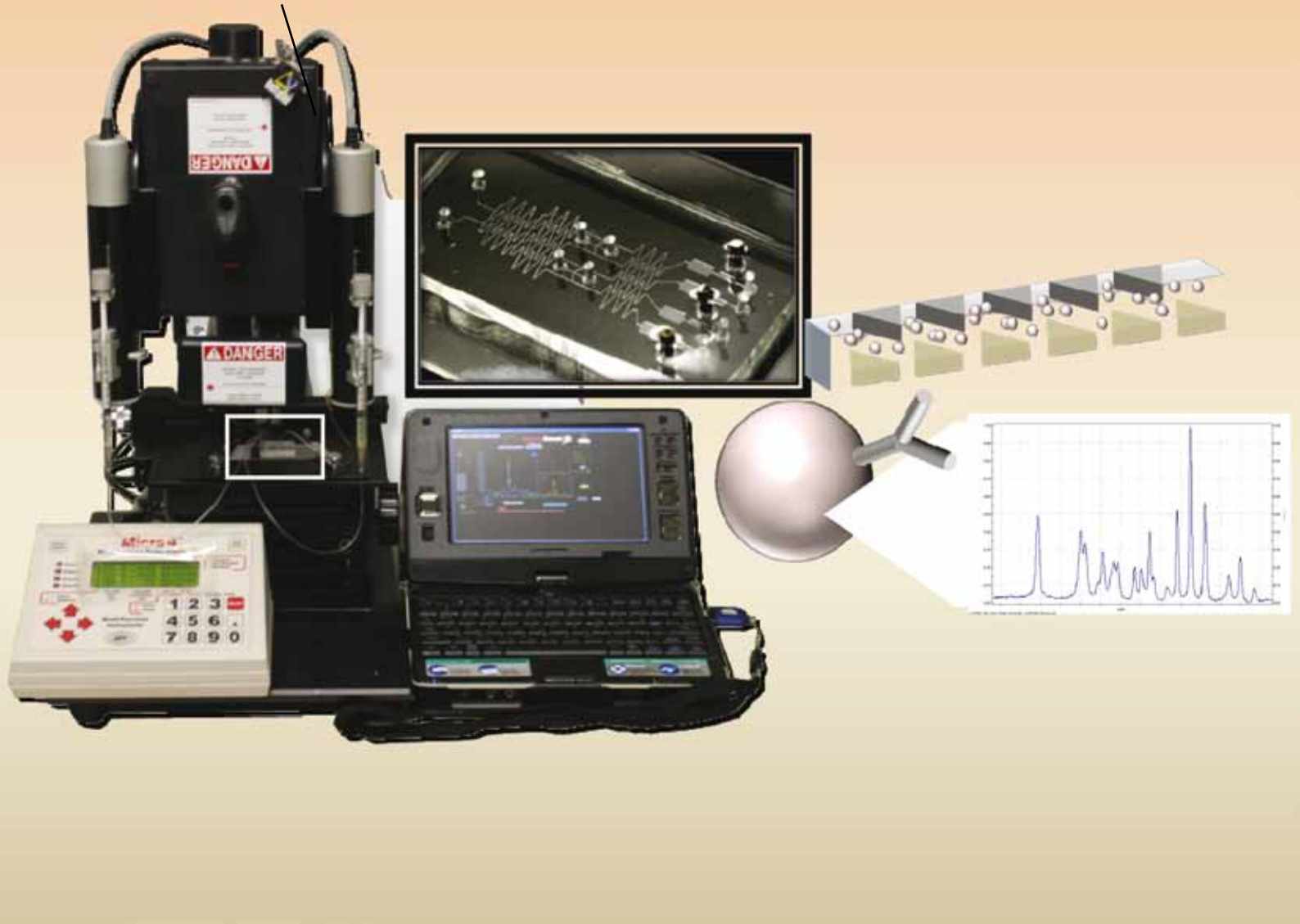
Analyst

Interdisciplinary detection science

www.rsc.org/analyst

Volume 135 | Number 5 | May 2010 | Pages 809–1156



ISSN 0003-2654

RSC Publishing

MINIREVIEW
Jaebum Choo *et al*.
Optofluidic platforms based on surface-enhanced Raman scattering

HOT ARTICLE
Peter Gardner *et al*.
An investigation of the RWPE prostate derived family of cell lines using FTIR spectroscopy

HOT ARTICLE
S. I. Smith and J. S. Brodbelt
Rapid characterization of cross-links, mono-adducts, and non-covalent binding of psoralens to deoxyoligonucleotides

Optofluidic platforms based on surface-enhanced Raman scattering

Chaesung Lim,†[a] Jongin Hong,†[b] Bong Geun Chung,[a] Andrew J. deMello[b] and Jaebum Choo*[a]

Received 21st September 2009, Accepted 22nd December 2009
First published as an Advance Article on the web 18th January 2010
DOI: 10.1039/b919584j

We report recent progress in the development of surface-enhanced Raman scattering (SERS)-based optofluidic platforms for the fast and sensitive detection of chemical and biological analytes. In the current context, a SERS-based optofluidic platform is defined as an integrated analytical device composed of a microfluidic element and a sensitive Raman spectrometer. Optofluidic devices for SERS detection normally involve nanocolloid-based microfluidic systems or metal nanostructure-embedded microfluidic systems. In the current review, recent advances in both approaches are surveyed and assessed. Additionally, integrated real-time sensing systems that combine portable Raman spectrometers with microfluidic devices are also reviewed. Such real-time sensing systems have significant utility in environmental monitoring, forensic science and homeland defense applications.

Introduction

Since the introduction of the miniaturized total analysis system (microTAS) in the early 1990s,[1] thousands of studies have reported the development of microengineered systems for use in chemical and biological science.[2–14] Much of this development has been driven by the necessity to perform fast and sensitive measurements on minute sample volumes. However, at a more basic level, interest in such systems has been stimulated by the fact that molecular phenomena can be easily controlled and exploited when instrumental dimensions are reduced to micron or sub-micron scale. Indeed, the benefits of minimal sample and reagent consumption, low unit cost, improved analytical performance, small instrumental footprints and facile integration of functional components are complementary. However, when any analytical system is miniaturized, the associated detection volume typically becomes significantly smaller thus demanding access to high-sensitivity detection techniques. In the early days, a range of optical detection methods, such as absorbance and fluorescence spectroscopies, were developed for such needs.[15–19] Optical methods are ideally suited to the continuous monitoring of species within microfluidic networks. However, an obvious disadvantage of fluorescence detection methods relates to the need to label molecules not containing an appropriate fluorophore. As a result, there has been much interest in integrating label-free detection techniques with microfluidics.

Raman spectroscopy is recognized as an important analytical method that can provide rich information about molecular structure and composition. Unfortunately, the extremely small cross-section associated with the Raman scattering process (typically *ca.* 10^{-30}–10^{-25} cm^2/molecule) precludes its use as an ultra-sensitive detection method under normal conditions. The issue has been addressed in large part by the discovery and development of surface-enhanced Raman scattering (SERS)

[a]*Department of Bionano Engineering, Hanyang University, Ansan 426-791, South Korea. E-mail: jbchoo@hanyang.ac.kr; Fax: +82 31 436 8188; Tel: +82 31 400 5201*
[b]*Department of Chemistry, Imperial College London, South Kensington, London, UK SW7 2AZ. E-mail: a.demello@imperial.ac.uk*
† Contributed equally to this work.

Chaesung Lim

Chaesung Lim is a Ph.D. student in the Department of Applied Chemistry at Hanyang University. He received his B.S. degree in 2007 from Hanyang University, Ansan, Korea. His research interests include a fabrication of microfluidic devices, lab-on-a-chip systems and their applications to biomedical diagnostics, forensic science, environmental monitoring and high-throughput biological assays.

Jongin Hong

Jongin Hong is a post-doctoral fellow in the Department of Chemistry at Imperial College London. He received his Ph.D. from KAIST in 2005. Subsequently, he held post-doctoral training at KIST and then a post-doctoral fellowship at the University of Pennsylvania in 2006. He has published over 30 research papers in refereed journals and 3 book chapters. He has been engaged in the development of nano/microfluidic systems to resolve chemical and biological problems.

spectroscopy, which affords enhancement factors in excess of 14 orders of magnitude by incorporation of metallic nanostructures or nanoscopically defined metallic surfaces.[20,21] Consequently, SERS techniques can provide for sensitivities comparable with fluorescence detection.[3,22] Apart from high sensitivities and low limits-of-detection, SERS possesses other intrinsic benefits, such as facile molecular fingerprinting, operation over a wide range of excitation wavelengths, reduced photobleaching and highly resolved spectroscopic bands. Accordingly, SERS methods are ideally suited for simultaneously detecting multiple species in complex analytical samples.

Nonetheless, the application of SERS in quantitative analysis is problematic due to the difficulties associated with reproducing SERS enhancements. A lack of control over factors such as the degree of aggregation, particle size and inhomogeneous distributions of analyte molecules on surfaces are all primary culprits. Implementation of microfluidic techniques has recently been shown to address some of these issues.[23–27] Microfluidic systems possess several useful advantages over conventional macroscale environments when performing SERS. For instance, the ability to operate within a continuous flow regime and to generate homogeneous mixing conditions within microfluidic networks has been shown to afford quantitative SERS-based analysis.[23] In this Minireview, we avoid presentation of the extensive literatures in the field and rather concentrate on the latest applications of SERS-based optofluidic platforms for biological and environmental analysis over the past three years. As noted we define a '*SERS-based optofluidic platform*' as an integrated analytical device composed of a microfluidic element and a sensitive Raman spectrometer.

Innovative SERS-based optofluidic platforms

Microfluidic technologies allow precise control of fluids on small spatial scales and thus can be used to control optical properties. In this respect, SERS-based optofluidic platforms can be categorized into two broad groups. In the first, nanocolloid-based microfluidic systems manipulate metallic nanoparticles (Ag or Au) within a liquid, and in the second, metal nanostructure-embedded microfluidic systems provide identical SERS-active sites. To date, the former have been more intensively investigated due to the facile solution-phase synthesis of silver and gold nanoparticles. In order to generate identical SERS-active sites for quantitative analysis, uniform and controlled mixing of reagents is essential. Importantly, a diverse range of passive and active microfluidic mixing devices have been developed over to the past decade to improve diffusive mixing efficiencies in laminar flow regimes.[28,29] Passive mixers rely on geometric properties of the channel or fluidic streams to maximize the area over which diffusion can occur and are popular because of their operational simplicity and flexibility. However, conventional flow lamination is relatively inefficient at generating high degrees of mixedness within short times and thus special geometries in the mixing channel that generate chaotic advection have been suggested in SERS detection.[23,30] For example, Fig. 1(a) shows a schematic of a microfluidic mixer containing an alligator teeth-shaped channel formed in polydimethylsiloxane (PDMS) using soft lithographic techniques. Such a device was shown by Choo and co-workers to allow efficient mixing of spermine-treated cyanide anions and silver colloids within short times.[30] The structured channel generates both vertical and transverse dispersion of confluent streams and provides for cyanide detection in water at the

Bong Geun Chung

Bong Geun Chung is an assistant professor of the Department of Bionano Engineering at Hanyang University, Ansan, Korea. He has published 18 papers, 17 proceeding abstracts, and 3 book chapters. He received his Ph.D. at the University of California Irvine, USA as well as his M.S. and B.S. at Hanyang University, Seoul, Korea. His research is focused on developing micro- and nano-fabricated platforms to control cellular behavior.

Andrew deMello

Andrew J. deMello has been on the faculty of the Chemistry Department at Imperial College London since 1997 and is currently Professor of Chemical Nanosciences. He obtained his Ph.D. in Molecular Photophysics at Imperial College London in 1995. His current research programmes are centred on the areas of miniaturized chemical analysis systems and ultra-high-sensitivity detection. He has given over 120 invited lectures in the USA, Europe and Asia, has published over 120 research papers in refereed journals, and co-authored a book.

Jaebum Choo

Jaebum Choo is a Professor in the Department of Bionano Engineering at Hanyang University. He is also a Director of Integrated Human Sensing System (ERC) Research Center. He received his Ph.D. from Texas A&M University in 1994. After one-year post-doctoiral experience, he joined as a faculty member of Hanyang Univesity. He has published more than 110 papers in peer-reviewed journals and has given over 80 invited lectures. His research interest is mainly centered on the development of highly sensitive optical detection technologies using metal nanoparticles.

0.5–1.0 ppb level. Similar alligator teeth-shaped microchannels have also been utilized for the rapid and highly sensitive detection of duplex dye-labelled DNA sequences[23] and the quantitative analysis of methyl parathion.[31] A zigzag-shaped microchannel containing silver nanocolloids has also been adopted for the trace analysis of malachite green in water[25] and single nucleotide polymorphism (SNP) detection using molecular beacon probes.[24]

A recognized problem associated with operation within continuous flow regimes is the deposition of nanoparticle aggregates on channel walls. This is ameliorated by the high surface-to-volume ratio environments typical of microfluidic systems and can affect both the sensitivity and reproducibility of quantitative analysis. To address this issue, Popp and co-workers have employed a two-phase liquid/liquid segmented flow in SERS measurements.[32,33] This system exploits flow instabilities between immiscible fluids to generate nanolitre-volume droplets dispersed within an immiscible carrier. A typical droplet-based microfluidic device (by Choo and co-workers[27]) is shown in Fig. 1(b). Importantly, the movement of the droplets within a microchannel causes an internal flow field and generates a high degree of mixing inside each and every droplet. Moreover, chaotic advection can be implemented through the use of a winding channel to achieve mixing on sub-milisecond timescales without analyte dispersion.[34,35] Indeed, Choo and co-workers[27] recently demonstrated a droplet-based microfluidic system combined with SERS detection for the trace analysis of mercury(II) ions in water. To allow both reproducible and quantitative analysis, aqueous samples were encapsulated and isolated by a continuous oil phase before being manipulated through a winding microchannel for rapid mixing of droplet contents. Specifically, mercury(II) ion detection was performed by using the strong affinity between gold nanoparticles and mercury(II) ions, which caused a change in the SERS signal of the reporter molecule Rhodamine B.

As stated, both the reliability and stability of SERS-active sites (or 'hot spots') are of significant importance in quantitative analysis since the SERS signal strongly depends on the aggregation of Ag or Au colloids and adsorbed target molecules. Fig. 2(a) shows an example of a novel platform that provides for uniform hot spot formation. Here Kameoka and co-workers[36,37] developed an optofluidic particle trapping device that contains a pinched and step microfluidic-nanochannel junction. Such a structure can reproducibly trap metallic nanoparticles and target molecules through capillary forces within the channel and provides for electromagnetic enhancement factors of *ca.* 10^8. This platform has been used for the trace detection of the conformational transition of β-amyloid peptide (Aβ), a biomarker for Alzheimer's disease (and other proteins including insulin and bovine serum albumin) from a predominantly α-helical structure to β-sheet.[38] More recently, Choi *et al.*[39] have demonstrated an optofluidic SERS compact disc platform that is capable of high-

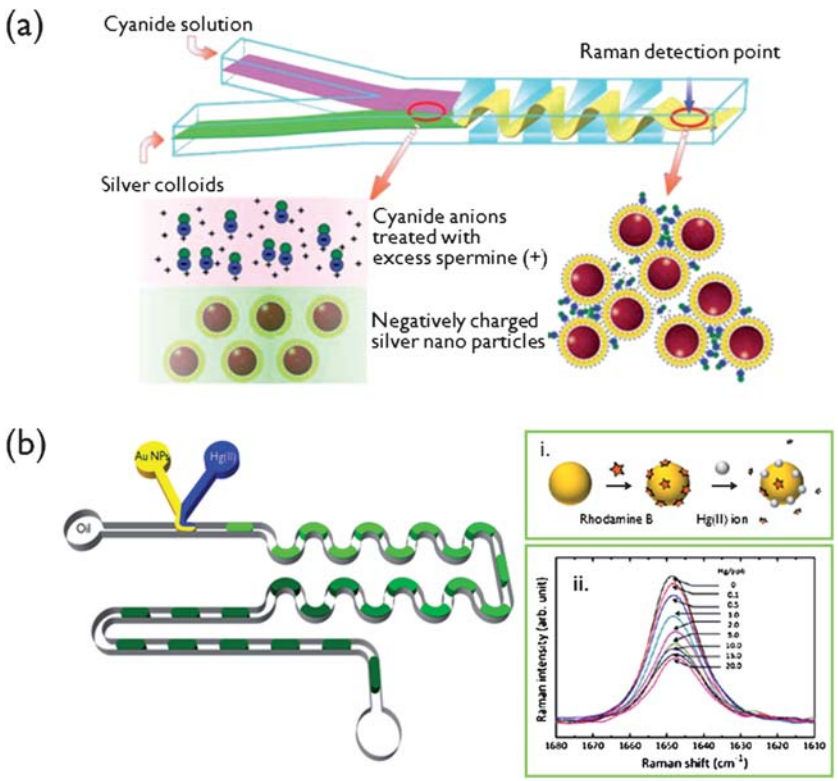


Fig. 1 (a) Schematic illustration of alligator teeth-shaped microfluidic channel. The confluent streams of silver colloids and trace analytes are effectively mixed in the channel through the triangular structures, which are located on the upper and lower surfaces of the channel in a zigzag. (Reproduced with permission from ref. 30.) (b) Schematic representation of the channel pattern used to create nanolitre-volume droplets; (i) replacement of Rhodamine B dye molecules through the reduction of mercury(II) ions on the surface of gold nanoparticles; (ii) variation of Raman intensity as a function of mercury(II) ion concentration. (Reproduced with permission from ref. 27. Copyright 2009, Springer.)

throughput biological analysis with additional SERS signal amplification (Fig. 2(b)). Using a rotating disc, centrifugal pumping provides a wide range of flow rates depending on disc geometry, rotational rate and fluid properties and different fluidic functions including valving, decanting, mixing, metering, sample splitting and separation can be implemented. Interestingly, an additional amplification of SERS signals can be performed by pre-concentrating molecules of interest *via* simple repetition of 'filling–drying' cycles.

To precisely control the aggregation of plasmonic particles, a number of interesting approaches involving external stimuli have been reported. For example, optical forces exerted by a strongly focused beam of light have been used to trap particles and control colloidal aggregation where an axial gradient force dominates.[40] Such an optical setup is illustrated in Fig. 3(a). Here laser radiation for Raman excitation and optical tweezing is coupled into a microscope and focused into the sample. Such a combination could prove hugely enabling for multiplexed assays in SERS detection. On the other hand, electrokinetic effects have been used to enhance solution-phase mixing between target molecules and Raman enhancers and to physically concentrate product into microwells embedded in microfluidic channels.[41,42] By controlling the electric potential between the upper and lower electrodes, species could also be either locally attracted into the microwells or repulsed from them. The device consists of a lower electrode layer on glass, a polyimide dielectric layer for electrical isolation and microfluidic geometries and an upper electrode layer on PDMS and is shown in Fig. 3(b). This platform has been tested for the quantitative detection of nucleic acid sequences associated with Dengue virus serotype 2 and single nucleotide polymorphisms (SNPs) in the human K-ras oncogene.

In contrast, metallic nanostructures have been directly incorporated into microfluidic devices to alleviate some of the issues associated with nanoparticle-based SERS detection. Liu and Lee have fabricated nanowell-based silver SERS substrates in microfluidic devices by soft lithography, thus allowing mass production of identical SERS-active sites.[43] They have also demonstrated that structured Ag/PDMS surfaces provide enhancements of more than 10^7 times when compared to smooth Ag/PDMS surfaces (Fig. 4(a)). More recently, Kho *et al.*[44] demonstrated the efficacy of a periodic SERS-active nanostructure in terms of SERS performance. The authors suggest that microfluidic systems containing immobilized nanostructures should be more stable in a biofluid analysis than colloid-based systems due to variations in the ionic strength of the biofluid. Additionally, a periodic array of sub-wavelength apertures (nanoholes) has been considered as a promising substrate for SERS analyses (Fig. 4(b)) because the strong electromagnetic field in the vicinity of the holes enhances inherently weak Raman signals and the nanostructures restrict the analyte to a defined region of space.[45–48] However, the enhancement factor of such circular nanohole arrays was found to be not as high as that of normal SERS substrates. Antenna structures, such as concentric rings and Bragg resonators, surrounding the arrays can act to confine surface plasmon energy within the area of the nanoholes and thereby improve their enhancement factors.[49–52] Arrays of nanoholes are compatible with the lab-on-a-chip concept and offer the possibility of high-throughput analysis.[48]

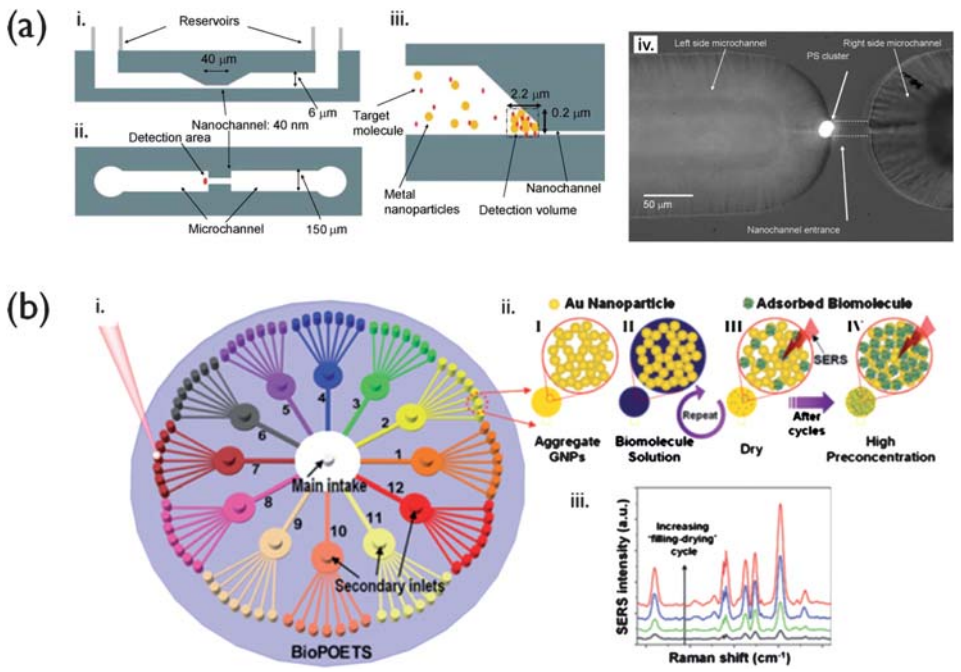


Fig. 2 (a) An optofluidic particle trapping device: (i) lateral view, (ii) top view, (iii) expanded lateral view of nanofluidic channel with aggregated nanoparticles, and (iv) a nanofluidic device consisting of a nanochannel between two microchannels. (Reproduced with permission from ref. 36.) (b) Optofluidic SERS-CD platform and pre-concentration mechanism: (i) schematic illustration of SERS-CD platform, (ii) pre-concentration consisting of four steps, and (iii) SERS intensity enhancement due to the pre-concentration of the target molecules. (Reproduced with permission from ref. 39.)

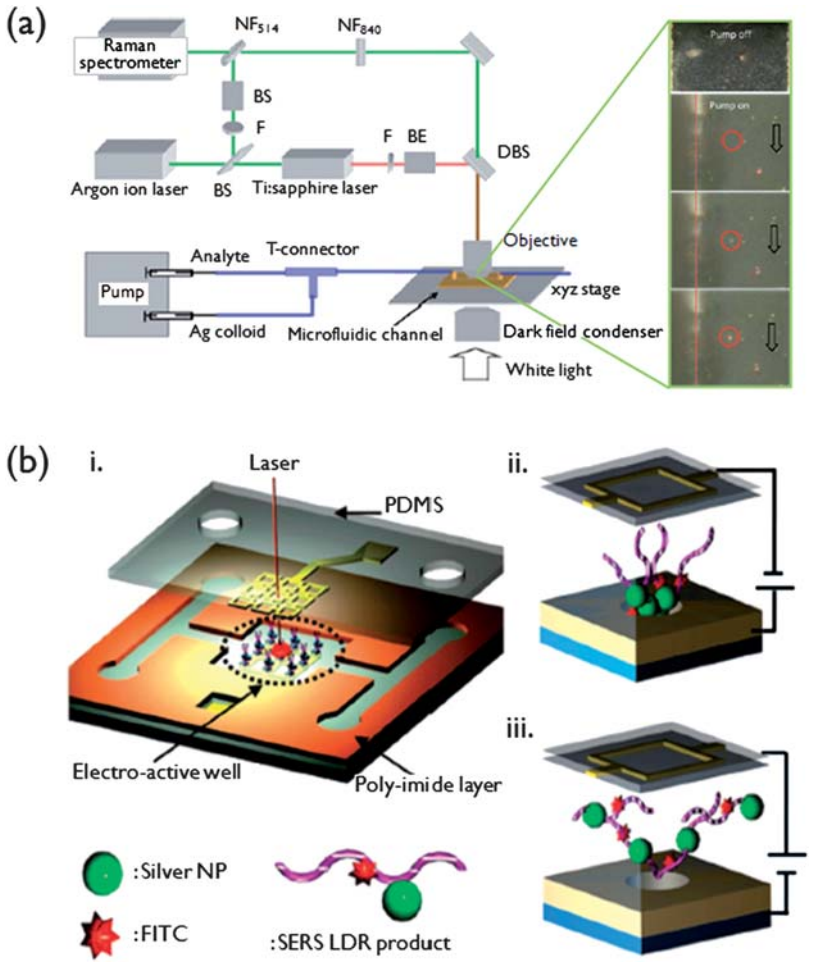


Fig. 3 (a) Schematic illustration of the optical detection setup. Aggregation was achieved through optical forces generated by laser tweezers. (Reproduced with permission from ref. 40.) (b) Schematic illustration of electroactive microwell device (i), application of the polarity shown in (ii) attracts particles and (iii) rejects them. (Reproduced with permission from ref. 42. Copyright 2009, Americal Chemical Society.)

System integration and miniaturization

Real-time analytical technologies are in high demand in a range of fields such as environmental trace analysis, water quality monitoring, homeland security, forensic investigations and medical diagnostics. Specifically, the rapid and sensitive identification of hazardous materials in-the-field is of significant importance. In this regard, a portable Raman system represents an excellent candidate for their real-time analysis. Nowadays, portable Raman spectrometers are commercially available (*e.g.* Fig. 5(a)). Although miniaturization of Raman spectrometers results in a lowering of spectral resolution, this can be offset by SERS enhancements. However, studies have focused on integrating SERS substrates with portable Raman spectrometers. Recently, Yan and Vo-Dinh have constructed a portable Raman sensor coupled with silver nanoparticle-coated substrates.[53] The entire instrument has a footprint of $22 \times 9 \times 8$ inches and weighs approximately 19 kg. A series of nickel metal hydride batteries power all components including a diode laser, a solid-state acousto-optic tunable filter, a photodiode and an embedded computer in the system for up to 3 h (Fig. 5(a)). This device has been used to perform trace analysis of various chemical and biological warfare agents including methyl parathion (a nerve agent stimulant) and dipicolinic acid (a biomarker for *Bacillus* endospores). Moreover, Quang *et al.*[26] have demonstrated a fully integrated portable Raman system combined with a micropillar array fluidic device (Fig. 5(b)). The micropillar array allows for highly efficient mixing between metal nanoparticles and hazardous trace materials, such as dipicolinic acid (DPA) and malachite green (MG). Using this system generated a limit of detection of 200 ppb for DPA and 500 ppb for MG. In addition, Wilson *et al.*[54] have reported a simple optical fiber-based SERS microflow cell to investigate distributions of scytonemin pigment within cyanobacteria (Fig. 5(c)). They demonstrate nanomolar sensitivity for scytonemin by using a dispersed colloidal substrate in the microfluidic device.

Conclusions and future perspective

In this Minireview, we have described some of the latest applications of the SERS-based optofluidic platforms in chemical and biological analysis. Because both the reliability and stability of SERS-active sites are difficult to be achieved, quantitative application of SERS has been hindered.

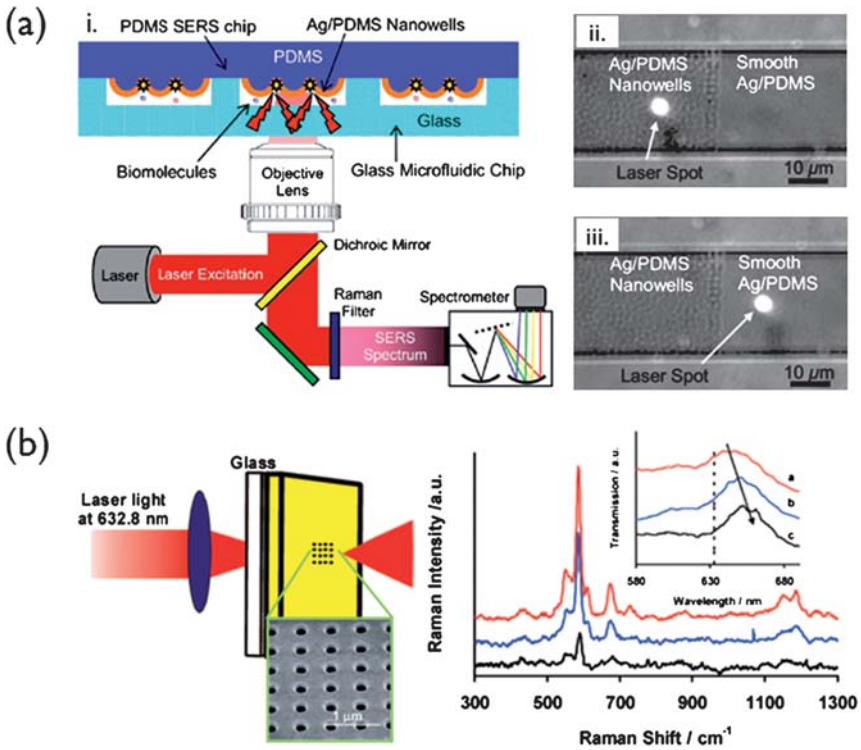


Fig. 4 (a) Schematic illustration of the microfluidic chip integrated with the SERS detection system (i), a laser spot illuminated (ii) on the surface of nanowell substrate and (iii) on the smooth surface. (Reproduced with permission from ref. 43. Copyright 2005, Americal Institute of Physics.) (b) Experimental setup for transmission Raman spectroscopy through nanohole arrays and SERS spectra of oxazine 720 from nanoholes with different periodicities for (a) 560 nm, (b) 590 nm and (c) 620 nm. (Reproduced with permission from ref. 48. Copyright 2008, Americal Chemical Society.)

Fortunately, the use of microfluidic environments allows some degree of control over mixing times, scattering geometries, localized heating and photo-dissociation and thus enables SERS to yield reproducible and quantitative outcomes. Consequently, a number of recent research papers have been published in the peer-reviewed literature within the last three years. We believe that SERS-based optofluidic platforms will undoubtedly have a substantial impact on environmental monitoring, clinical diagnostics, forensic science and global health. It should also be realized that a closer collaboration between the photonic and microfluidic communities has been critical in creating robust platforms.

However, there remains a range of issues to be tackled. First of all, microfluidic devices based on PDMS are rapidly becoming a ubiquitous platform in cost, simplified fabrication procedures and biocompatibility when compared to those based on glass and silicon. However, it should be noted that the PDMS has its own Raman signals and absorbs Raman signals from analytes because it is a Raman-active polymer.[23,55] In addition, PDMS is not compatible with many solvents, such as acids, bases and organic solvents, and shows adverse effects including swelling that can be pronounced in microscale environments.[56] There are alternatives, such as poly(methyl methacrylate) (PMMA), polycarbonate (PC) and cyclic olefin copolymer (COC), but these materials have not been intensively investigated for a SERS-based optofluidic platform. We speculate that critical parameters would be auto-fluorescence, chemical resistance, optical transparency, permeability (for living cells) and analyte/nanoparticle adsorption when choosing an appropriate material. Clearly, further research should be directed at determining it for future disposable optofluidic devices. Secondly, most of Raman spectrometers have incorporated bulky and expensive optical components. Encouragingly, however, a number of recent reports have described the construction of portable SERS-based optofluidic platforms.[26,53,54] The development of lab-on-a-chip technologies will also allow the design and fabrication of monolithically integrated devices comprising excitation light sources, waveguides, optical filters and detectors with microfluidic networks. Thirdly, in order to obtain a higher SERS enhancement factor, the selection of metal relies on the refractive index and complex permittivity of metals at the wavelength of interest. It should be noted that a frequency-domain finite element method (FEM) solver can provide guidelines for the initial design and development of nanocolloids or nanostructures for future platforms.

Acknowledgements

This work was supported by the National Research Foundation of Korea (Grant Numbers R11-2009-044-1002-0 and K20904000004-09A050000410), and the KRIBB Research Initiative Program. This work was also partially supported by the Ministry of Knowledge Economy (MKE) and Korea Industrial Technology Foundation (KOTEF) through the Human

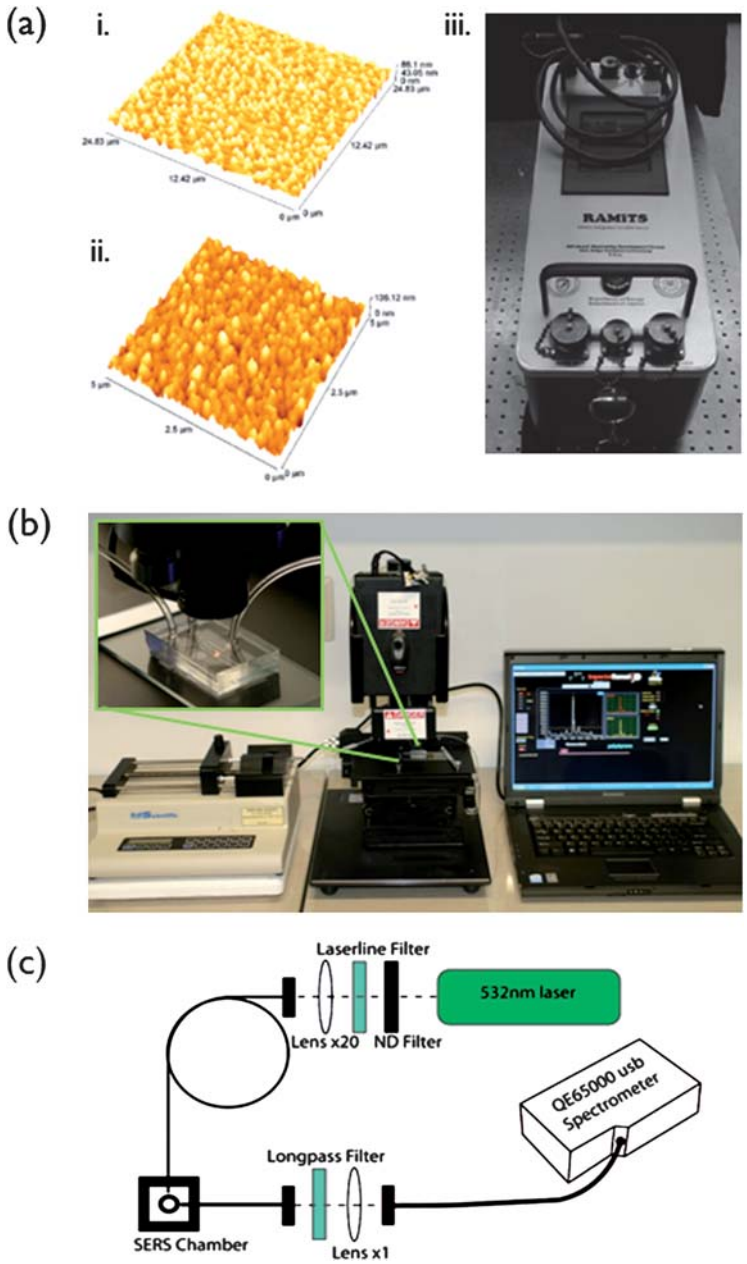


Fig. 5 (a) AFM images of silver island films prepared by (i) physical vapor deposition and (ii) chemical bath deposition techniques. (iii) a portable Raman integrated sensor system. (Reproduced with permission from ref. 53. Copyright 2007, Elsevier.) (b) A schematic of a portable Raman system integrated with a pillar array microfluidic channel. (Reproduced with permission from ref. 26.) (c) A schematic of the Raman setup combined with a capillary tube SERS chamber. (Reproduced with permission from ref. 54. Copyright 2007, Americal Chemical Society.)

Resource Training Project for Strategic Technology. J. H. and A. J. dM. acknowledge the RCUK-funded Microdroplets Basic Technology Project for financial support.

References

1 A. Manz, N. Graber and H. M. Widmer, *Sens. Actuators, B*, 1990, **1**, 244–248.
2 D. J. Beebe, G. A. Mensing and G. M. Walker, *Annu. Rev. Biomed. Eng.*, 2002, **4**, 261–286.
3 S. K. Sia and G. M. Whitesides, 2003, 24((21)), pp. 3563–3576.
4 T. M. Squires and S. R. Quakes, *Rev. Mod. Phys.*, 2005, **77**(3), 977–1026.
5 A. Khademhosseini, R. Langer, J. Borenstein and J. P. Vacanti, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**(8), 2480–2487.
6 D. N. Breslauer, P. J. Lee and L. P. Lee, *Mol. BioSyst.*, 2006, **2**(2), 97–112.
7 A. J. deMello, *Nature*, 2006, **442**, 394–402.
8 J. El-Ali, P. K. Sorger and K. F. Jensen, *Nature*, 2006, **442**, 403–411.
9 P. Watts and C. Wiles, *Chem. Commun.*, 2007, 443–467.
10 D. B. Weibel, W. R. DiLuzio and G. M. Whitesides, *Nat. Rev. Microbiol.*, 2007, **5**(3), 209–218.
11 L. X. Chen and J. Choo, *Electrophoresis*, 2008, **29**, 1815–1828.
12 J. Hong, *Biochip Journal*, 2008, **2**(1), 12–26.
13 H. F. Li and J. M. Lin, *Anal. Bioanal. Chem.*, 2009, **393**, 555–567.

14 J. Hong, J. B. Edel and A. J. deMello, *Drug Discovery Today*, 2009, **14**, 134–146.
15 P. S. Dittrich, K. Tachikawa and A. Manz, *Anal. Chem.*, 2006, **78**, 3887–3907.
16 P. A. Auroux, D. Lossifidis, D. R. Ryes and A. Manz, *Anal. Chem.*, 2002, **74**, 2637–2652.
17 P. J. Viskari and J. P. Landers, *Electrophoresis*, 2006, **27**, 1797–1819.
18 H. Craighead, *Nature*, 2006, **442**, 387–393.
19 D. Psaltis, S. Quake and C. Yang, *Nature*, 2006, **442**, 381–386.
20 A. Campion and P. Kambhampati, *Chem. Soc. Rev.*, 1998, **27**, 241–250.
21 K. Kneipp, H. Kneipp, I. Itzkan, P. R. Dasari and M. S. Feld, *Chem. Rev.*, 1999, **99**, 2957–2975.
22 Y. S. Huh, A. J. Chung and D. Erickson, *Microfluid. Nanofluid.*, 2009, **6**, 285–297.
23 T. Park, S. Lee, G. H. Seong, J. Choo, E. K. Lee, Y. S. Kim, W. H. Ji, S. Y. Hwang, D. G. Gweon and S. Lee, *Lab Chip*, 2005, **5**, 437–442.
24 J. Jung, L. Chen, S. Lee, S. Kim, G. H. Seong, J. Choo, E. K. Lee, C. H. Oh and S. Lee, *Anal. Bioanal. Chem.*, 2007, **387**, 2609–2615.
25 S. Lee, J. Choi, L. Chen, B. Park, J. B. Kyong, G. H. Seong, J. Choo, Y. Lee, K. H. Shin, E. K. Lee, S. W. Joo and K. H. Lee, *Anal. Chim. Acta*, 2007, **590**, 139–144.
26 L. X. Quang, C. Lim, G. H. Seong, J. Choo, K. J. Do and S. K. Yoo, *Lab Chip*, 2008, **8**, 2214–2219.
27 G. Wang, C. Lim, L. Chen, H. Chon, J. Choo, J. Hong and A. J. deMello, *Anal. Bioanal. Chem.*, 2009, **394**, 1827–1832.
28 M. Kakuta, F. G. Bessoth and A. Manz, *Chem. Rec.*, 2001, **1**, 395–405.
29 N.-T. Nguyen and Z. Wu, *J. Micromech. Microeng.*, 2005, **15**, R1–R16.
30 K. Yea, S. Lee, J. B. Kyong, J. Choo, E. K. Lee, S.-W. Joo and S. Lee, *Analyst*, 2005, **130**, 1009–1011.
31 D. Lee, S. Lee, G. H. Seong, J. Choo, E. K. Lee, D.-G. Gweon and S. Lee, *Appl. Spectrosc.*, 2006, **60**, 373–377.
32 K. R. Strehle, D. Cialla, P. Roesch, T. Henkel, M. Koehler and J. Popp, *Anal. Chem.*, 2007, **79**, 1542–1547.
33 K. R. Ackermann, T. Henkel and J. Popp, *ChemPhysChem*, 2007, **8**, 2665–2670.
34 H. Song, D. L. Chen and R. F. Ismagilov, *Angew. Chem., Int. Ed.*, 2006, **45**, 7336–7356.
35 A. Huebner, S. Sharma, M. Srisa-Art, F. Hollfelder, J. B. Edel and A. J. deMello, *Lab Chip*, 2008, **8**, 1244–1254.
36 M. Wang, N. Jing, I.-H. Chou, G. L. Cote and J. Kameoka, *Lab Chip*, 2007, **7**, 630–632.
37 M. Wang, M. Benford, N. Jing, G. Cote and J. Kameoka, *Microfluid. Nanofluid.*, 2009, **6**, 411–417.
38 I.-H. Chou, M. Benford, H. T. Beier, G. L. Cote, M. Wang, N. Jing, J. Kameoka and T. A. Good, *Nano Lett.*, 2008, **8**, 1729–1735.
39 M. D. Choi, T. Kang, H. Cho, Y. Choi and L. P. Lee, *Lab Chip*, 2009, **9**, 239–243.
40 L. Tong, M. Righini, M. U. Gonzalez, R. Quidant and M. Kall, *Lab Chip*, 2009, **9**, 193–195.
41 Y. S. Huh, A. J. Chung, B. Cordovez and D. Erickson, *Lab Chip*, 2009, **9**, 433–439.
42 Y. S. Huh, A. J. Lowe, A. D. Strickland, C. A. Batt and D. Erickson, *J. Am. Chem. Soc.*, 2009, **131**, 2208–2213.
43 G. L. Liu and L. P. Lee, *Appl. Phys. Lett.*, 2005, **87**, 074101.
44 K. W. Kho, K. Z. M. Qing, Z. X. Shen, I. B. Ahmad, S. S. C. Lim, S. Mhaisalkar, T. J. White, F. Watt, K. C. Soo and M. Olivo, *J. Biomed. Opt.*, 2008, **13**, 054026.
45 A. G. Brolo, E. A. Arctander, R. Gordon, B. Leathem and K. L. Kavanagh, *Nano Lett.*, 2004, **4**, 2015–2018.
46 J. R. Anema, A. G. Brolo, P. Marthandam and R. Gordon, *J. Phys. Chem. C*, 2008, **112**, 17051–17055.
47 Q. Min, M. J. L. Santos, E. M. Girotto, A. G. Brolo and R. Gordon, *J. Phys. Chem. C*, 2008, **112**, 15098–15101.
48 R. Gordon, D. Sinton, K. L. Kavanagh and A. G. Brolo, *Acc. Chem. Res.*, 2008, **41**, 1049–1057.
49 A. Lesuffleur, L. K. S. Kumar, A. G. Brolo, K. L. Kavanagh and R. Gordon, *J. Phys. Chem. C*, 2007, **111**, 2347–2350.
50 N. Sedoglavich, J. C. Sharpe, R. Kunnemeyer and S. Rubanov, *Opt. Express*, 2008, **16**, 5832–5837.
51 N. C. Lindquist, A. Lesuffleur and S.-H. Oh, *Appl. Phys. Lett.*, 2007, **91**, 253105.
52 N. C. Lindquist, A. Lesuffleur, H. Im and S.-H. Oh, *Lab Chip*, 2009, **9**, 382–387.
53 F. Yan and T. Vo-Dinh, *Sens. Actuators, B*, 2007, **121**, 61–66.
54 R. Wilson, P. Monagham, S. A. Bowden, J. Parnell and J. M. Cooper, *Anal. Chem.*, 2007, **79**, 7036–7041.
55 T. Park, M. Lee, J. Choo, Y. S. Kim, E. K. Lee, D. J. Kim and S.-H. Lee, *Appl. Spectrosc.*, 2004, **58**, 1172–1179.
56 J. N. Lee, C. Park and G. M. Whitesides, *Anal. Chem.*, 2003, **75**, 6544–6554.