Bio-insprired Optoelectronic Digital Nose for Breath Analysis

Mehmet Bayindir[1,2,3], Adem Yildirim[1,2], Mecit Yaman[1,2], Mert Vural[1,2]
[1]UNAM-National Nanotechnology Research Center, [2]Institute of Materials Science and Nanotechnology,
[3]Department of Physics, Bilkent University, 06800 Ankara, Turkey, bayindir@nano.org.tr

ABSTRACT

A novel electronic nose device is presented that can be used in disease diagnostics by exhaled breath analysis. Exhaled breath contains more than a thousand organic compounds that can be analysed to insect various diseases and metabolic activity. The novel device is an electronic nose, based on photonic bandgap fibers that can selectively guide infrared radition inside a hollow core plastic fiber. Instead of a laser line source, a broadband balackbody source is used that exploits the filtering/ guiding properties of the fibers to scan the whole mid-infrared region, making it high selectivity of volatile organic compounds possible. In addition waveguiding inside the fiber enhances the electromagnetic radiation intensity, resulting in improved infrared absorption cross-section. The fiber electronic nose can be integrated and deployed as a portable electronics device to point-of-care institutes.

Keywords: electronic nose, photonic bandgap fibers, infrared absorption spectroscopy, disease diagnostics, breath analysis.

1 INTRODUCTION

The emergence of integrated optofluidic systems has brought with it the possibility of high precision optical characterization of fluid samples within microfluidic chambers. In effect, this is really the bringing in of spectrometers, lasers and other tools of the photonics toolkit into the micro-world of integrated lab-on-a-chip systems. Not surprisingly, a good number of promising and even market ready applications followed, further catalyzing the field [1].

Here we introduce and demonstrate the capabilities of a novel integrated optoelectronic-microfluidic sensor array that can rapidly distinguish thousands of, trace level volatile organic chemicals (VOC), based on their spectroscopic fingerprints inside flexible optofluidic channels (Fig. 1) [2]. The system consists of an array of hollow core fibers that have integrated dielectric mirrors to guide infrared light. Dielectric mirrors are reflectors that can be fabricated to reflect any selected spectral region according to their nanostructure [3]. For the first time, we show that wavelength scalable hollow core fibers can be used as 'wavelength selectors' to selectively guide blackbody radiation without necessitating expensive bulk tunable laser systems. We then use this array of micro-channels to detect VOCs as they pass inside the channels. The transducing mechanism is waveguide enhanced infrared absorption using a simple blackbody radiation source and an inexpensive integrative infrared detector.

In the presence of an infrared active complex molecule in a spectrally coinciding photonic channel, the transmission signal is quenched to a degree to deduce the absorbing bond. The collective response from the sensor array, the response matrix, is used to distinguish and identify the analyte either from other analytes or from a database. The sensitivity of the prototype optoelectronic 'nose' is low 20 ppm (parts per million) and ppb (parts per billion) level sensitivity is expected to be reachable due to enhanced infrared absorption of electromagnetic radiation inside a waveguide channel. The selectivity can be increased arbitrarily to match that of commercial Fourier Transform Infrared (FTIR) Spectrometers.

In this paper we discuss, the design and fabrication of the spectrally varying hollow core photonic fibers as flexible optofluidic channels and their use as a wavelength selector and cross responsive sensors. The unusual nature of the sensor array in terms of its specificity and cross responsiveness is compared to the current nose technologies. Upon this unique feature, a novel binary identification of the infrared spectra is introduced. The potential and feasibility of a market ready system and its application to medical diagnostics in the case of exhaled breath diagnosis of diabetes is briefly discussed. Possible uses in disease diagnostics follows since exhaled breath (EB) and breath condensate (EBC) provide a complex image of the biochemical processes in the human body

Figure 1: Schematic description of the optoelectronic nose. An array of photonic bandgap fibers (PBG) are used as infrared absorption gas cells for the detection of volatile organic chemicals. A blackbody source radiation is spectrally selected by the PBG fibres, and filtered radiation is sent through the optofluidic channel that results in a quenching depending on the IR absoprtion of the inspected chemical. A quenching in the integrated intensity of the radiation is registered spectrally to record the fingerprint of the chemical.

which can be correlated to the physiological status of the patient [4].

2 IR ABSORPTION SENSOR ARRAY

Wavelength scalable infrared fibres can be used as an array can for chemoreception of airborne molecules to identify and distinguish a large number of these species. First, we explain the working principle of the binary fibre array by showing the distinct responses, one obtains from two fictitious analytes, Analyte A and B. The analytes have their unique absorption spectra as shown in Fig. 2a. The spectral absorption bands are generally not overlapping, except in the case of one where the absorption peak width is narrower for Analyte A. One can select, for example, seven fibres with spectrally-equally-spaced transmission bands in the 2-20 µm wavelength range (5000–500 cm^{-1}). Here, the number of fibres is selected intentionally to demonstrate the redundance of the fibres for sensing. The transmission bands of the fibres are scaled so that the transmission in the larger wavelengths is wider compared to the smaller wavelengths. The fiber bundle transmission in the absence of any absorbing molecules in the optical path, is shown Fig. 2b. The signal registered with the infrared sensors are not spectral, but only cumulative infrared beam intensity.

Let's assume, we deliver Analyte A into the fiber bundle. Because of its coinciding absorption peaks, fiber 1, 2 and 4's transmission signals will be quenched, depending on the respective (a) infrared absorption cross section of these lines, (b) concentration of the analyte, (c) optical path, according to Beer's law and the quality factor of the transmission band of the fiber. The response from each fiber can be registered by the recording the transmitted infrared energy as an analogue signal and, also by choosing an appropriate threshold value, as a binary signal. In this case a binary signal of "1101000" (decimal equivalent 94) will be recorded when Analyte A is present in the optical channel using an appropriate threshold to distinguis quenched fibres from unquenched ones. Upon delivering another analyte, Analyte B, which will have its unique absorption spectra, the fibre bundle response will change according to the spectral aligning of the absorption and transmission lines. For Analyte B, fibers 2, 3, 5 and 6 will quench, resulting a binary code of "0110110" (decimal equivalent 54). Thus, the fibre bundle differentiates these two chemicals by assigning them unique binary codes based on their distinct infarred absorption peaks. Furthermore, there is high redundancy, that is fibers that are not required in differentiating the analyte set. In this example, two analytes could be differentiated by using only one fiber that has a transmission peak that coincides with only one of the chemical. For example, fiber 1, 3, 4, 5 or 6 alone is sufficient to successfully differentiate Analyte A from Analyte B. Theoretically, *n* fibres can be designed to differentiate 2^n chemicals. However, in reality this can never be reached, and some redundancy in the sensor array is desirable since it increases the reliability and selectivity of the array.

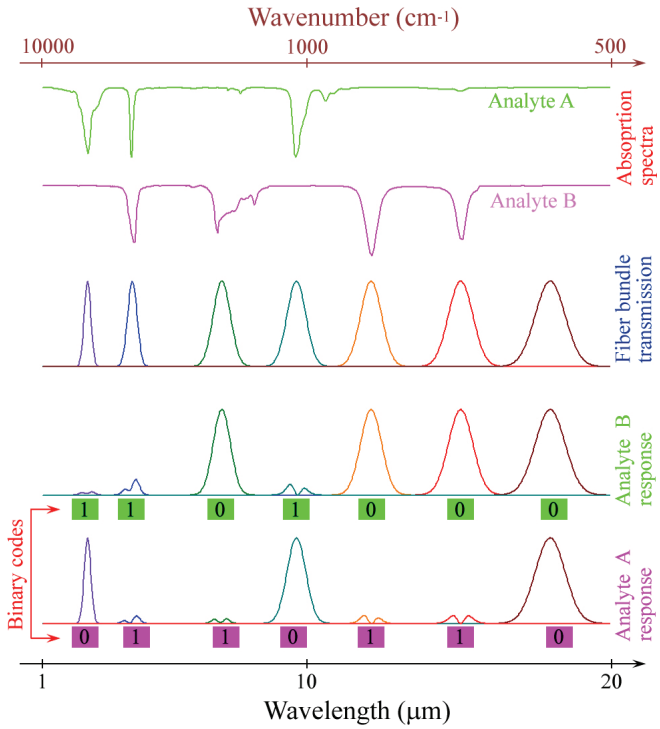

Figure 2: Simplified infrared absorption spectra of typical volatile organic chemicals are shown, indicated by Analyte A and Analyte B. Both analytes have four absorption peaks between 10000–500 cm^{-1}. A fiber bundle composed of seven fibres have seven distinct transmission bands in the same region that may or maynot coincide with one of the absorption peaks of the analytes. Upon the insertion of analytes, some transmission signals are quenched depending on the presence of a corresponding absorption peak in the respective chemical. The signal are registered as 0/1 using a threshold value for the integrated intensity. Analyte A is recorded as "1101000" and B as "0110110".

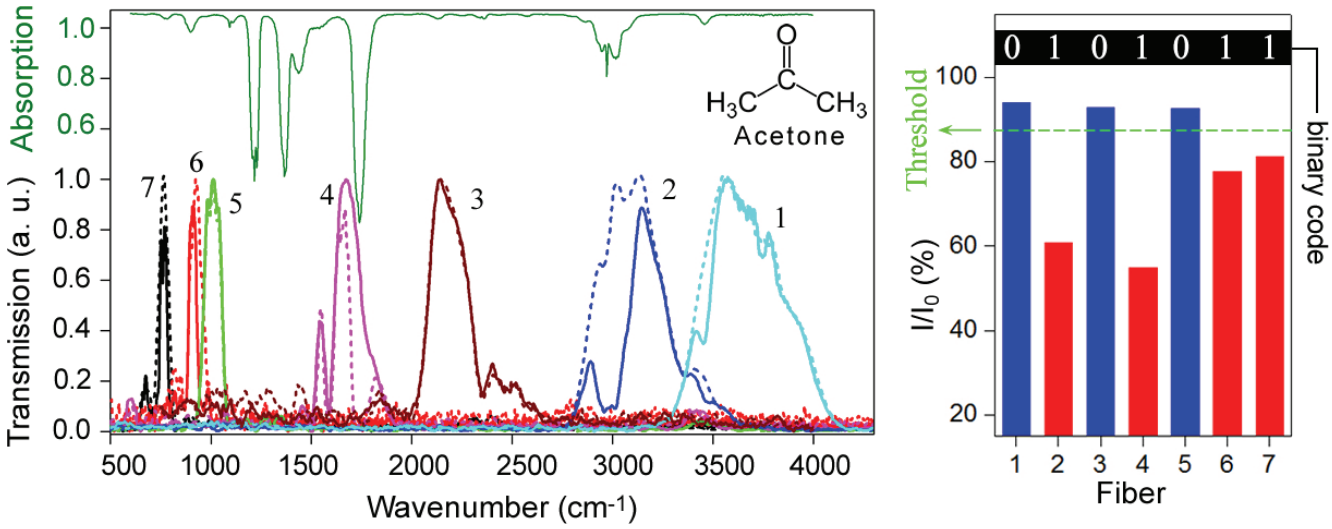

Figure 3: Detection of acetone gas using the fiber array based electronic nose. The array consists of seven infarred transmitting fibers that selectively transmit different bands of the mid-infrared spectrum. Fiber transmission peaks are at 3650, 3050, 2250, 1650, 1012, 910 and 770 cm^{-1}. Fiber transmission bands are partially quenched or punctuated by the infrared absorption peaks of the analyte (acetone.) The transmission bands are without the analyte in the gas cell (solid lines) and quenched bands with the analytes (dashed lines). The integrated intensity ratios are used to detect the presence of the analyte from its infrared fingerprint. The response of the fibers are shown also shown with a binary code, using 85% threshold value.

3 EXPERIMENTAL

The photonic bandgap fibers are fabricated from a single thermal draw and described elsewhere [2]. Seven fibers are selected with transmission bands at 3650, 3050, 2250, 1650, 1012, 910 and 770 cm^{-1}. The selected fibers are cut to approximately 30 cm and combined to obtain an array gas cell of 200 microlitre volume. Experimental setup consists of a broadband infrared source, wavelength selective fibre cell array and an infrared detector. We used the SiC filament and collimator optics of an FTIR system (Bruker Tensor) and a ZnSe convex lens to couple the infrared beam to the hollow core of the fibres, one at a time. A Hg-Ca-Te (MCT) infrared detector is used to record the infrared energy transmitted through the fibre. The blackbody radiation is weaker in intensity compared to lasers, but this is compensated by the waveguide enhancement. The gaseous acetone analyte was delivered into the fibre gas cell, from a flask saturated with vapour pressure of the analyte using nitrogen carrier gas and exhausted from the other end of the fibers.

4 RESULTS

The acetone detection capability of the electronic nose, which can be used in the diagnosis of diabetes mellitus, is demonstrated at its vapour pressure, 33 mmHg. The IR absorption band of acetone gas is given in Fig. 3a. The transmission bands of the fibres before (dashed) and after (solid) analyte introduction are are shown. The quenching percent is calculated from

$$Q(i) = \frac{\int P\, A(\lambda)\, T_i(\lambda) d\lambda}{\int T_i(\lambda) d\lambda} \qquad (1)$$

where A is the partial atmospheric pressure and $A(\lambda)$ is the infrared absorption of acetone The total integrated intensity of the fibers are quenched upon analyte introduction if there is an absorption band in the range of fiber's transmission. After acetone introduction the tranmission signals of fibers are observed as 94.4%, 61.1%, 93.2%, 55.2%, 92.8%, 77.9% and 81.5%, respectively. The transmission signals are significantly quenched for fibre 2, 4, 6 and 7 and only slightly changed for fibers 1, 3 and 5. The quenching ratios are shown as a bar chart in Fig. 3b. Quenching ratio depends on the fiber transmission band width, exact fiber length, analyte vapour pressure and the infrared absorption cross section of the corresponding anlayte peak. Combined fiber array response can be processed as an analog signal using statistical analysis tools, such as the hierarchical clustering (HCA); but it can be digitally processed by setting an appropriate threshold value. By using a threshold value of 85% and coding the values greater than the threshold 1, and vice versa the resulting response array can be decoded as "0101011" and converted to its decimal equivalent (43). The sensitivity of the fiber quneching is initially determined to be low ppm levels. Our initial analysis indicate that fiber based gas cells can detect absorption peaks superior to standard FTIR systems due to enhanced radiation confinement into the gas cell. Exact determination of the sensitivity requires exponential

dilution flask experiments. The selectivity of the detection system can be customized to fit any infrared absorption spectrum, since the blackbody source emits in the whole mid-IR spectra and photonic bandgap fibers are completely wavelenght scalable in the same region.

5 IR SENSORS IN BREATH DIAGNOSTICS

Exhaled breath contains more than 1000 organic volatile compounds that can potentially serve as biomarkers for specific diseases or for the inspection of metabolic activity. Oxidative stress, lung disesaes, gastroenteric diseases and metabolic disorder such as diabetes can be monitored from the exhaled breath [6]. Acetone is the earliest and most extensively studied biomarker in exhaled breath [4]. In diabetes mellitus, acetone concentration in the blood increases, resulting in higher diffusion across the alveolar membrane, reaching 100 ppb. All compounds present in the exhaled breath are IR active due to their organic bonds, making it possible to detect them using electronic nose technologies. Sensitivity, selectivity and portability are the most important aspects of an electronic nose technology in order to use them in clinical setups. In these respect, fiber based electronic nose have high sensitivity and selectivity. Initial analysis of quenching data indicate that infrared absorption data can be detected with much higher sensitivity compared to standard cell FTIR spectroscopy [7]. Classical FTIR detection limits are in the 0.1 ppm levels [8], therefore any improvement on this sensitivity can make electronic noses ameanble for the breath analysis. Using coherent sources it was shown that fiber gas cells can be used for ppt level gas detection in the [9]. On the other hand, a line source, for example cascade lasers, can be used only for single chemical detection. multiple absorbing analytes that is present in EB result in overlapping peaks that require using addition sensors.

In the presence of multiple absorbing analytes, as it is the case with EB, overlapping peaks require addition sensors for each chemical and for identifying the concentration of detected analytes. A broadband blackbody source is a continuum source unlike laser line sources that can traverse the whole mid-IR spectrum. As we have demonstrated here, therefore, it is possible to detect any species when coupled to special fibers that act as filters and gas cells. Computer simulations indicate that the selectivity of the fiber electronic nose increases with the addition of extra fibers. It is for example possible to selectively detect 100 chemicals with 25 fibers [7]. For the first time an electronic nose has the capacity to detect all biomarkers with a broad range of small number of sensing units. Additionally we think that the sytem can be integrated and deployed as a point-of-care system to medical institutions.

6 CONCLUSION

It has been long known that exhaled breath can be used in disease diagnostics, however the EB analysis has been nearly untouched in modern medicine, in need of an integrated high selectivity and sensitivity device that can rapidly detect the constituents in exhaled breath at the point-of-care. We demonstrated the detection of diabetes mellitus biomarker, acetone detection for diagnosis of the disesase. Due to the used light source and filter nature, the system is scalable to a large number of biomarkers. Infrared absorption based fiber nose presented here has necessary requirements to be widely used in medicine. Electronic nose technologies have the additional advantages of being non-invasive, provides direct information on respiratory function,and is more complicated mixture than serum or urine and is ameanable for complete anlaysis of all compounds present in EB. This rapid, inexpensive and yet extraordinarilyselective and sensitive optoelectronic 'nose' is likely to have an impact in point-of-care noninvasive diagnostics and prognosis.

REFERENCES

[1] G. M. Whitesides, The origins and and the future of microfluidics, Nature, 442, 368, 2006.

[2] A. Yildirim, M. Vural, M. Yaman, and M. Bayindir, Bio-inspired optoelectronic nose with nanostructured wavelength scalable hollow-core infrared fibers, Adv. Mater. 23, 1262 (2011).

[3] A. F. Abouraddy, M. Bayindir *et al.*, Nature Mater. 6, 336 (2007).

[4] S-S Kim, C. Young, B. Vidakovic, S.G.A. Gabram-Mendola, C. W. Bayer, B. Mizaikoff, Potential and challenges for mid infrared sensors in breath diagnostics, IEEE Sensors J., 10, 145, 2010.

[5] C. Monat, P. Domachuk, B. J. Eggleton, Integrated optofluidics: A new river of light, Nature Photonics, 1, 106, 2007.

[6] W. Cao, Y. Duan, Breath Analysis: Potential for clinical diagnosis and exposure assessment, Clinal Chemistry, 52, 800, 2006.

[7] M. Yaman *et al.*, manuscript in preperation.

[8] D. A. Skoog, D. M. West, F. J. Holler, S.R. Crouch, Analytical Chemistry, Thomson Brooks/Cole, 2004.

[9] C. Charlton, B. Temelkuran, G. Delleman, B. Mizaikoff, Midinfrared sensors meet nanotechnology: Trace gas sensing with quantum cascade lasers inside photonic band-gap hollow waveguides Appl. Phys. Lett., 86, 194102 (2005).