Label-free detection with micro optical fluidic systems (MOFS): a review

A. Q. Liu · H. J. Huang · L. K. Chin · Y. F. Yu · X. C. Li

Received: 8 December 2007 / Revised: 9 January 2008 / Accepted: 10 January 2008
© Springer-Verlag 2008

Abstract The paper reviews the state-of-the-art for micro optical fluidic systems (MOFS), or optofluidics, which employs optics and fluidics in a microsystem environment to perform novel functionalities and in-depth analysis in the biophysical area. Various topics, which include the introduction of MOFS in biomedical engineering, the implementation of near-field optics and also the applications of MOFS to biophysical studies, are discussed. Different optical detection techniques, such as evanescent wave, surface plasmon resonance, surface enhanced Raman scattering, resonators and transistors, have been studied extensively and integrated into MOFS. In addition, MOFS also provides a platform for various studies of cell biophysics, such as cell mass determination and cell Young’s modulus measurement.

Keywords Micro optical fluidic system · Surface plasmon resonance · Surface enhanced Raman scattering · Resonator · Cell biophysics · Optofluidics

Introduction

Different detection methods have been widely applied in biomedical analysis. These methods can be broadly categorized into two groups, namely labeling methods and label-free methods. In labeling methods, cells or molecules (DNA or proteins) are detected by fluorescent labeling, which has been broadly used in the study of cellular and molecular interactions in biochemistry and cell biology [1] for a decade now. The drawback of this method is the labeling of the cell with fluorescence markers, which is normally time-consuming, complex and expensive. Moreover, this fluorescence labeling method, which is mainly used for biochemical and molecular interactions, is not suitable for the biophysical characterization of living cells. As a result, researchers have been exploring the area of label-free detection in order to attempt to overcome these problems. Several label-free optical techniques have been developed, including autofluorescence [2], confocal Raman spectroscopy [3], intracavity spectroscopy [4] and optical scattering [5]. Most of these techniques have been developed for biophysical studies, focusing on the structure [6], refractive index [7], bonding energy [8] and Young’s modulus [9] of cytoskeleton, DNA, cytoplasm, membranes and the extracellular matrix. In normal environments, cells are affected by the gradients of cytokines and proteins secreted from neighboring cells [10], biochemical and mechanical interactions with the extracellular matrix (ECM), and direct cell–cell contacts [11]. However, biophysical studies are hindered by the bulky and expensive equipment needed, and limited cell and biomolecule manipulation techniques. Therefore, researchers have been trying to develop new technologies that combine easy and effective cell and biomolecule manipulation and small sample size with highly sensitive detection. Consequently, the micro optical fluidic system (MOFS), consisting of a microfluidic system (with sample manipulation and light-guiding functions) and an optical system (with optical components and a detection system), has been introduced. This system, which provides all of the required characteristics, is expected to play an increasing role in biophysical studies.

This paper focuses on the development of MOFS. Several important near-field optical methods used in MOFS aimed at
MOFS can be used for single-cell diagnosis. By combining medical knowledge with this information, easily and reliably obtained from small-volume samples.

The microfluidic system provides a platform for single-cell biophysics studies and future trends in MOFS are then described. Evanescent waves, which form the basis for total internal reflection microscopy and also surface enhanced Raman scattering, are then discussed. The following section reviews surface plasmon resonance and its applications to optofluidic microscopy. Surface enhanced Raman scattering and its applications to biomolecule detection are then presented. Following that, different resonators implemented in MOFS, including mechanical, optical and photonic crystal resonators, are explored. The penultimate section presents the study of cell biophysics in MOFS. The last section draws conclusions.

Micro optical fluidic system (MOFS)

MOFS is a single-chip solution which aims at combining fluids and light in microchannels to realize different optical components and to create a highly versatile microsystem. Optical components such as lenses, waveguides, couplers or light sources which have previously been used outside the chip can now be integrated into a micro- or nanoscale chip. When the optical components are realized through microfluidic manipulation, they provide tunability and adaptivity for the optical system. Within MOFS, fluids act as media which carry targeted substances such as biomolecules in the microchannels for detection. The optical components developed include adaptive optical lenses [12, 13], waveguides [14–20] and a light source [21]. Many devices based on a liquid/liquid waveguide have also been reported. First, an optical switch which uses the pressure from side channels to push core flow into different outputs has been demonstrated [14]. Second, an evanescent coupler which uses two liquid/liquid waveguides to couple light from one waveguide to another waveguide has also been studied [14]. Third, a low-threshold and high-efficiency dye laser has been reported [15]. An on-chip light source has opened the door to different micro-optical circuits [16, 17]. Finally, a liquid/liquid waveguide can be used as a 3-dB splitter if the direction of the flow and the light is reversed [18]. In this liquid/liquid waveguide, the refractive indices of different streams can be controlled by manipulating the temperatures of the streams [19] or using different liquids. The widths of the core and cladding can be fine-tuned by the flow rates [20]. Under the MOFS framework, many kinds of small systems, such as those used for cell culture [22], treatment [23], selection [24] and analysis [25], can be developed. Most of the small systems can be integrated into a single chip to perform several functions in a compact system. Using the chips, cell biophysical parameters can be easily and reliably obtained from small-volume samples. By combining medical knowledge with this information, MOFS can be used for single-cell diagnosis.

MOFS normally adopts the fabrication process of micro-electrical mechanical systems, which has been widely explored and exhibits high reproducibility and feature sizes below the wavelength of light. However, the most commonly adapted process is soft lithography, which allows the rapid fabrication of complex structures in flexible polymer substrates such as polymethyl methacrylate (PMMA) or polydimethylsiloxane (PDMS), etc. PMMA and PDMS have the advantages of optical transparency and quality, which are suitable for optical detection in the biomedical field, such as studies of cell properties, and protein and DNA analysis.

MOFS is intended to be an enhanced platform for biomedical analysis, with various advantages. First, it is adaptable and compatible with biology and nanotechnology. Different materials can be explored and different surface treatments can be employed to increase the biocompatibility of the materials. Second, microfluidic components can be easily fabricated and combined for the realization of different applications, such as diffusion mixing [26], gradient formation [27], electrokinetic and electrowetting manipulation [28], multiphase manipulation [29] or particle separation [30]. The microfluidic system provides a platform for single-molecule, DNA, protein or single-cell manipulation inside MOFS for high-throughput chemical reactions and bioanalysis. Third, MOFS is an ultracompact and thus portable system with various potential applications, such as DNA extraction for the realization of deep-sea in situ gene analysis [31].

While MOFS was initially developed with the intention of creating portable and controllable devices with optical detection technology, challenges related to sample size, optical signal detection, and interface issues between the system and off-chip instrumentation remain. Therefore, even though typical methods based on geometrical optics can be used to describe the light traveling in the MOFS, near-field optics has been studied extensively in order to enhance our understanding of MOFS when applied to bioanalysis.

Evanescent wave techniques

Evanescent waves can be induced through the total internal reflection (TIR) of light due to the propagation of electromagnetic waves through the interface between two dielectrics with different refractive indices under certain boundary conditions. Evanescent waves are normally detectable adjacent to the interface but within one-third of the wavelength of light, which is known as the near-field region. They are widely used in, for example, the Mach–Zehnder interferometer, fiber sensors, fluorescence induction, etc. As the evanescent wave also has a larger wave vector than the original light in free space, it can be used to cool down the thermal vibration of atoms [32] or to induce surface plasmon
resonance. The former is an excellent approach to use in the construction of integrated optics components at the nanoscale. The latter is widely used in biological detection or surface-enhanced Raman scattering, which will be discussed later in this paper.

The biological behavior of a sample can be imaged by evanescent wave techniques, which involve blocking out the incident light as it is reflected internally in order to stop it from being detected. As shown in Fig. 1, the behavior of a neuroendocrine cell line on the surface of a living PC12 cell was studied with total internal fluorescence microscopy [33]. The PC12 cell is labeled with the enhanced green fluorescent protein-tagged Rab3A, one of the small G proteins involved in the fusion of secretory vesicles to the plasma membrane in PC12 cells. The movement of the secretory vesicles of PC12 cells within the evanescent range (<200 nm) can be traced during stimulation by high K+.

As transparent PDMS is cured from a high-viscosity liquid, the structure of the microchannel can be made perfectly clear with a well-fabricated mold. Therefore, the plane-type microprism embedded in the MOFS is designed to be a refractive index detector [34]. In MOFS, the hollow Abbe prism is filled with sample solution and two optical fibers linked to a PDMS biconvex microlens provide the input/output channels for the light source. Another type of vertically oriented prism with a light path that is perpendicular to the plane of the MOFS chip has also been demonstrated [35]. As shown in Fig. 2, a 54.7°-inclined clear surface that has been etched by KOH onto a {100} silicon wafer is coated with a Cr/Au thin film and this works as a micromirror. The etched cavity is fully filled with UV curable polymer on a silicon substrate, which is sandwiched and fixed between two thin glass substrates. Long focal length light is reflected by the micromirror and redirected to the glass/PDMS or glass/water interface. TIR occurs and the evanescent wave is generated and used to image the Brownian motion of the 1 μm fluorescent microsphere in the microfluidic channel. In this design, the hybrid vertical integration of a laser diode and a CCD camera was demonstrated, resulting in a compact optical system. However, the implementation of the cavity with a micromirror sidewall requires precise but heavy tools to align the excitation light beam within the system. The concepts of a high degree of integration and miniaturization were the main driving forces for this innovation.

The whole system can easily be constructed from PDMS microoptics, a thin glass slip and an optical fiber. The predesigned passive alignment system can be investigated by theoretical simulation and ray-tracing methods. The incident light is supplied by a fixed optical fiber and manipulated by an embedded PDMS microlens. After this, the incident light is launched into a PDMS prism, where TIR occurs. The chip simply generates evanescent waves at the PDMS/water interface and induces TIR illumination at the samples in water. This provides flexibility when delivering samples and is not limited to the microfluidic

Fig. 1 Localization of Rab3A proteins expressed in PC12 cells is confirmed by immunocytochemistry using confocal microscopy. a EGFP–Rab3A transfected PC12 cells in green fluorescence; b rhodamine-conjugated anti-Rab3A antibody in red fluorescence; c combination of (a), (b) and DIC image [33].

Fig. 2 Cross-sectional view of the monolithic TIR-based chip with its light path.
channel. In addition, the light is injected into the system with an optical fiber such that the range of incident light is from the UV to IR, which is suitable for different biological applications, ranging from DNA to protein analysis.

The concept of evanescent waves has also been extended to realize the coupling of light in MOFS. Liquid–liquid waveguide coupling has been suggested [3], in which two core streams are separately sandwiched within three cladding streams in a single fluidic channel. The application of liquid claddings can generate a smooth interface between the core and cladding streams without being affected by the roughness of the sidewall of the PDMS channel (about 5% of the total width of the channel). This results in high polarization maintainability (100:1, indistinguishable from the light in the input fiber). The cladding fluids are doped with FITC-dextran (1 mg/ml), which enables the evanescent field to be imaged by fluorescence microscopy, since it excites the fluorophores. The light power in one core stream is demonstrated to be evanescently coupled to another core stream.

**Surface plasmon resonance**

From the work of Ritchie [36], waves of collective electron motion that propagate along a joint dielectric/metal interface are known as surface plasmon resonance (SPR). By solving Maxwell’s equations under the boundary conditions of the interface, the SP dispersion relation is found to be [37]:

$$ k_{sp} = k_0 \sqrt{\frac{\varepsilon_d \varepsilon_m}{\varepsilon_d + \varepsilon_m}} $$

where $k_{sp}$ is the wave vector of SPR, $k_0$ is the wave vector in free space, and $\varepsilon_d$ and $\varepsilon_m$ are the dielectric constants of the dielectric material and the metal, respectively. As $k_{sp}$ is larger than $k_0$, SPR cannot be directly induced by direct shining light onto the metal surface. Typically attenuated total reflection or diffraction gratings are employed to induce SPR [38].

SPR prism-based sensors are highly sensitive to changes in their surroundings or the attachment of biological/chemical species. They are usually handled by measuring the intensity of the reflected light wave [39, 40], the resonant angle of the incident light wave [41, 42] or the resonant wavelength of the incident light wave [43]. Other interesting research work focuses on antigen–antibody interaction studies [44] and dye-labeled DNA detection through SPR-enhanced fluorescence readout [45]. These advanced studies are described in the review paper [46], and are therefore not discussed further in this paper.

Since SPR can be generated by evanescent waves, bent polished fibers [47], tapered or cladding-stripped fibers [48] or integrated optical waveguides [49–52] with metal coatings on their surfaces can also be used as very compact biosensors. In addition, a conical fiber tip at the cutting end of an optical fiber coated with gold film can be used as another type of ATR coupler [53, 54]. The incident light propagates in the optical fiber, triggering SPR at the gold-coated tapered surface and the readout is then inversely extracted via the same light path. As introduced by Feynman in 1959, if the size of the bulk material is reduced to several nanometers, it shows specific surface, size and quantum effects and thus exhibits totally different physical or chemical behavior from the bulk, including quantum confinement, localized surface plasmon resonance, and significantly increased numbers of surface atoms with dangling bonds. Since metallic nanoparticles with different sizes and shapes carry different modes of SPR on their surfaces [55–57], the distribution of high-intensity electromagnetic hot spots varies, as shown in Fig. 3. The intensity of the electric field adjacent to the surface of the metallic nanoparticles is strongly increased. Therefore, target species close to the hot spot are affected such that spectral absorption [58] or Raman scattering [59–64] is further enhanced.

Typical near-field scanning optical microscopy (NSOM) uses a nanosized aperture to collect or illuminate the sample with an aperture–sample distance in the near-field range. In
addition, an apertureless apex can be used as the scattering center in the NSOM system. The localized near-field signal that does not radiate to the far-field region is thus extracted. Even though atomic force microscopy (AFM) and NSOM can be used to image DNA, some pretreatment steps for DNA are necessary and DNA must be bound onto a flat substrate. The surface morphology and optical signal are extracted by mathematical convolution of the DNA and the substrate. Deformation occurs and the DNA sequence is not correctly resolved. Furthermore, AFM and NSOM are time-consuming measurement methods. To overcome these problems, an ultrafast parallel DNA analysis based on MOFS has been demonstrated [65]. As shown in Fig. 4, Chansin fabricated a micro inner container with a silicon nitride membrane substrate. The hole array is milled on a silicon nitride membrane with a focused ion beam (FIM) and coated with 100-nm aluminum thin film. The inner container is fully filled with a solution containing DNA labeled with YOYO-1 (molecular probes), and placed into another outer container with a substrate of a glass cover slip coated with indium tin oxide. The inner solution is negatively biased and the outer buffer solution is positively biased. DNA starts to drift down to the outer buffer solution through 50–300 nm channels. Light is illuminated from the top of the inner container. The variation in the local light intensity of each pore is monitored by a confocal optical microscope and an emCCD camera. Since each section of the DNA passes through the nanopore, which has a size that is several factors smaller than the incident light, near-field interactions between the nanopore and each section of DNA are sequentially detected. Therefore, the sequence of DNA is resolved optically in MOFS.

Near-field optical imaging on large living animals is usually challenging. However, Cui et al. has recently implemented a complete on-chip optofluidic microscopy (OFM) system that measures living C. elegans within 0.5 s [66, 67]. OFM is based on a microfluidic channel with a line of transparent submicron holes on the bottom of a metallic layer. The line of holes crosses the fluidic channel with a small angle. The light that shines onto the channel will be transmitted to the nanopores and the intensity of each hole is collected onto an individual CMOS pixel. As the target flows over the line of holes, the time-varying transmission trace represents a line scan across the object. The slanted hole arrangement ensures that adjacent line scans overlap and that the object is fully scanned. By stacking the line traces together appropriately, the image of the object can then be constructed.

Surface-enhanced Raman scattering

Surface enhanced Raman spectroscopy (SERS), which is a surface-sensitive technique, can detect the enhancement in Raman scattering when molecules are adsorbed onto rough metal surfaces. For some specific cases, even the measurement of single-molecule Raman scattering can be achieved [59, 60]. Therefore, it is an important technique for the detection of biomolecules, such as DNA/RNA [61], rhodamine 6G [62, 63] and enzymes [64].

Leung et al. [68] have developed a continuous flow microfluidic reactor which uses a confocal Raman microscopic detector for online monitoring. In this MOFS, the measurement time is greatly reduced from 48 h to 10 mins. Since the work of Connaster et al. [69], SERS measurements have also been carried out in a fluid channel [70, 71]. As described earlier, MOFS is relatively small compared to conventional measuring instrumentation. The quantity of the sample in the microfluidic channel is limited, and the signals cannot be easily extracted. Therefore, some manipulation skills, such as electroosmotic cell sorting (to achieve high concentrations of samples) [72, 73] or laser trapping [74] or micropipetting [75] (to capture a single cell) are used.

It is widely known that a specially organized surface profile can induce stronger SPR and subsequently a stronger SERS signal [70, 71]. Therefore, the electroosmotic force resulting from applying a voltage bias to the sample solution can push the target molecules directly onto the surface of a hemispherical array, as shown in Fig. 5 [76]. Subsequently, a Raman shift at 735 cm$^{-1}$ is clearly identified within 10 mins.

![Fig. 4 A schematic of the experimental setup used for the translocation detection of DNA sequences](image)
As shown in Fig. 6, it has been suggested that if Au nanoparticles and a targeted organic sample colloidal solution are injected into a channel with a limited thickness, the SERS signal can be collected at a specific position [70]. As the distance between the nanoparticles is very small, the induced SPR is very high. The SERS signal can thus be enhanced by this strong localized electromagnetic hot spot and easily retrieved (Fig. 7).

Resonator

Microresonators are commonly used in MOFS as one of the main cell/biomolecule detection techniques. Microresonators provide an advantage in label-free detection with high sensitivity in the analysis of biomolecules or single living cells. Microresonators integrated into MOFS can be broadly categorized as mechanical resonators, optical resonators and nanophotonic resonators. The following subsections will discuss the different types of resonators and their applications in cell/biomolecule analysis.

Mechanical resonator

A suspended microchannel resonator which can weigh single nanoparticles, single bacterial cells and submonolayers of adsorbed proteins in water with sub-femtogram resolution (1 Hz bandwidth) has been demonstrated [77]. Microfluidic channels are embedded on the suspended resonator such that samples can be directed to the resonator for detection. Changes in mass ($\Delta m$) inside the suspended resonator are detected by the shift in the resonance frequency ($f$):

$$ f = \frac{1}{2\pi} \sqrt{\frac{k}{m_{\text{eff}} + \alpha \Delta m}} $$

where $k$ is the spring constant, $m_{\text{eff}}$ is the effective mass and $\alpha$ is a numerical constant that depends on the geometric localization of the added mass. To measure the frequency response, the vibration amplitude is monitored with a laser and a position-sensitive photodetector while the cantilever is driven electrostatically at different frequencies. The resonance frequency of the suspended microfluidic channel.
is highly sensitive to the presence of molecules/particles with mass densities that differ from that of the solution. This leads to intriguing applications, such as mass-based flow cytometry and the direct detection of pathogens. A sample that is evenly absorbed onto the inner surfaces can be resolved to 0.01 ng cm$^{-2}$. For suspended sample particles, the sensitivity is the highest near the cantilever tip, with a precision of 300 attograms possible. The author has demonstrated the measurement of the binding of goat anti-mouse immunoglobulin-$\gamma$ (IgG) molecules to anti-goat IgG antibodies that are immobilized on the channel walls. The exact masses of the different layers can be quantified by the changes in the resonant frequency before and after each injection. The size of the suspended channel is appropriate for the characterization of nanoparticles and bacteria. However, it is too small for the passage of most eukaryotic cells.

**Optical resonator** In optical resonators, microcavity resonators are commonly used for biomolecule analysis. In an optical ring resonator, light propagates in whispering gallery mode (WGM) and results from the TIR of the light along a curved surface. The guided light interacts repeatedly with the samples on the surface of the ring through the evanescent field. The ring resonator utilizes the change in refractive index to perform detection because the WGM resonant wavelength ($\lambda$) is determined by [78]:

$$\lambda = \frac{2\pi r n_{\text{eff}}}{m}$$

where $r$ is the ring outer radius, $n_{\text{eff}}$ is the effective refractive index and $m$ is an integer related to the WGM angular momentum. Although the size of the microcavity ring is small, it has better sensing capabilities than an optical waveguide and enables high-density sensor integration in MOFS.

A highly specific and sensitive optical sensor based on an ultrahigh quality factor, ($>10^8$) whispering gallery microcavity has been reported [79]. The microtoroid resonator has a silica surface which functions as a binding site for targeted molecules and they are detected by the resonant wavelength shift resulting from the thermo-optic mechanism. The microtoroids are coupled to a tunable laser and a detector by a tapered optical fiber waveguide. Label-free and single-molecule detection of interleukin-2 has been demonstrated in serum with a dynamic range of $10^{12}$ in concentration.

In parallel with the standalone microsphere or planar ring resonator, the liquid core optical ring resonator (LCORR) is regarded as another type of ring resonator biomolecular sensor [80, 81]. In LCORR, a micro-sized glass capillary is employed as a ring resonator, such that the sample is passed through the capillary [82]. A tapered optical fiber is positioned perpendicular to the capillary, and this couples light into the LCORR wall evanescently. The LCORR is used in the measurement of bovine serum albumin molecules [83] that are absorbed onto the surface of the LCORR, which is activated with 3-aminopropyltrimethoxysilane.

In addition to the microcavity resonator, another type of optical resonator has been employed to analyze the biophysical properties of a single living cell: , a Fabry–Pérot (FP) resonator. The realization of a FP resonator using a pair of gold-coated optical fibers in MOFS and its application to the measurement of the refractive index of a single living cell has been demonstrated [75]. The pair of fibers are aligned and separated to form a resonant cavity of 20 microns. A single Mardin–Darby canine kidney (MDCK) cell is trapped by a micropipette. The cell’s refractive index is measured by a buffer modulation technique, i.e., the surrounding buffer is changed to observe the change in the resonant cavity, similar to the approach used for the microcavity resonator. However, the shift in the resonant wavelength is determined by the optical path length in the cavity. As the cell is trapped physically, cell deformation and subsequently deviations in measurements may occur. To avoid this problem, the FP resonator has been further improved by applying a pair of fiber Bragg gratings (FBGs) [84]. The resonant cavity is formed from the pair of FBGs without any coating such that the cell can be optically trapped inside the cavity by laser force. As the cell is perfectly aligned along the cores of the fibers, the measurements are greatly improved in terms of their precision (up to 0.001) and stability. The refractive index of the cell can provide an important indicator during cell analysis for, e.g., oncology or blood diseases (thalassemia or anemia) [85, 86].

---

**Fig. 7a–c** Optical resonators: a liquid core optical ring resonator; b Fabry–Pérot interferometer; c cell encapsulation with an integrated fiber Bragg gratings interferometer
**Photonic crystal resonator** Photonic crystals are one of the most attractive sensing platforms because of their strong light confinement characteristics [87]. Unlike ring cavity resonators, which use the interaction between the evanescent wave and the analyte, photonic crystals are designed to localize the electromagnetic field in the low refractive index region, i.e., in air pores. A defect is introduced by reducing the central pore diameter such that a resonant peak can be seen in the output spectrum [88]. This is highly sensitive to small changes in the refractive index due to the immobilization of biomolecules on the pore walls. Highly selective probe molecules are immobilized on the internal surface and targeted molecules can be captured and induce a peak shift. In the research, glutaraldehyde–bovine serum albumin (BSA) binding is used as the model system and BSA proteins are measured.

**Cell biophysics**

Cell mass and volume are parameters that are often demanded in biological studies and drug screening. For example, these are the important parameters needed in studies of the osmotic water permeability of the cell membrane [89]. The cell “dry mass” is the mass of all substances excluding water inside the cell. Therefore, the cell mass is the sum of the dry mass and the water mass. However, the measurement of cell mass is very challenging, especially for a single living cell. Optical interferometry [90] is a commonly used method for cell dry mass measurement, but it requires bulky instruments and does not provide water mass/volume information.

A MOFS [91] which combines the fiber Mach–Zehnder interferometer with a fiber optical trap has been presented. It can be used to determine the size and the refractive index of a single living cell. Based on these measurements, the cell dry mass, water mass, and the cell volume can all be determined. An MDCK cell is used and the results show that the deviations in the cell dry and water masses are less than 5%.

Several methods have been proposed to measure the Young’s modulus of a cell, such as micropipette aspiration studies [92], atomic force microscopy [93], or cell poking [94]. However, the response of cell to externally applied force is affected by these invasive methods due to deformation. In addition, as the mechanical properties of cells are different in different areas, a large deviation in Young’s modulus measurements is observed.

To overcome these problems, a MOFS which integrates a force-generating device has been designed for measuring the Young’s modulus of a single living cell in real time using hydrostatic pressure, as shown in Fig. 8 [95]. In this design, hydrostatic pressure is exerted uniformly at all parts of the cell without direct contact, so that dissipative forces, such as friction, which give rise to undesirable inaccuracies can be avoided and the accuracy of the Young’s modulus measurement is improved. Studies on the mechanotransduction of THP-1 cells and the effects of the addition of toxins (i.e., lipopolysaccharide (LPS) and colchicine) on the biophysical properties of these cells have been carried out. The results show that the THP-1 cells are stimulated to secrete more chemicals as the LPS concentration is increased. The disruption of the microtubule networks and parts of the cytoskeleton resulting from the presence of colchicine also causes a drastic reduction in Young’s modulus.

**Conclusions**

The application of MOFS in biophysics studies represents a natural trend for replacing bulky manipulating and measuring devices with more compact ones, and introduces significant improvements in many areas, such as easier sample manipulation, faster detection speed, lower volume sample and higher sensitivity. More importantly, MOFS provides a platform that enables a microfluidic system to be integrated with an optical detection system, and it performs novel functionalities that cannot be achieved by conventional devices. Various near-field optical detection techniques have been developed for use in MOFS, including evanescent wave techniques, surface Plasmon resonance, surface-enhanced Raman scattering and resonators. Instead of optical signal detection, MOFS can also be integrated...
with different functionalities, such as cell cultures for biophysics studies. One of the main challenges in the development of MOFS is to ensure the stability and reliability of devices. More work will need to be conducted before MOFS is capable of providing a single-chip solution in real biomedical analysis.

References