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INSIDE

Short research papers and reviews on micro- and nanoengineered-based methods and applications in cellular biomechanics and mechanobiology

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Editorial

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Mechanical factors play important roles in the regulation of various biological processes, such as gene expression, adhesion, migration, cell fate, and tissue homeostasis. Compared with the effect of biochemical factors, however, the extent and importance of mechanical factors are under explored.

The advent of micro- and nanoengineered platforms portends great prospects for new insights into interactions between cells and their microenvironment that underlie the physiology of human tissues. Micro- and nanofabrication technologies are increasingly used for controlling the biomechanical properties of *in vitro* cellular microenvironment and for enabling accurate, quantitative measurements of cellular responses in high-throughput experiments. These capabilities also have significant implications for mechanical control of cell and tissue development as well as cell-based regenerative therapies.

Novel biomechanical assays and measurement techniques based on microfluidics, surface patterning, and MEMS tools have been under significant development in recent years. This special issue highlights some of these efforts, in which micro- and nanofabricated tools were developed for studying the roles of mechanical factors in cell biology.

K. Wang and co-workers used microfluidic channels integrated with nanopillar arrays to detect the dynamics of single DNA molecules (doi:10.1049/mnl.2010.0215). Jung-Woog Shin and his co-workers developed a microfluidic chip to analyse the dynamic changes in intracellular calcium ion concentrations ([Ca2+]i) under various flow-induced shear stresses (doi:10.1049/mnl.2011.0018). B. Helmke and co-workers nanofabricated substrates with different feature sizes and spacing and studied the rolling behaviour of HL60 cells as a function of wall shear stress (doi:10.1049/mnl.2011.0184).

M.L. Han and colleagues present a vision-based non-contact force sensing technique for real-time stressing of biological cells (doi:10.1049/mnl.2010.0230). D. Felekis and colleagues describe a microrobotic system capable of performing automated mechanical characterisation of living plant cells *in situ* as plant cells proliferate and grow (doi:10.1049/mnl.2011.0024). K.Y. Kim and co-workers present elastomer micropost array-based sensors for quantitative force measurements of isolated cardiomyocytes (doi:10.1049/mnl.2011.0031). R.D. Sochol and co-workers utilised a microfabricated post array with variable spacing and stiffness to investigate the effects of these biophysical factors on cell motility (doi:10.1049/mnl.2011.0020).

This special issue also contains two critical reviews. Y. Zheng and co-workers review most recent microfluidic technologies for single-cell mechanical characterisation (doi:10.1049/mnl.2011.0010). X.Y. Zheng and co-workers discuss advances of various optomechanical systems in studying several aspects of cell mechanics (doi:10.1049/mnl.2011.0030).

As guest editors of this special issue, we thank all the contributors and reviewers. It is certain that we will witness even more intense development of innovative micro- and nanoengineered platforms for cell mechanobiology studies in the next few years. These new platforms will enable intriguing new findings in this relatively new area and will answer a multitude of questions that currently remain elusive.

Deok-Ho Kim and Yu Sun
Guest Editors

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Microfluidic devices for mechanical characterisation of single cells in suspension

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This Letter provides an overview of microfluidic technologies for single-cell mechanical characterisation. In particular, the most recent literature is discussed to summarise the working principles and development trend of the state-of-the-art microfluidic devices for mechanical characterisation of biological cells in suspension. The techniques are classified into constriction channel, fluid stress, optical stretcher, electrodeformation, electroporation and microfluidic pipette aspiration, according to the mechanism of mechanical stimuli. The principles are explained along with representative examples demonstrating their applications. The research highlighted in this letter has great potential in realising high-throughput single-cell mechanical characterisation.

1. Introduction: The mechanical properties of living cells are mainly determined by the cytoskeleton and the interaction between the cytoskeleton and organelles. Cellular function changes can lead to the cytoskeletal reorganisation and consequently, influent the cell mechanics. Hence, cells of different lineages, disease states and cell cycle stages may exhibit drastically different mechanical properties [1, 2]. While conventional assays typically rely on phenotype-specific biochemical markers for identifying abnormal cells, differences in mechanical properties between healthy and diseased cell states may provide additional information for diagnosis. For example, it is well known now that the red blood cell (RBC) becomes stiff and cytoadherent when malarial parasites invade and mature within RBCs, and the Young's modulus of leukemic patients' leukocytes is much less than benign leukocytes [3–5].

For investigating cells' mechanical properties, a wide variety of experimental biophysical tools have been developed. However, it is notable that existing techniques for mechanical characterisation of individual cells, such as atomic force microscopy, micropipette aspiration, optical tweezers, magnetic tweezers are all tedious and difficult to use, and more importantly have a low testing speed [6, 7]. Incorporated with other techniques, microfluidics offers the potential of high-throughput single-cell mechanical measurements. In the meanwhile, microfluidic devices are also able to provide an *in vivo* capillary-like microenvironment to avoid mechanical property changes caused by measurement processes [8]. For those merits, there was a substantial growth in the research on microfluidics-based single-cell mechanical characterisation during the last decade.

To measure the mechanical properties of individual cells, the cell must be deformed in some way. Correspondingly, classification of the microfluidic devices for single-cell mechanical characterisation is based on the mechanism of how mechanical forces are exerted on the cells (see Table 1).

2. Technologies

2.1. Constriction channel: Constriction channel provides a convenient way to generate mechanical stimuli. These devices use constriction channels with channel width and height both (or only width) being smaller than the diameter of tested cells. When the cells are squeezed through the constriction channel by hydraulic pressure differences, the cells are deformed. Transit time, elongation and shape-recovery time are recorded via a camera through a microscope. Moreover, the constriction channel can be easily fabricated with standard microfabrication techniques and is able to provide an environment to mimic the *in vivo* capillaries. Based on these advantages, constriction channels have been widely used to assess the mechanical properties of the RBCs [10–14], leukocytes [9, 15, 16] and cancer cells [17].

Transit time is the most widely used parameter measured by constriction channel-based microfluidic devices, since it is convenient to record and quantify via image processing. Rosenbluth *et al.* [9] reported a simple bifurcating microfluidic device containing 64

Table 1 Summary of microfluidic devices for single-cell mechanical characterisation

Method	Mechanical stimuli	Cell sample	Parameters	Throughput	Source
Constriction channel	mechanical squeezing	RBCs, leukocytes, MCF-7 and MCF-10A, yeast cells	transit time, elongation, recovery time, pressure drop	50–100/min [14] 80–85/min [11] >600/min [10] ~30/min [17]	[9–18]
Fluid stress	fluid shear stress or fluid impact	RBCs, MCF-7 and MCF-10A	deformation index	~2000/min [21] ~1000/min [20]	[19–22]
Optical stretcher	laser induced surface force	RBCs, myeloid cells, oral squamous cells	deformation index	1/min [23] 0.9–1.5/min [24]	[23–33]
Electro-deformation	dielectric force	CHO-K1 and U937, SiHa and ME180	Young's modulus, viscosity	–	[34–37]
Electroporation	electroporation induced swelling	MCF-7 and MCF-10A	deformation index	5/min [39]	[38, 39]
Aspiration	vacuum	HeLa	Young's modulus	40 cells/test [41]	[41]

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constriction channels in parallel that can generate clinically useful data about the leukostasis states (Fig. 1). Their device showed a clear distribution difference of the transit time between leukostasis-symptomatic and asymptomatic samples. By combining several parameters (transit time, elongation and recovery time), cell types can be better distinguished. For instance, Hou *et al.* [17] demonstrated a microfluidic straight channel to distinguish benign breast epithelial cells (MCF-10A) and non-metastatic tumour cells (MCF-7). In their study, the transit time was not significantly affected by cell types, but according to a scatter plot of the entrance time and elongation index, different cells can be clearly distinguished with the aid of a mathematic model [18]. Transit time, elongation and recovery time were also used together to obtain three-dimensional scatter plots, proven effective for the discrimination of cancerous RBCs and normal RBCs [13].

Gifford *et al.* [12] used wedge-shaped constriction channels to measure the surface area and volume of a large population of RBCs. They characterised the progressive changes of the surface area and haemoglobin (Hb) content in RBCs. Herricks *et al.* [14] further demonstrated that the geometry of the individual cells can be used to predict the filtration rate when the cells pass through micropores. Abkarian *et al.* [11] proposed a microfluidic manometer, similar to a fluidic pressure comparator. They were able to measure the pressure drop owing to the presence of the cell in the constriction region by observing the displacement of the downstream fluid–fluid interface, which was also proven to correlate with the stiffness of cells.

2.2. Fluid stress: Fluid stress can be readily generated in microfluidic channels. By elaborately designing the configuration of microchannels, cells can be exposed to various fluid stress stimuli. The rigidity of RBCs has been investigated using shear flow in narrow channels [20] and extensional flow in the hyperbolic converging channel [21].

Most recently, Gossett *et al.* [19] reported a deformability cytometry with a high throughput of ~2000 cells/s (which is comparable with traditional cytometry). They used the inertial force to focus cells to the centre of a microchannel and deliver the cells to a region where the cells underwent mechanical stretching. Scatter plots of morphological changes of MCF-7 cells and MCF-10A cells were obtained. Cell deformations were captured using a high-speed camera through an optical microscope. To overcome the speed limitation of image recording and processing, Katsumoto *et al.* [22] demonstrated an electrical classification microfluidic chip to characterise the RBCs deformability (Fig. 2). In the device, embedded electrodes were used for detecting the resistance change

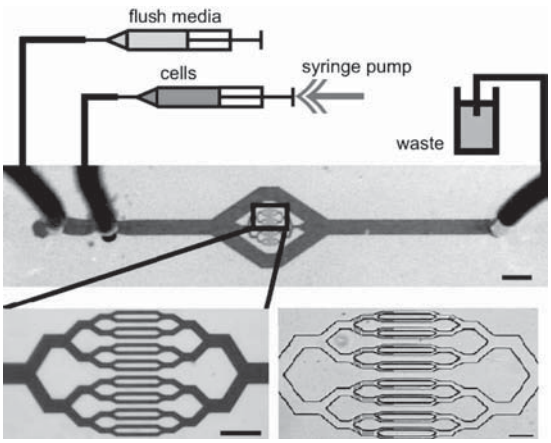

Figure 1 *Constriction channels*
Cells are loaded into the constriction channels network via a syringe (top). Sixteen of these microchannels are shown here (bottom-left). Using video microscopy, cells are tracked as they pass through the smallest of the capillary channels (bottom-right). Reproduced with permission from [9]

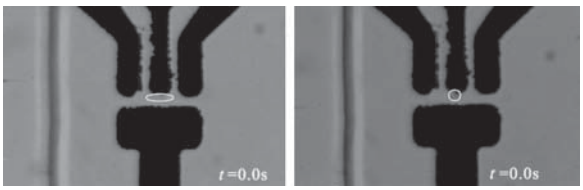

Figure 2 *Fluid stress*
Micrographs of a normal RBC (left) and rigid RBC (right) passing between electrodes. As the RBCs flow in the channel, they are stretched and deformed by the high shear stress provided by the steep velocity gradient of the flow. The time series profile of the measured resistance is affected by the shape of the RBC. Reproduced with permission from [22]

when the RBCs pass through the surface of the electrodes in the microchannel. The half-width of the maximum resistance distribution was correlated to the RBCs deformation induced by fluid shear stress.

2.3. Optical stretcher: The optical stretcher traps and stretches a cell based on laser-induced momentum transfer. Unlike laser tweezers, which uses a single focused beam to trap and move a bead attached to the cell membrane [6, 7, 23, 24], the optical stretcher manipulates cells using two counter propagating divergent laser beams without contacting the cell [25, 26]. The setup of microfluidic optical stretcher did not change much in the past decade. It universally consists of a microchannel or capillary for cells to pass through and dual-beam laser fibres located on both sides of the passageway (Fig. 3). At low laser intensities, the laser beams act as a stable

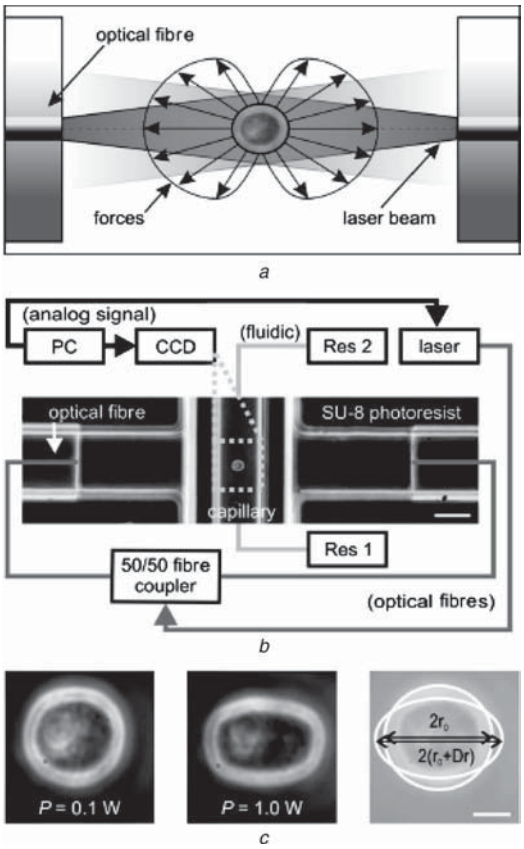

Figure 3 *Optical stretcher*
a Two-counter propagating laser beams emanating from the optical fibres
b The flow of the cell suspension passing through the capillary is controlled by a hydrostatic pressure differential
c Phase-contrast images of acute promyelocytic leukemia (APL) cell being optically trapped (C-left), stretched (C-middle) and definition of the deformation index (C-right). Reproduced with permission from [32]

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trap. At higher intensities, measurable deformations occur owing to forces induced at the surface [27].

In recent years, more and more types of cells were characterised with microfluidic optical stretchers, such as oral squamous cells [28], RBCs [29–31] and myeloid cells [32]. The precise alignment between optical and microfluidic components is critical for microfluidic optical stretchers to function properly since the alignment determines trapping stability. To improve the alignment, Lai *et al.* [29, 33] developed an automatic platform capable of cell delivery, positioning and stretching by integrating micropumps, microvalves, dielectrophoretic electrodes, fibre manipulators and optical stretcher to a monolithic microfluidic chip. Cell samples were delivered and confined to the trapping site, and the laser fibres were aligned accurately using the pneumatic manipulators. It is also worth noting that femtosecond laser fabrication has been applied to the construction of monolithic optomicrofluidic chips for mechanical characterisation of single cells. This method is able to provide direct writing of both optical waveguides and microfluidic channels, facilitating the accurate alignment between the optical and fluidic components [30, 31].

2.4. Electro-deformation: Dielectric force is exerted on a dielectric particle when the particle is polarised in an electric field. The magnitude and direction of the dielectric force depend on the dielectric properties of the particle and the suspending medium, magnitude and frequency of the applied electric field. Electro-deformation utilises dielectric force to apply mechanical stimuli to deform a cell, which was first demonstrated about 30 years ago. With recent advance of microfabrication, the construction of well-defined microelectrode arrays becomes straightforward. However, the complex physical phenomena involved in electro-deformation and unknown cell electric properties pose difficulty in extracting forces experienced by an electro-deformed cell [34, 35].

MacQueen *et al.* [36] recently reported an electro-deformation device with an array of planar Ti/Pt electrodes for trapping and stimulating suspended cells (Fig. 4). They also derived a mathematical expression for the average value of uni-axial stress of the whole cell and calculated the Young's modulus and viscosity of Chinese hamster ovary cells (CHO-K1) and human promonocyte cells (U937). In contrast to using mathematical expression to calculate the force exerted on the cell, in the study reported by Chen *et al.* [37], finite-element simulation based on the Maxwell stress tensor formulation was shown to obtain the magnitude of stretching force and determine the Young's modulus values of SiHa cells and ME180 cells.

2.5. Electroporation: Besides for the purpose of introducing foreign molecules into cells, electroporation has also been used for cell mechanical characterisation. An increase of the electrical conductivity and permeability of the cell plasma membrane occurs when the cell experiences an externally applied electrical field, a phenomenon known as electroporation. Swelling or expansion in cell size always accompanies the cell's electrical property changes [39]. This swelling or expansion behaviour is caused by the influx of small molecules through the open pores in the cell membrane (against dielectric force in electro-deformation). By correlating the swelling behaviour induced by electroporation with the deformability of cells, Bao *et al.* [38] developed a microfluidic electroporative flow cytometry to study the deformability of individual cells (Fig. 5). A constant voltage was established across the microchannel, and when cells flow through the microchannel, the swelling of cells was recorded by a camera. Their results revealed that the swelling ratio of cells in the electroporative microchannel reflect malignant and metastatic situations of the cells.

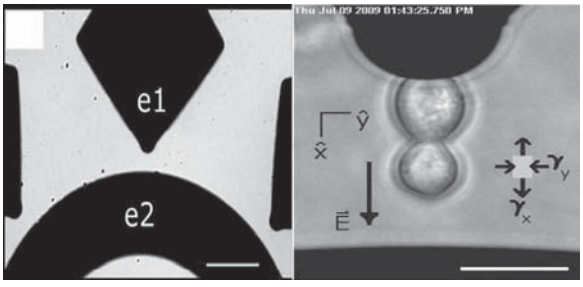

Figure 4 *Electro-deformation*
Geometry of the planar electrodes for electro-deformation. e_1 and e_2 are driven with opposite polarity (left). Trapping and stretching of U937cells (right). Reproduced with permission from [36]

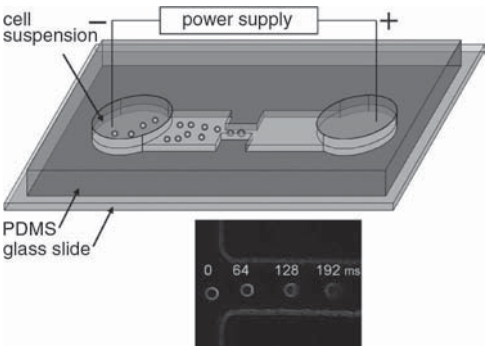

Figure 5 *Electroporation deformation*
Schematic drawing of electroporation microfluidic chip (top). Cell size change of MCF-7 cells at different time points flowing in the channel with the field intensity of 400 V/cm in the narrow section (bottom). Reproduced with permission from [38]

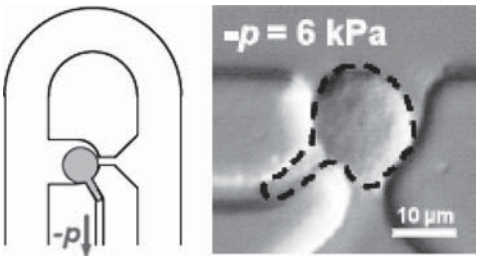

Figure 6 *Microfluidic pipette aspiration*
Schematic drawing of individual cell trapping and aspiration by negative pressure (left). A single HeLa cell aspirated into the aspiration channel at 6 kPa (right). Reproduced with permission from [40]

2.6. Microfluidic pipette aspiration: Micropipette aspiration is a conventional technology for measuring cells' mechanical properties. A cell is partially aspirated into a glass micropipette typically with a diameter of 1–5 μm. The elongation of the cell measured by a microscope and a camera is used to infer the Young's modulus and viscosity of the cell [41]. To conduct micropipette aspiration in a parallel fashion, Kim and Han [40] demonstrated a micro-aspirator chip for characterising HeLa cells. As shown in Fig. 6, individual cells were trapped by the different flow resistance inside microfluidic channels [42]. After all trapping sites were filled with cells, a negative pressure was applied to the 40 aspiration channels simultaneously to deform the cells. The multilayer device was fabricated using a polydimethylsiloxane membrane vacuum expansion technique to keep the cells in the centre of the microchannels and form a seal between the aspiration channel and cell membrane. The seal can be improved with the use of microchannels with circular cross-sections [43]. Compared to other techniques, micropipette aspiration has a number of well-established mathematical models

available for assessing experimental data and extracting the Young's modulus and viscosity values of a cell.

3. Discussion and conclusion: In this focused mini-review, we summarised the state-of-the-art microfluidic technologies for single-cell mechanical characterisation and categorised these devices on the basis of mechanical stimulation mechanisms. Despite the numerous devices reported in the literature, three major issues await solution and/or improvement: (i) the throughput of current technologies is lower than those demanded by many biological and clinical applications; (ii) the use of bulky equipment (e.g. bench-top microscopes) limits the compactness and portability of microfluidic systems and (iii) the lack of appropriate theoretical models for interpreting raw data to extract parameters such as the Young's modulus and viscosity.

Mechanical characterisation of cells does not only have importance in fundamental biophysics for understanding cellular structures but also have been shown in a number of recent work to have clinical relevance for disease diagnostics. The development of more advanced microfluidic devices for characterising mechanical properties of cells will continue to grow within the next decade. Microfluidic devices are inherently matched in scale with cells. Advances in microfabrication are enabling more integrated and automated microfluidic systems, which will further reduce human intervention. Furthermore, the parallelism that microfluidics has to offer will enable massively parallel characterisation of cells to realise truly high-throughput operation. In addition, cells' mechanical differences are also more often used for other microfluidic operation, such as cell separation (e.g. [44, 45]), which is also under intensive research but beyond the scope of this mini-review.

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