Molecular recognition of chemical and biological analytes has traditionally been carried out using immobilized receptors on a variety of sensor platforms. Adsorption of target analytes on the immobilized receptors results in the variation of certain selected physical properties of the transducer to generate a measurable signal. One excellent example of an ideal microsensor is a microfabricated cantilever beam that resembles the plank of a miniature diving board. Microcantilever sensors have attracted much attention because of their unique advantages such as extremely high sensitivity, miniature size, low-power consumption, label-free detection, and array-based sensing of multiple analytes in real-time. The cantilever platform can be used for simultaneous monitoring of both resonance frequency (dynamic mode) and cantilever deflection (static mode), which allows the detection of multiple properties of the analyte molecules adsorbed on a cantilever surface. Molecular adsorption on a cantilever surface results in a shift in its resonance frequency due to mass loading. When the adsorbed molecules are confined to a single side of the cantilever, an additional signal of cantilever deflection is also generated. The cantilever deflection is attributed to adsorption-induced forces on the cantilever. Both the resonance frequency shift and the cantilever deflection vary in proportion to the type of molecular interactions and the number of adsorbed molecules. Despite the fact that microcantilever sensors have been demonstrated to detect molecular adsorption with very high sensitivity they do not have any intrinsic chemical selectivity. Just as in the case of other physical sensors, such as QCM, SAW, SPR, etc., selectivity of a cantilever sensor is always based on adsorbate interaction with surface immobilized receptors. This approach has an advantage that the immobilized receptor layer often acts like a pre-concentrator that increases the surface concentration of the adsorbates by orders of magnitude higher than their concentrations in fluid phase.

Much of the research activity aimed at enhancing the selectivity of micro/nano sensors is devoted to the development of receptors and chemical interfaces that can provide higher selectivity. However, receptors for a targeted analyte, that are immune to interfering chemical compounds, are extremely rare. Also, immobilization of receptors on a sensor surface requires the use of molecular tethers that allow the formation of a uniform monolayer. Self-assembled monolayers (SAM) are routinely used as selective interfaces. Surface functionalization of microcantilever surface with SAMs routinely result in the formation of discontinuous monolayers which, in turn, cause large variations in sensor reliability and reproducibility. The use of receptors with limited specificity results in poor or partial selectivity in chemical and biological detection. Therefore, poor selectivity and reproducibility remain as the main challenges in translating lab-based miniature sensors into marketable chemical and biological sensors. For chemical sensors, reversible chemical interactions such as hydrogen bonding are far too general for obtaining high selectivity. Poor selectivity in detection stems from the lack of uniqueness in the molecular interaction mechanisms, and overcoming this challenge through chemical approaches can be a labor-intensive endeavor. Therefore, lack of selectivity still remains as a major challenge in small molecule detection, especially when molecules are present in vapor phase.

Biological receptors, such as antibodies, offer higher selectivity for the detection of biological analytes. Ndieyira et al. successfully demonstrated bio receptors to induce surface stress on a microcantilever, in order to measure therapeutic efficacy and antimicrobial resistance. Most often the process of immobilization receptors can result in the formation of sub-monolayers, which in turn causes large variations in the sensor response. This problem of sub-monolayer formation is much severe in biological receptors compared to receptors for small molecules. Unlike large area sensors such as QCM and SPR, a cantilever sensor has an extremely small surface area, generally in the range of $10^{-4}$ cm$^2$. Therefore, the probability of formation of sub-monolayer defects on the surface of a cantilever is much higher than that for conventional sensors with larger areas. At present, cantilever-to-cantilever response variation for biological sensing is too large for their application in any commercial applications. It is also worth mentioning that immobilized biological receptors on a cantilever surface have limited shelf life if not stored properly.

The problems faced with immobilization of receptor layers as well as their poor selectivity could be overcome by coupling the microcantilever sensors with well-known infrared (IR) spectroscopy. Using such a combination, Barnes et al. first reported the use of bi-material microcantilever as an IR radiation detector with femtosecond sensitivity. This extremely high thermal sensitivity of a bi-material cantilever can be exploited for obtaining spectroscopic information of adsorbed molecules calorimetrically. Resonant excitation of vibrational energy levels of molecules physisorbed on the cantilever using specific IR wavelength can generate extremely small amounts of heat energy due to non-radiative decay. The change in the temperature of
the cantilever is reflected as cantilever deflection and it offers a new way of conducting IR spectroscopy of adsorbed molecules. This approach combines the selectivity of the IR spectroscopy with a very high sensitivity of the cantilever deflection.

In the cantilever-based photothermal spectroscopy, IR absorption-induced cantilever deflection, as a function of illumination wavelength shows a linear relationship to the concentrations of the adsorbed analyte molecules. Therefore a cantilever based IR spectroscopy is an excellent method for molecular recognition of physisorbed molecules on the cantilever. Recently, Van Nest et al. and Kim et al. reported the use of photothermal spectroscopy for detecting surface adsorbed explosives such as RDX, PETN and TNT with exceptional selectivity. Unlike the near IR, the mid-IR region is known as the molecular fingerprint regime, as it is free from interfering overtones. Monitoring the locations of multiple peaks as a function of IR wavelength used for excitation allows unique identification of the adsorbed chemicals. The demonstrated sensitivity of the technique is in the range of pico to femtograms. Combining a microcantilever with very high thermal sensitivity with a tunable infrared source provides a basic platform for performing spectroscopy of picogram amounts of samples on the cantilever.

Though the photothermal spectroscopy of adsorbed molecules is an excellent technique for chemical sensing in vapor phase, it can only be used for biomolecules dried on a cantilever. In general, IR spectroscopy is not suitable for analytes dissolved in water because of the very high extinction coefficient of IR in water. Since plain cantilevers cannot accommodate liquid samples in a reproducible manner, the use of cantilever-based photothermal spectroscopy for liquid analytes remained unexplored until the advent of microchannel cantilevers. Although a microcantilever has very high sensitivity for detection of adsorbed molecules in air or vacuum conditions, severe damping limits its mass sensitivity in liquid environments. To overcome the challenge of poor mass sensitivity in liquid environments, Manalis group introduced the technique of suspended microchannel resonator (SMR), where the liquid sample is confined in a microchannel. The SMR can be excited into resonance while placed in air or vacuum. Since the liquid is inside the cantilever, it eliminates the damping issues experienced when it is resonated in a liquid medium. Sensitive monitoring of the resonance frequency and the quality factor of a microfluidic cantilever has allowed simultaneous characterization of various physical parameters, such as density and viscosity of the confined sample. These resonators were mostly used for demonstrating mass sensing based on resonance response. Measuring the Q-factor of resonance allows detection of viscosity of the confined liquid. Many different variations of the resonating microfluidic channels now exist. Barton et al. reported a nanofluidic bridge which was tested to measure density of various solutions. Recently, Kim et al. reported fabrication of hollow microtube resonators for density measurements. Although the microchannel mechanical resonance techniques have made major advances in chemical and biological sensing, selectivity still remain as a major challenge.

In the recent past, we have demonstrated bi-material microfluidic cantilever (BMC) as an analytical tool to perform characterization of liquid analytes with high sensitivity and selectivity. Unlike the aforementioned SMR, the BMC has an ability to exploit the ability of materials to be recognized through optical spectroscopy. Because of challenges in the technology, this area is still in its infancy but has the potential widespread applications in industries such pharmaceuticals, diagnostics and point-of-care devices.

Theory

In order to incorporate selectivity in the detection of analytes in small volumes of liquid, the BMC is considered an ideal tool. During the process of photothermal spectroscopy using a BMC, resonant optical excitation of confined liquid analyze results in the generation of a small amount of localized heat. This is due to non-radiative relaxation process. Detecting spectroscopic signals mechanically as deflection of a BMC offers an elegant method for characterizing pico liters liquid analytes with high selectivity and sensitivity. Simultaneous measurement of resonance frequency shifts can provide real time information on the mass of the confined liquid sample. Since the volume of the channel is known, the density of the fluid sample can be directly determined. The sensitivity of this technique depends on the deflection sensitivity of the cantilever, which in turn is dependent on the geometry and material properties of the cantilever. Analytically, the temperature dependent deflection of a cantilever can be expressed as:

\[ \frac{d^2 z}{dx^2} = 6 \left( \alpha_1 - \alpha_2 \right) \left( \frac{t_1 + t_2}{K} \right) \left[ T(x) - T_0 \right] \]  

where \( z \) is the vertical deflection, as a function of position \( x \) along the length of the cantilever, \( \alpha_1, \alpha_2 \) and \( t_1 \) and \( t_2 \) are the coefficients of thermal expansion and the thickness of the bi-material constituents, respectively. \( T_0 \) is the temperature of the cantilever at zero deflection while \( T(x) \) is the temperature profile of the cantilever along its length. The parameter \( K \) is defined as:

\[ K = 4 + 6 \left( \frac{t_1}{t_2} \right) + 4 \left( \frac{t_1}{t_2} \right)^2 + \left( \frac{E_1}{E_2} \right) \left( \frac{t_1}{t_2} \right)^3 + \left( \frac{E_2}{E_1} \right) \left( \frac{t_2}{t_1} \right) \]  

where \( E \) is Young’s modulus, subscripts 1 and 2 refer to constituents of the bi-material cantilever.

For the analytes in liquid states, the resonance frequency of the BMC is highly sensitive to their density. A general resonance behavior of a BMC can be described by:

\[ 2\pi f = w_r = \sqrt{\frac{k}{m}} \]  

where \( k \) is the spring constant and \( m \) is the mass of the cantilever. Once the liquid analyte is loaded in the BMC, the resonance frequency decreases. The total mass is given as:

\[ m = m_{BMC} + m_L = V_{BMC-BMC} + V_L \rho_L \]  

where \( m_{BMC} \) and \( m_L \) are the mass of BMC and the liquid analyte, respectively. Superscripts, \( V \) and \( \rho \) represent volume and density, respectively. Considering that \( V_{BMC-BMC} \) and \( V_L \) remain constant during the measurement, the density can be estimated from:

\[ \rho_L = \frac{A}{\sqrt{B + \rho_f}} \]  

where the \( A \) and \( B \) are the calibration constants and determined from measurement of two well-known liquids.

Since the thickness of the confined liquid is very small (~3μm), the IR extinction in the liquid does not pose a serious problem. Also as the molecular vibrations are linearly independent, mixture of molecules do not pose a problem with selectivity. Therefore, analyzing the centimeter nanomechanical spectrum in a wider spectral range could identify mixtures and complex molecules confined inside the microfluidic channel.

Experimental Techniques

In order to demonstrate the selectivity in the detection of analytes in small volumes of liquid, we have fabricated and demonstrated a BMC for various applications. The cantilever was fabricated on a 500 μm Si wafer with diameter of 100 mm. First, unreleased cantilever beams with dimensions of 44 μm width, 500 μm length and 500 nm thickness were fabricated using a 500 μm thick silicon wafer. A U-shaped silicon nitride microfluidic channel with dimensions of 16 μm width, 1050 μm length and 3 μm height was fabricated on the top of a plain silicon cantilever, as shown in Fig. 1. The starting material in the fabrication was 500 nm thick layer of silicon nitride, deposited by chemical vapor deposition technique. This layer constituted the sacrificial layer. Next, a 1 μm to 4 μm thick layer of poly silicon was deposited, which acted as a sacrificial layer. By using UV lithography and reactive ion etching, the sacrificial layer was patterned into a U-shaped structure, followed by deposition of a 500 nm thick
layer of silicon nitride that forms the outer walls of the hollow channel. As a last step, the sacrificial layer was removed by etching using potassium hydroxide. This processing generally takes many hours. The silicon substrate used for the fabrication of the main cantilever beam also provided substrate for fabrication of microfluidic inlets and outlets for delivering samples into the microchannel. Later, the main cantilever structure was converted into a bi-material beam by depositing a 500 nm thick layer of aluminum on its bottom side, using E-beam evaporation.

As the BMC simultaneously provides two orthogonal signals (change in resonance frequency and static deflection), it is important to design the cantilever that can provide optimized resonance frequency as well as lower spring constant for detection based spectroscopy measurements. For photothermal applications, the desired spring constant is around 0.3 N/m. For simultaneous mass measurements, the optimum resonance frequency is in the range of 20 kHz to 40 kHz.

For photothermal mid-IR spectroscopy, the BMC (with an analyte in its microfluidic channel) is irradiated from an IR light source. The critical requirements for a light source include: tunable wavelength, relatively high optical power, and a focused beam spot. The selection of the optical spectral window depends upon the optical absorption characteristics of the targeted analyte. For most of the organic compounds, the IR region is ideally suited for molecular recognition, as many organic compounds have fingerprint signatures in the IR wavelength window. Therefore, in order to meet the critical requirements for photothermal spectroscopy, we used quantum cascade lasers (QCLs) as the light sources. The QCLs are highly tunable with optical power in the range of hundreds of mW. These sources have many advantages such as pulsed operation (up to 200 kHz), high optical power (up to 500 mW peak power), room temperature operation, broad tunability, and high spectral resolution (down to 0.1 nm). In order to perform photothermal spectroscopy of various compounds, we have used multiple QCL lasers (MIRCat (bandwidth: 1587 cm\(^{-1}\) to 800 cm\(^{-1}\)), UT-7 (bandwidth: 1540 cm\(^{-1}\) to 1345 cm\(^{-1}\)), and UT-8 (bandwidth: 1408 cm\(^{-1}\) to 1145 cm\(^{-1}\))) of these QCLs were acquired from Day Light Solutions (San Diego, CA, USA). The resonance frequency and the deflection of the cantilevers were monitored by using an optical lever technique, where a red diode laser (λ = 635 nm, spot size: ~50 μm) reflected off the free end of the cantilever onto a position sensitive detector (PSD) as shown in Fig. 1c. The UT-8 QCL is pulsed at 200 kHz while the UT-7 and MIRCat are pulsed at 100 kHz. The pulse frequency is further modulated at an optimized burst frequency of 10 Hz to 80 Hz using a DS345 function generator (Stanford Research Systems). The cantilever was, therefore, exposed to an IR pulse every 6.25 milliseconds. This time period was enough to provide thermal relaxation of the BMC. To find the amplitude of a signal at 80 Hz, the y-axis signal of the PSD was fed into a SR850 lock-in amplifier (Stanford Research Systems). In order to continuously measure the resonance frequency of the cantilever, a SR760 spectrum analyzer (Stanford Research Systems) was used to carry out the fast Fourier transform (FFT) of the y-axis signal from the PSD. An oscilloscope was used to monitor the laser spot in order to keep it in the center of the PSD’s sensitive area. The data from the lock-in amplifier and the spectrum analyzer were stored in a computer using a data acquisition card and Labview software. The signal was then plotted with respect to the wavenumber of IR light to generate the nanomechanical IR spectrum of the analyte inside the microfluidic channel.

**Results and Discussion**

Using the BMC, we performed photothermal spectroscopy for different mixtures of ethanol-water solutions. As a result, we successfully measured their nanomechanical IR spectra by monitoring static deflection of the BMC as a function of IR wavelength, as shown in Fig. 2a. Each ethanol-water solution was injected into the inlet of the microfluidic channel using a standard pipette. The capillary forces, due to the hydrophilic nature of silicon nitride, pull the liquid into the channel. The nanomechanical IR spectrum was recorded as cantilever deflection when the BMC was irradiated with IR light from 1180 cm\(^{-1}\) to 1000 cm\(^{-1}\) using the QCL (MIRCat) in a sequential fashion. The experiments were performed for different concentrations of ethanol-water mixtures.

In order to obtain the spectrum of ethanol, a differential spectroscopy technique was needed to eliminate the background in a common mode rejection approach. First, as a background, the IR spectrum of DI water was measured using the BMC. Then the ethanol-water mixtures of different concentrations were individually loaded inside the cantilever. For each experiment, the QCL was scanned three times from 1180 cm\(^{-1}\) to 1000 cm\(^{-1}\). This helped in reducing noise by averaging the data. The ethanol-water solutions showed strong absorption peaks at IR wavelengths of 1083 cm\(^{-1}\) and 1045 cm\(^{-1}\) revealing C–O–H bending and C–O stretching, respectively (Fig. 2a). These molecular vibrations are the characteristic of the ethanol molecules. After each measurement, the BMC was flushed multiple times with
To obtain the nanomechanical spectrum of DI water was also acquired for reference for subtraction from water and ampicillin solution spectrum. This provided the spectrum of only ampicillin molecules dissolved in water. Fig. 2b shows the differential nanomechanical IR spectrum of 10% wt of ampicillin/water solution. Similar to the results observed for ethanol/water mixtures, a linear trend was also obtained for the static BMC deflection amplitude as a function of various concentrations ampicillin. In order to compare the results with an accepted conventional technique, the IR spectra of the solutions were also measured using an FTIR spectrometer operated in ATR mode. The nanomechanical spectra obtained with BMC showed excellent agreement with the FTIR data.

The BMC can also be used for characterizing pico liters of biological analytes such as metabolites. Metabolites are generally small molecules, and therefore, possess a special challenge for absorption based spectroscopic techniques. In this study, powder forms of two different metabolites, creatinine and glucose, were separately dissolved in DI water. Just like aforementioned experiments for ampicillin, differential spectroscopy was performed for all the metabolites. Since these metabolites absorb IR light at different wavelengths, the BMC with targeted samples were irradiated with different IR wavelengths. For creatinine with a concentration of 110 mM, the QCL was scanned from 1400 cm$^{-1}$ to 1150 cm$^{-1}$. Because of absorption IR light, the BMC exhibited a strong deflection at the wavenumbers of 1375 cm$^{-1}$ and 1250 cm$^{-1}$, as shown in Fig. 3a. For a comparison, the measurements were also performed with ATR-FTIR spectrometer (Fig. 3b). The BMC results match very well with those from ATR-FTIR. To characterize glucose solution with a concentration of 5.4 mM, the QCL was scanned from 1250 cm$^{-1}$ to 950 cm$^{-1}$. Within this spectral window, the BMC showed a large deflection at around 1075 cm$^{-1}$, showing IR absorption by glucose molecules as shown in Fig. 3c. Matching spectra were also obtained with FTIR spectrometer in ATR mode. These results show that BMC is capable of obtaining IR spectra of pico liters of confined liquids by using photothermal spectroscopy. In conventional FTIR, photons are detected and analyzed using Beer-Lambert’s principle while BMC based photothermal spectroscopy is based on detecting the heat generated during the non-radiative relaxation process. This approach is complementary to that of conventional IR spectroscopic techniques. As a result, the intensities of the peaks observed with BMC may not match with those obtained with FTIR spectroscopy. However, the wavelength at which the absorption occurs matches very well for both techniques. The resolution in the obtained spectra from the BMC depends on the resolution of the incident light. The intensity of a peak obtained with BMC depends on the intensity of the light and the concentration of the liquid analyte. It is observed that the signal-to-noise ratio (SNR) for photothermal technique increases with increasing power of the light source. For the techniques that use Beer-Lambert principle, SNR decreases with increasing intensity of the light source.

Because the concentration of the analyte determines the signal strength, pre-concentrating techniques are routinely used in many sensing applications. Such pre-concentrating techniques can be incorporated into BMC for enhancing the sensitivity of the sensor for high value applications in life sciences. In order to convert the BMC into a pre-concentrator, it is possible to functionalize the interior of the BMC microchannel. To demonstrate the ability of the BMC to perform as a pre-concentrator, anti-Listeria monocytogenes (L. monocytogenes) monoclonal antibody (mAb) was immobilized on the inner surface of the BMC channel. Different strains of the bacteria were then injected into the sensor at various concentrations. Adsorption of bacteria on the functionalized internal walls of the BMC changes the resonance frequency of the cantilever. Nanomechanical calorimetric deflections also show an enhancement due to sample enrichment.

In general, a BMC with a microfluidic channel (fabricated on one of its sides) is a mechanically asymmetric structure. Therefore adsorption of bacteria on the inside of the microfluidic channel can also result in a very small cantilever deflection. The results showed that a bacteria attachment to the receptors inside the cantilever could generate cantilever deflection due to adsorption stress (Fig. 4a). In order to obtain a

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**Figure 2.** Nanomechanical IR spectrum of different concentrations of (a) ethanol-water mixtures, (b) ampicillin sodium salt, measured by using bimaterial microchannel cantilever (BMC). Different colors show different analyte concentrations. For both types of the samples, the amplitude of absorption peaks relate linearly to the concentration of the solutions. The data has been plotted after smoothing using a Savitzky–Goaly filter. (Adapted from our previous work.28)
nanomechanical photothermal spectrum of the bacteria, the BMC was illuminated with IR light from the QCL (spanned from 1500 cm$^{-1}$ to 1400 cm$^{-1}$). This generated nanomechanical infrared spectrum of the bacteria as shown in Fig. 4c. To demonstrate the selectivity of nanomechanical IR spectrum for identifying bacterial strains, responses of the BMC sensor for *L. monocytogenes* and other strains of Gram-positive and Gram-negative bacteria were collected. The spectra show a distinct spectrum for *L. monocytogenes* compared to the other strains.

To establish sensitivity, different concentrations of bacteria, ranging from $10^3$ to $10^6$ c.f.u. ml$^{-1}$, were also tested using BMC. The signals from BMC showed an increase of the nanomechanical deflection with the increase of bacterial concentration in the sample. The plotted data (Fig. 4c) suggests a direct relationship to the number of bacterial cells bound to the immobilized receptors inside the hollow channel and the observed intensity of the peak. This was very similar to the experimental results obtained with ethanol and ampicillin solutions in water. Here the minimum detection limit was found to be 100 cells per 100 μl (an estimate of a single cell μ1$^{-1}$) for a signal-to-noise ratio of 3.

Performing photothermal spectroscopy using a BMC does not need any chemical receptors or immobilized interfaces for molecular recognition. However, immobilizing receptors can increase the sensitivity of the sensor, and may also provide additional selectivity. In general, the cantilevers used in this technique have no immobilized surface functional groups. The technique offers very high selectivity, since the signal generation is based on the resonance excitation of various molecular bonds in the analyte. Molecular vibrations in the mid-IR range are extremely selective. In a complex mixture, the resultant signal is a linear combination of molecular vibrations from various constituents. Therefore, it is possible to analyze the signal from the target analyte using pattern recognition methods. This technique combines the extreme high thermal sensitivity of a bi-material cantilever beam with the selectivity of mid-IR molecular spectroscopy. The magnitude of the IR absorption-induced cantilever bending is proportional to the amount of analyte on the cantilever. This can be further quantified by measuring the resonance frequency of the cantilever (mass loading).

Since the heat generation due to non-radiative decay is instantaneous (with deflection time constant less than 10 ms), the photothermal spectroscopy technique is capable of real-time monitoring of the analytes. Other obvious advantages include compact size and lower cost (once inexpensive light sources are developed).

Molecular recognition of confined liquids using bimaterial microfluidic cantilevers offers some challenges. For example, higher sensitivity is still a challenge for analytes in liquids since they remain in a free state in the liquids. In the photothermal spectroscopy, using plain cantilevers for vapor phase applications, the analytes are adsorbed on the cantilever and have enhanced concentrations compared to free molecules in the vapor phase. In the BMC, the analyte molecules in the confined liquid are in a free-state and generally do not pre-concentrate on the surface. Since they remain in the liquid, heat transfer will involve transmission through the liquid medium. Therefore, the BMC without the pre-concentration effect has reduced sensitivity. Another disadvantage comes from the higher heat capacity of the confined liquid, which increases the thermal background as a function of time. Liquid samples with high heat capacity reduce the heat transfer rate to the cantilever and reduce BMC sensitivity. This can be compensated by fabricating the BMCs with lower deflection time constant so that they exhibit deflection before a major loss of heat through the anchor of the cantilever. Through such optimizations, the BMC can also be used as a sensor for thermal characterization of small amount of liquid based reagents.

Figure 3. A BMC is irradiated with two different QCLs to produce nanomechanical IR spectra of (a) 110mM of creatinine sample (c) 5.4 mM of glucose. For comparison, the FTIR spectroscopy is performed for (b) 110mM of creatinine sample (d) 5.4 mM of glucose. Photothermal spectroscopy using the BMC is based upon measurement of localized heat generation while FTIR follows Lambert-Beer Law.
Figure 4. BMC for real-time detection of *L. monocytogenes*: a) BMC demonstrates a nanomechanical deflection of the cantilever as bacteria adsorbed into the cantilever channel. When the cantilever illuminated with Infrared light, b), an infrared spectrum shows a signature of the bacterial contents inside the BMC; c), BMC nanomechanical deflection in response to various concentrations of bacteria (concentration dependent). A sensitivity of one bacterium per μL was estimated based on injection of 100 cells per 100 μL. The corresponding fit in (c) is a linear function and error bars represent the corresponding s.d.’s. (Adapted from our previous work.31)

Conclusions and Future Prospects

Molecular recognition of picoliter volumes of liquid analytes using BMC-based nanomechanical calorimetry offers unprecedented opportunities in both analytical chemistry and life sciences. By monitoring the static deflection, the resonance frequency and the quality factor of the BMC, multiple properties, such as mass density, viscosity, and chemical composition, of target samples can be determined simultaneously. Illuminating the cantilever with mid-IR light provides spectroscopic molecular identification of the confined liquid. Mid-IR spectroscopy together with mass measurements of confined liquids offers molecular recognition without using receptors. This receptor-free sensing technique eliminates the need for long and tedious process of surface functionalization for obtaining selectivity. As a result, the geometrical and functional uncertainties of immobilized selective layers that acted as the source for irreproducibility in cantilever-based chemical and biological sensors is eliminated. It is possible to increase the sensitivity of the BMC by optimizing the geometrical parameters of the bi-material cantilever (mass and spring constant) as well as increasing the power of the illuminating IR source. For example, by selecting the proper bi-material elements and by optimizing the thickness of the layers, it is possible to make a bi-material cantilever very sensitive to thermal changes. Sensitivity can be further increased by restricting the heat flow from the cantilever onto the base of the cantilever, which can be accomplished by using a smaller contact area with the supporting substrate. Many exciting applications, such as drug discovery, direct monitoring of products from micro-bioreactors, and investigation of chemical composition of microbes/cells await this novel tool. In the future, by following the same fabrication technique, more complex operations such as microfluidic separation could be incorporated for additional separation-based selectivity. Therefore, incorporation of BMC-based photothermal spectroscopy into the existing lab-on-chip systems would enable more versatile applications in the field.33

Acknowledgments

This work was supported by the Canada Excellence Research Chairs (CERC) Program. We thank Profs. Anja Boisen and S.K. Kim for their immense support during the research on the BMCs. We would like to thank Alberta Innovates Health Solutions (AIHS) Collaborative Research and Innovation Opportunities (CRIO) program for providing part of the funds for this research work.

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