corresponding cellular force is quantified by measuring the deflection of the force sensing beams. The cell stretching experiments showed a linear force-deformation relationship before the cell was detached from the semi-circular plates, and the force required to detach a cell was determined to be ~1.5 μN. A revised design of this tensometer was later reported to allow simultaneous cell streching and fluorecence imaging [124]. The key idea of this design is a new SOI-based microfabrication process that forms semi-transparent cell culture plates using thin-film Si_3N_4.

3.3. Measuring the mass and density of single cells

Direct measurement of the mass or density of single cells could elucidate the intrinsic mechanism for the coordination between cell cycle and growth, and also predict physiological states of a cell [125]. Conventional methods for cell mass measurement are population-based, and cannot provide the growth rates of individual cells. Thanks to the ultrahigh sensitivity of MEMS resonators, the quantification of single cell mass and density has been realized [126, 127, 130–132].

Although nanoelectromechanical systems (NEMS) resonators have been developed with ultrahigh resolution for mass detection [128, 129], their resonant structures are usually of sub-micrometer sizes and this mismatch to typical cell sizes make them unsuitable for cell mass measurement. Ilic *et al* developed the first MEMS oscillator for measuring the mass

of a single bacterial cell [126]. The oscillator is based on a compliant Si_3N_4 cantilever beam, whose surface is coated with an antibody monolayer to immobilize bacterial cells. The cantilever was activated by thermal noise and its vibration was detected optically. The attachment of a cell onto the cantilever will cause a shift in the resonant frequency of the cantilever, which can be used to calculate the mass of the attached cell. Note that the sensitivity of such a cantilever resonator depends on the position where the cell is attached to, and becomes the highest when the cell is attached to the tip of the cantilever. Experiments showed that this device can effectively measure the mass of a single *Escherichia coli* cell in air. The mass resolution of this sensor is relatively limited because it has a low quality factor (*Q*-factor) of 50 caused by air damping. When this kind of resonators operate in air or solution (where cell mass is usually measured), the viscous effect of medium surrounding the resonator significantly affects the mass sensing performance [130].

To eliminate the performance degradation caused by the damping effect of the resonator surrounding medium and in the meanwhile maintain cells alive, Manalis and co-workers [131, 132] fabricated an air-tight microfluidic channel inside a resonant cantilever beam and operated the resonant beam in an vacuum environment (figure 3(A)). This sensor is actuated electrostatically and provides a high *Q*-factor up to 15 000. It was experimentally confirmed that the damping of the resonator does not increase when filling the channel with water, and a sub-femtogram resolution was achieved on this device [132]. This mass sensor can also be used to determine the density of a cell by measuring the mean resonant frequency shift when the cell is placed in two solutions with different densities [131].

To circumvent the nonuniform mass sensitivity of cantilever resonators that is dependent on the loading position, Park *et al* [127] proposed a MEMS resonant mass sensor with a unique pedestal design (figure 3(B)), which retains uniform mass sensitivity irrespective of the cell position on the sensor. A central cell-carrying platform tethered by four beams was designed to minimize the variation (<4%) of the vibration amplitude of the central platform caused by the cell position change on the platform. An array of resonant mass sensors
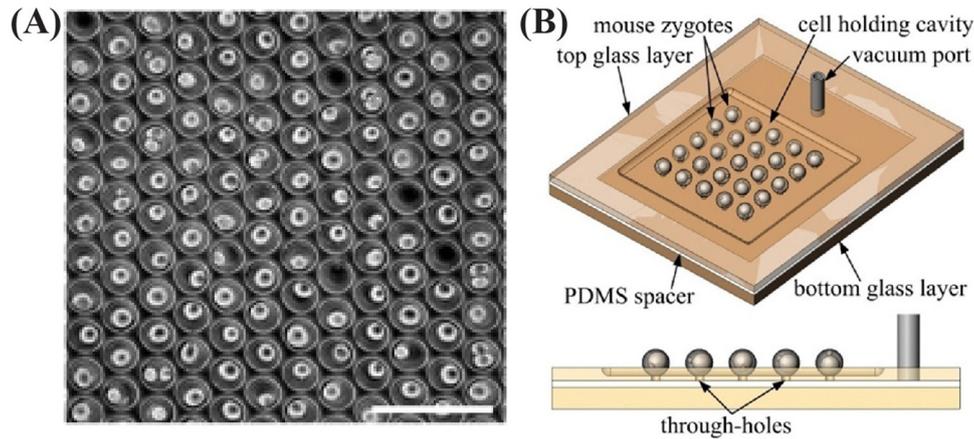
Figure 4. MEMS devices for patterning and immobilization of single cells. (A) A PDMS device with microwells for single cell patterning. Reprinted with permission from [134]. Copyright (2005) American Chemical Society. (B) A glass device capable of immobilizing mouse zygotes for robotic cell injection. [135] (2009) (© Springer Science+Business Media, LLC 2009). With permission of Springer.

was constructed through a SOI process, and used for batch growth and mass measurement of individual adherent cells for >50 h. To account for the cell-elasticity-induced vibration amplitude/phase differences between the central platform and the cell, an improved 2-DOF dynamic model of the resonant sensor was also proposed to estimate the ratio of the measured apparent mass to the actual mass of the cell. Using this sensor, the growth rate of human colon epithelial cells was measured to be approximately linear with an average of 3.25% h^{-1}.

4. MEMS-based devices for single cell patterning and immobilization

In many applications like cell injection and mechanical characterization, target cells need to be positioned into a regular pattern and sometimes immobilized. Many microfabricated devices have been devised for patterning and immobilization of single cells based on different mechanisms [6, 7, 133–140].

Several devices rely on mechanical confinement to pattern single cells. Rettig and Folch [134] developed PDMS microwell arrays (figure 4(A)) for large-area single cell patterning, and achieved a single cell capture rate up to >90% by optimizing the microwell dimensions based on the cell type. Liu et al [6, 77] constructed PDMS cell holding devices serving two purposes: (i) to hold single zebrafish embryos and mouse zygotes in microwells for robotic cell injection, and (ii) to measure injection forces through vision-based force measurement (whose mechanism has been discussed in section 3.1). Leveraging surface micromachining, Teichert et al [133] fabricated novel MEMS spatial mechanisms for immobilizing single cells. Two symmetric cylindrical mechanisms were actuated by a single slider to form a cell trap. The two mechanisms can realize self-centering of the cell and provide a firm hold after immobilization. However, this device is less practical for repeated use in cell studies since the surface-micromachined mechanisms are prone to wear and damage by structure stiction.

Other devices utilized vacuum (negative pressure) to capture/immobilize cells [135–138]. Lee and co-workers [136, 137] used hydrodynamic suction forces to capture single cells; and employed this mechanism to perform single cell

electroporation [137] or bring multiple pairs of cells in contact for cell–cell communication studies [136]. Liu and Sun [135] fabricated a glass device (figure 4(B)) through wet etching and used it for vacuum-based immobilization of mouse zygotes, which greatly enhanced the throughput of robotic mouse zygote injection. A revised design of this device was later realized by Lu et al [4] through injection molding, eliminating the need for microfabrication and allowing for device mass production. Park et al [138] developed a microfabricated cell processor capable of not only immobilizing a mouse embryo through vacuum suction but also controlling its orientation using dielectrophoresis (DEP).

Researchers also employed magnetic force to capture cells [139, 140]. Lee et al [140] designed a custom-made CMOS chip with an array of micro-electromagnets, which could generate microscale magnetic field patterns to capture and transfer cells tagged with magnetic beads. Rajapaksha et al [139] also developed a MEMS device including micro-electromagnets for capturing rare circulating tumour cells (CTCs) that have been labelled with magnetic beads. Proof-of-concept experiments were performed using human breast tumor cells, and a capture efficiency of 95.2% was achieved.

5. MEMS-based cell injectors

Cell injection is usually performed using a glass micropipette loaded with injection materials, and automated robotic systems have been developed to improve the injection accuracy, consistency, and throughput [3, 75, 141]. Researchers also developed MEMS-based cell injectors aiming at parallel cell injection or improved post-injection cell survival.

Microneedle arrays with solid or hollow structures have been fabricated using a variety of microfabrication processes [142–146], and successfully employed to introduce different biological materials into skins, tissues, and single cells. Using a microneedle array as the cell injector allows for parallel injection of many cells, thus providing a higher throughput than the conventional technique with a glass micropipette. For cell injection, the tip of a microneedle needs to match the size of the cell type to be injected.
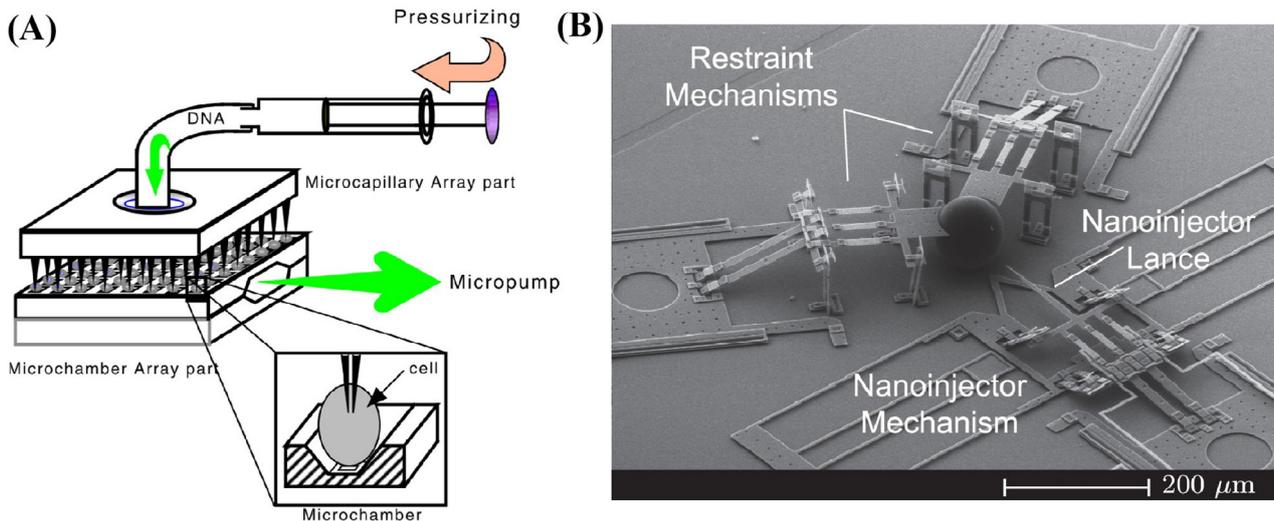
Figure 5. MEMS-based cell injectors. (A) Schematic diagram of parallel cell injection using a MEMS hollow microneedle array and a vacuum-based cell holding device. Reproduced from [147]. © IOP Publishing Ltd. All rights reserved. (B) A surface-micromachined cell injector including a pair of cell holding meachanisms and an injection mechanism. Reprinted with permission from [149]. Copyright (2014), AIP Publishing LLC.

Several microneedle arrays have been designed specifically for parallel cell injection. Trimmer *et al* [142] fabricated an array of pyramid-shaped silicon microneedles through a single-mask process, and used it to penetrate plant cells and deliver DNA solutions. The diameter of these microneedles is smaller than 0.1 μm. The microneedle array was also used to inject DNA into the gonad of the nematode worm *C. elegans*, with 8% of the first-generation descendants of the injected worms expressing the injected DNA [142, 143]. Although this kind of microneedle is simple to fabricate, the less-controlled injection process led to a relatively low success rate of injection. To improve the cell viability after penetration, Teichert *et al* [144] fabricated arrays of high-aspect-ratio microneedles through a three-step DRIE process, and designed a compliant suspension mechanism to restrain rotations or transverse motions of the microneedles during cell injection and thus avoid tearing of the cell membranes. Thousands of HeLa cells were injected with high survival and injection success rates of 97.7% and 97.9%, respectively.

Both microneedle designs discussed above [142, 144] adopt solid structures without solution-delivering channels, and the biological materials to be delivered can only be either coated on the microneedle surfaces or placed in the culture medium surrounding the cells for delivery after cell penetration. The volume of materials delivered to a cell is uncontrollable. In order to precisely control the injection volume, Chun *et al* [147] fabricated a hollow microneedle array, and also proposed an experimental setup for parallel cell injection (figure 5(A)). The setup includes a vacuum-based device for immobilization of many cells into a regular pattern, and a hollow microneedle array with a pitch aligned with the immobilized cell grid. Although this proposed setup is promising for efficient parallel cell injection, no injection experiments were conducted to test its effectiveness. Ichiki *et al* [148] fabricated an array of glass hollow microneedles through surface micromachining, and integrated it inside a microfluidic channel for injection of RBCs. These microneedles are horizontally anchored on a

substrate, and a single cell was moved toward a needle using optical trapping for penetration.

Besides the development of microneedle arrays as cell injectors, there are also integrated cell injection systems completely realized on micro-chips [149, 150]. Adamo and Jensen [150] developed a cell injection system on a microfluidic device, where a glass micropipette was integrated at the end of a cell delivery channel with its tip exposed inside the channel. When a cell is transported to the end of the channel, it will hit the exposed micropipette tip and get penetrated for material delivery. The microfluidic device can continously deliver single cells to the micropipette tip and transport the injected cells to the downstream for collection. This design provides a new way to realize automated cell injection. Aten *et al* [149] developed a MEMS-based platform for on-chip mouse zygote injection (figure 5(B)). The platform, fabricated through surface micromahining, integrates the MEMS-based cell immobilization mechnism [133] previously discussed in section 4 and a nanoinjector mechanism, allowing cell immobilization and injection realized on the same chip. However, both the cell immobilization mechanism and the nanoinjector machanism were actuated by a manually controlled micromanipulator; therefore, the cell injection process is operator-skill-dependent and time-consuming.

6. Concluding remarks

MEMS technologies have provided unparalleled capabilities of manipulating single cells, studying their functions and mechanisms, and characterizing their physical properties. In this review, we summarized the existing MEMS-based platforms that have been applied to different cell manipulation and characterization tasks, including grasping and transfer, patterning and immobilization, injection, mechanical property characterization, cellular force sensing, and mass and

density measurement. Special designs have been adopted to make these MEMS devices suitable for interacting with live cells. Their perfect size matching, high accuracy and sensitivity, and high level of integration have led to many unique features benefiting their operations in various studies involving cell manipulation and characterization. Proof-of-concept experiments have been conducted using these platforms, and their significant potential for practical use has been demonstrated.

Despite many advances made in the past few decades, there are still many exciting topics requiring further investigation. To realize high-performance actuation and sensing, many existing platforms adopt conventional MEMS micro actuators and sensors constructed on silicon-based substrates. This brings certain design challenges and/or application limitations of these devices such as electrical and thermal managements and compatibility issues with aqueous environments. Compared to silicon-based materials, polymer materials such as elastomers have several merits for use in MEMS such as low cost, high transparency, high stretchability, good mouldability, and excellent chemical inertness. There is a trend in bioMEMS designs to adopt polymer materials, such as PDMS and other biocompatible polymers, for device construction [151]. Particular attention should be paid to functional polymer materials such as shape memory polymers [152, 153], conductive polymers [154], electroactive polymers [155], which hold huge potential for MEMS applications. Accordingly, research efforts on new designs and microfabrication processes of polymer-based actuators and sensors are required.

In addition, most of the existing MEMS platforms we have reviewed were developed for single tasks of cell manipulation and characterization. It would be desirable to develop integrated bioMEMS platforms including multiple MEMS sensing and actuation components, serving as on-chip 'factories' for realizing sequential/parallel, multi-step manipulation procedures of single cells [156]. For example, If a new bioMEMS platform can be designed to automatically transport cells to mutilple on-chip regions and sequentially perform different manipulation tasks, it could significantly improve the efficiency of different kinds of cell studies and potentially enable new studies that cannot be realized using current cell manipulation techniques.

Finally, one should note that the practical use of these MEMS platforms in real biological and medical research is still relatively rare, which is partially due to the mentality barriers and experimental challenges that biologists and medical scientists have to face when adopting these fancy but unconventional engineering tools. Therefore, as techonologists, we should not limit ourselves to proof-of-concept demonstrations of our new MEMS technologies, but proceed further down the road of transfering them to the hands of their real users. This long-term goal should be pursued by close collaobrations with biological/medical practioners throughout the entire period of technology development, and by efforts on technology transfer from laboratory prototypes to reliable, user-friendly platforms. With the rapid development of MEMS technologies and the increasingly close collaborations between MEMS technologists and biological/

medical users, it is expected that more and more MEMS cell manipulation platforms will be practically used in biology and medicine in the near furture.

Acknowledgments

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