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Biomimetic Cross-Reactive Sensor Arrays: Prospects in Biodiagnostics

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Abstract

Biomimetic cross-reactive sensor arrays have been used to detect and analyze a wide variety of vapour and liquid components in applications such as food science, public health and safety, and diagnostics. As technology has advanced over the past three decades, these systems have become selective, sensitive, and affordable. Currently, the need for non-invasive and accurate devices for early disease diagnosis remains a challenge. This review provides an overview of the various types of Biomimetic cross-reactive sensor arrays (also referred to as electronic noses and tongues in the literature), their current use and future directions, and an outlook for future technological development.

1. Introduction

1.1. Importance of non-invasive, early diagnosis

Many conventional methods of diagnosis are costly, painful, and inaccurate in early stages.¹ Thus, there remains a need for devices that target all of these facets to provide early diagnosis and analysis for each individual patient that is altogether more cost effective, accurate, and non-invasive.

For example, cancer detection and treatment remain a significant challenge that affects many Americans. In 2008 alone, of the 1.6 million new diagnoses of lung cancer in the United States, 1.4 million died of the disease;² in that same year, 1.38 million women were diagnosed with breast cancer globally, comprising 23% of invasive cancer cases in females worldwide.³ For these and all other types of cancer, treatment and maintenance costs are high. In 2010, the national cost of cancer was estimated to be \$124.57 billion.⁴ Recent research has shown, however, that early diagnosis is a key factor for cancer survival and treatment cost, with the five year survival rate increasing from 4% to 24%, to 52% for local, regional, and distant stage disease, and the overall cost of cancer decreases for those treated in the early stages.^{2,4}

Another prevalent challenge in medical treatment methods is the increase in highly antibiotic-resistant bacteria that cause various types of infections for many people worldwide. In 2009, over 50% of healthcare associated infections (HAIs) were caused by a

resistant strain. HAIs have been estimated to be the fifth-leading cause of death in acute care hospitals, with 5-15% of patients contracting HAI during their stay. HAIs contracted resistant strains cause, on average, a 9 day increase in hospital stay, and \$29,379 in additional medical costs.⁵ Prolonged bacterial growth in the body leads to the formation of bacterial biofilms, which are increasingly resistant to antimicrobial agents.⁶ Thus, early diagnosis of these infections is necessary for optimal infection treatment.

Concerning the accuracy of diagnosis, there remains a need for analytical tools for patients with chronic illnesses, such as inflammatory bowel disease, asthma, and chronic mental illnesses. Mental illness specifically is a widespread issue in the United States. In 2012, the NIH reported that 43.8 million adults suffered from a mental illness.⁷ In 2006, 36.2 million people paid for mental health services totalling \$57.5 billion.⁸ In 2010, asthma was the cause for 1 in every 250 deaths worldwide due mainly to suboptimal management and delay in obtaining help during the final attack.⁹ The cause of many of these illnesses remains unknown. Treatment is administered on a trial-and-error basis, which reduces effectiveness and raises the risk of serious side effects. An accurate device that can provide a unique patient profile would contribute significantly to the development of a specific treatment method based on the individual's needs, and could act as a tool to understanding the physiological processes involved for each illness.

1.2. Mammalian olfactory system as a model for biomimetic sensors

Over the past 3 decades, many research efforts have looked to the mammalian olfactory system as a model for the development of a medical diagnostic device that meets all of these requirements. In March of 2015, The Guardian newspaper published an article about a dog named Frankie who could detect thyroid cancer with 88% accuracy among patients. Thyroid cancer is notoriously difficult to detect by conventional methods, and it is hard to tell if the entire tumour has been removed post-surgery. Frankie, however, was trained to lay down after smelling patients' urine samples if he detected metastatic cancer.¹⁰ Researchers have been working to develop biomimetic devices, called “electronic/artificial noses” and “electronic tongues” to detect certain olfactory elements present in both vapours and liquids that can indicate a certain disease or illness.

It is estimated that the human nose can detect as many as 10,000 to 100,000 chemicals in the form of “odorants,” which are small volatile molecules.¹¹ Upon entering the nasal cavity, the odorants reach the olfactory epithelium and interact with the olfactory sensory neurons by dissolving into the nasal mucus, and reaching cilia extended into the nasal lumen.¹¹ This releases a signalling cascade, whereupon the activated neurons send information to the olfactory bulb section of the brain, which then sends this information to the olfactory cortex. The cortex processes the information, and sends it to appropriate other areas of the brain responsible for odour determination and the emotional and physiological responses associated with each odour.¹¹ Importantly, each sensory neuron has odorant receptors (ORs), which are a type of G-protein coupled receptor (GPCR), and are encoded by a multi-gene family to detect a wide variety of different odorants. Upon binding to odorants, ORs undergo conformational change, thereby converting the received chemical information into electrical information for the sensory neurons.^{11–14} Overall, there are about 1000 genes that encode

ORs, and each OR has multiple sites for odorant binding, enabling detection of more than one odorant for each OR—a characteristic called cross-reactivity.^{11,14} Each combination of activated receptors creates a unique signalling code for a specific odorant, making it possible to distinguish between thousands.^{11–13} This review aims to provide a brief history and examination of current technology and future directions of both electronic noses and tongues that aim to mimic the mammalian olfactory system. These devices have proven to be successful for a wide variety of applications, providing cost-effective, minimally invasive, and highly accurate vapour and fluid component analysis.

2. History and Background Technology

The first use of the term “electronic nose” was at a conference in 1987, with the first conference dedicated specifically to artificial olfaction in 1989.¹⁵ In a 1994 publication, Gardner and Bartlett defined an “electronic nose” as: *“an instrument, which comprises of an array of electronic-chemical sensors with partial specificity and an appropriate pattern recognition system, capable of recognising simple or complex odours.”*¹⁵

The earliest attempts at creating such a device involved passing an odorant over sets of unique active materials, each connected to its own sensor. Upon activation of its material, the sensor would transmit an electrical signal to a processor, which would then compile an array of activated sensors to alert the user of the odorants present by cross referencing a database of known “odours” (i.e. analytes).^{15,16} The earliest designs employed metal oxide semiconductors as an electrical sensor to detect gases such as NO₂.^{17,18} This was based on the principle that the conductivity of semiconductor metals changes upon variance in the atmospheric gas surrounding the sensor.¹⁸ Additionally, some of the early sensors were metal oxide semiconducting field effect transistors (MOSFETs). MOSFETs are usually constructed from a SiO₂ insulating layer, with a semiconductor metal deposited on top as the gate in the circuit. A voltage is applied to maintain a constant current, and as the gas adsorbs onto the gate, the conductance of the FET changes, thereby causing the voltage to change.^{19,20}

As more became known about the physiology of the mammalian olfactory system, sensors advanced to take advantage of these new findings, from incorporating sensors that were able to detect multiple analytes,²¹ to the development of a biomimetic flow chamber to enhance analyte detection at low levels.²² This allowed for a great number of analytes to be recognized using a smaller array of multi-selective sensors.^{16,21} The types of sensors employed in these devices vary, including gravimetric, or mass,^{23–32} electrical,^{33–40} and optical^{41–58} sensors for optimal analyte detection.

Within the last two decades, electronic tongues for liquid detection have also been developed, mimicking the olfactory signalling pathways. These devices use mass,^{59–63} electrochemical,^{64–74} and optical sensors^{75–78} for chemical detection. Table 1 gives an overview of the different types of sensors in both electronic noses and tongues, and outlines some of the advantages and disadvantages of each one.

The subsequent sections describe both electronic nose and tongue technology using different types of sensors, explore their use in medical diagnostics and outline future directions in device development.

3. Cross-Reactive Sensor Arrays for Volatiles (CRSA-V)

3.1. Mass Sensors

The most common mass CRSA-V devices are piezoelectric (PZ) crystals, which are usually quartz crystals. The crystals are coated with various materials that attract specific analytes. These coating materials include chemicals such as amines,^{24,29} enzymes,²⁹ proteins,^{25,28} and polymers.²⁹ Coated crystals are arranged in a microbalance, and their resonant frequency is recorded during exposure to a desired vapour. As analytes adsorb to the surface of the PZ crystals, the added mass leads to a reduction in the crystals' resonant frequency. A drop in frequency may also be attributed to both viscoelastic and gravimetric effects.²⁹ Once the frequency change is recorded, the mass adsorbed to the crystal surface is determined by:

$$\Delta F = -F \Delta m / (A * r * t)^{25,29}$$

Where ΔF is the change in resonant frequency (Hz), F is the initial crystal resonant frequency (MHz), A is the total surface area (cm²), r is the density of crystal (g/cm³), t is the thickness of the crystal (cm), and m is the mass adsorbed (g).^{25,29}

Mass sensors have been used in a wide variety of applications. For example, Filipov, et. al. in 2007 used quartz PZ crystals coated with Cu(II) stearate and octadecylamine to attract and detect volatile organic compounds (VOCs), known to be produced by certain types of cancer.^{79–82} As illustrated in Figure 1, they placed a coated quartz crystal microbalance (QCM) in a thermostatic chamber filled with purified air and sealed at a relative humidity of 45%. Next, a vapour saturated with VOCs was injected into the chamber and passed over the QCM. The QCM/chamber system was connected to a frequency counter, which in turn fed the output to a computer to analyze frequency change, with results shown in Figure 2. To better calibrate the sensor to account for frequency changes caused *only* by VOCs, properties of the coated crystals were studied in diffused, ambient conditions as a correction factor. They further optimized the system by testing different ratios of metal ion to fatty acid/amine concentrations to promote affinity of the coatings to VOCs.²⁴

Park et al. have used OR proteins in crystal coatings to test the ligand specificity and dose dependence of individual ORs as biosensors.^{25,28} For these two studies, commercially available QCMs were purchased and functionalized with desired ORs. In 2004, Ligand specificity and dose dependence of rat ORs were analyzed. Heterologous cells were induced to express a specific type of OR on their surface, then seeded and dried on a gold substrate to be used as a coating for the QCM.²⁵ In 2005, an OR expressed in *C-elegans* was grown on *E. coli*, and the membrane fraction containing the OR was harvested for use as a coating. This OR coating was tested for specificity to a variety of different analytes, and optimized using the membrane fraction that showed the most sensitive affinity for diacetyl.²⁸ This group has successfully shown that the use of ORs as biosensors can be highly efficient and

selective. Furthermore, they discuss the use of the cross-reactivity of the OR sensors to create a sensor array, capable of detecting a wide variety of analytes.^{25,28}

Some mass devices use changes in microcantilever oscillations as an indicator of analyte adsorption. Microcantilevers, such as those on an Atomic Force Microscope, are fabricated as a bilayer system, typically composed of silicon or silicon nitride and a chemically selective layer.^{23,26,30–32} These two layers have a difference in thermal expansion, which causes the cantilever to oscillate at a specific fundamental frequency, calculated using Newton's second equation of motion³⁰:

$$f_i = \frac{\lambda_i^2}{2\pi L^2} \sqrt{\frac{EI}{\rho A}}$$

The mass of the chemically selective layer changes upon analyte adsorption, which in turn causes a change in oscillation frequency, as shown in Figure 3. Though mass sensors have been proven to be successful, there are many limitations with this device setup. The sensors are prone to inaccuracy due to subtle changes in coating amount on the surface, humidity, temperature, etc., and thus need to be calibrated very often. The setup, preparation, and calibration process is delicate and time consuming.^{21,24,25,28,29}

3.2. Electrical Sensors

Electrically sensing e-noses use an electronic circuit connected to a network of sensory materials that provide an electrical response upon binding with a specific known analyte. In addition to the MOS and MOSFET electrical sensors, a popular and more recent sensory material is conductive polymer. There are two types of conductive polymer sensors: intrinsically conductive and composite conductive polymers. To create intrinsically conductive sensors, thin polymer films are electropolymerized across a narrow electrode gap,^{21,34} and their chemical composition tuned to attract a desired analyte.³⁴ Composite conductive polymers are produced when an insulating polymer is doped with a conductive material, such as carbon black.³⁸ The polymer sensors are then placed in an electrical circuit, and act as resistors, reflecting a decrease in their conductance upon binding with the analytes in the vapour, as shown in Figure 4.^{21,33,34} This decrease in conductance is most likely due to polymer swelling upon analyte binding—as the polymer swells, gaps between polymer chains increase, lowering conductivity.⁸³ There are a wider variety of conductive polymers available for analyte binding compared to metal-oxides, and thus a larger catalogue of unique sensors for vapour analysis can be created.²¹ Additionally, the incorporation of several uniquely functionalized polymer sensors in a single circuit allows for the simultaneous detection of multiple vapour components. Data from these sensors can then be arranged in multiple matrices, which in turn creates a unique pattern for each type of vapour analysed.³⁴

Conductive polymer sensors have recently taken advantage of advances in microchip technology to decrease the size of circuits and increase the number of sensors. Beccherelli, et. al. have designed a large chemical sensor based on the olfactory system that has

incorporated up to 65,536 resistive sensing elements. Using a modular approach, each module is capable of reading a 64×64 sensor array, and 16 modules work in parallel to analyze and report all data gathered. The chip utilizes an inkjet printer system to deposit conductive polymers on the chips with high accuracy and low cost; furthermore, this deposition technique allows for faster diffusion of vapour elements into and out of the film, affording faster response and recovery time for each sensor.³³

Electrical sensors for electronic noses have also progressed to incorporate new materials as a replacement for conductive polymers. Single-walled carbon nanotubes (SWNTs) have recently been used as a type of FET, where either change in conductance or capacitance is measured.³⁹ In 2006, *Star, et. al.* developed a sensor that utilizes single-walled carbon nanotubes (SWNTs) functionalized with metal nanoparticles as ligand-binding sites, as shown in Figure 5. The device created was a nanotube field effect transistor (NTFET). In short, SWNTs were grown on doped silicon wafers via chemical vapour deposition (CVD). Using photolithography, SWNTs were overlaid with electrical leads made of 30 nm thick Ti films capped with 120 nm thick Au layer. Each 2.54×2.54 cm² wafer can hold about 1000 dyes, and each dye consists of randomly assorted SWNTs patterned into several devices in between two parallel electrodes. The NTFET devices were then decorated with a metal/metal oxide via electron beam (e-beam) deposition. E-beam deposition methods allowed for each NTFET device on a single chip to be paired with a different catalytic metal, if desired. The devices were then exposed to various combustible gases, H₂, CO, and H₂S and two toxic gases, NH₃ and NO₂. Response to these gases was recorded as a change in conductance versus gate voltage, shown in Figure 6. Each gas exposure resulted in a specific curve, showing the ability of the device to distinguish between gases.³⁹ SWNTs can also be coated with various polymers to tune their sensitivities.^{36,40}

3.3. Optical Sensors

Optical sensors in e-nose systems have shown much promise to provide a facile, cost-effective, and accurate way of identifying analytes in vapour. Optical sensors work by displaying a shift in emission or absorption of different types of radiations upon binding with a desired analyte. There are two popular means of detection: fluorescent sensors^{41–52,55,57,58} and colorimetric sensors.^{53,54} Optical sensors offer significant benefits compared with the sensor systems mentioned above; they can provide multiple complex data types simultaneously, including changes in intensity, fluorescence lifetime, wavelength, and spectral shape.⁵⁰ This increases the ratio of recognizable analytes to number of sensors used.

Fibre optic chemical sensors mimic both the temporal and spatial signalling pathways of the mammalian olfactory system. Walt et al. have developed an e-nose using these fibre optic bundles. Briefly, fibres are coated with a single solvatochromatic dye (Nile Red), which has been mixed with a different polymer species for each fibre. These polymers differ in pore size, baseline polarity, hydrophobicity, flexibility, and swelling tendency, which leads to a unique interaction of each fibre with the analytes presented. Nile Red shows large shifts in emission wavelength maximum with changes in local polarity; the unique analyte-dye/polymer interactions causes a specific local polarity change, resulting in different fluorescent

responses for each sensor. These responses have both spatial and temporal components, making it possible to track intensity and spectral changes over time.^{50,52,56–58}

Walt *et al.* have also implemented fluorescent microsphere arrays in their e-nose devices. Similar to fibre optic arrays, microspheres with different chemical properties can be synthesized from various polymers. These microspheres are then dyed with Nile Red and arranged on glass coverslips.^{47,55} Microsphere arrays provide an advantage over other multi-sensor systems because billions of beads that produce an identical response can be made simultaneously, in comparison to many sensors for which the fabrication process is tedious.^{47,55} Imaging of these arrays produces a 3D video which tracks fluorescence, time, and spatial orientation of the sensors for decoding and pattern recognition.⁴⁷ Each stock of unique sensors can be used in multiple arrays with high fidelity, creating a unique “fingerprint” for each analyte in vapour.⁵⁵

In collaboration with other labs, Walt *et. al.* have also combined the fibre optic bundles with microspheres.^{41,44–46,49} The fibre ends were etched to create microwells in which microspheres were placed. The microwells were etched into the distal end of the fibre by submerging the polished end into a buffered hydrofluoric acid solution for 70s; the fibre was then transferred to a beaker of DI water to stop the reaction, run under tap water, and sonicated to remove excess salts that may have formed during etching.⁴⁹ The microspheres fabricated and suspended in droplets of solution were placed on a clamped imaging fibre, as shown in Figure 7.^{45,49} The beads then fill the microwells (one bead per well), and packing density (number of filled wells) is directly proportional to the bead solution concentration and the number of drops applied.⁴⁹ Beads may also be loaded into microwells by a dry deposition method—creating a slurry of beads and rubbing them into the surface via a latex glove^{44,45}—or a block and load method, which uses a razor blade to control spatial separation and orientation of different types of beads.⁴¹ Each type of bead has a distinct, intrinsic response to the vapours presented, which eliminates the need for additional encoding for bead identification, as shown in Figure 8. The fibre/microsphere composite bundles have also been incorporated in portable devices for applications in the field as well. These devices consist of batteries for a CPU laptop and the electronic nose, an imaging and processing system, and the etched fibres that are connected to an optical block and vapour-sensing unit.^{41,46}

Suslick *et al.* has also employed optical sensors for their electronic nose device. Their approach uses immobilized dyes that have chemoselective reactions when exposed to a variety of different ligands in vapour, shown in Figure 9.^{53,54} Metalloporphyrines were used because they display both open coordination sites for axial ligation, large spectral shifts upon ligand binding, and intense coloration.⁵³ In addition, the array can be expanded to include bis-pocketed Zn porphyrines to detect for the size and shape of the analyte, acid/base indicators to differentiate Brønsted basicity, and solvatochromic dyes to report on the polarity of the analyte.⁵⁴ The use of these additional sensors made it possible to create a 36 sensor array, capable of distinguishing between similar classes of amines at very small concentrations (<1ppmv).⁵⁴ Briefly, dyes were deposited on a hydrophobic, benign surface such as reverse-phase silica gel, and the device placed on an ordinary flatbed scanner. Images were taken before and after exposure at 1200 dots per inch in RGB color mode.

Color difference maps were then produced by subtracting the “before” image from the “after” image; a 314 pixel average was used in this process, taken from the center of each dye spot. Each analyte is represented as a multi-dimensional vector, i.e. 72 in a 24-sensor array, one each for the red green and blue differences of 24 dyes. Image processing and spectral analysis create a unique color map for each analyte, and while similar analyte types show a correlation in clusters present, it is still possible to identify individual analytes by their color maps.⁵⁴

4. Electronic Tongues

Along with the development of electronic noses, liquid sensors have been produced that work in a similar way. The main methods are electrochemical, mass, and optical electronic tongues.

4.2. Mass Sensors

Piezoelectric sensors, similar to those used for vapour analysis, have also been used in liquids. Sensors have been fabricated both from quartz^{84,85} and thin films,^{59–63} and their frequency change can be analyzed using either surface acoustic wave (SAW)^{84,85} or bulk acoustic wave (BAW)^{59–63} resonance. Recently, thin film BAW sensors have taken precedence over the common quartz crystal microbalance, as thin films are much smaller, can reach higher frequencies, and are more sensitive because frequency is directly related to film thickness.⁶⁰ Resonance-active films are functionalized to bind to a desired analyte, and attached to the base of the fluid flow chamber. Most of the thin film resonators are operated in shear mode, with resonance-active films sitting in a plane orthogonal to the fluid flow direction.^{60,61,63,85} In 2008, *Wingqvist et. al.* showed that thin film BAW sensors have enhanced sensitivity upon the addition of a layer that has low acoustic impedance.⁶²

4.2. Electrochemical

The earliest, and most popular type of electrochemical tongues used potentiometric sensors. Potentiometric sensors consist of ion selective electrodes, and detection of desired analyte is accomplished by tracking changes in the potentiometric electrode versus a control electrode in zero current conditions. The ion activity in the solution is functionally related to the potential of the sensor. Each electrode provides a unique response upon exposure to a specific analyte, creating “taste” profiles for each substance identified.

The first commercialized electronic tongue was created by Toko in 1996. His goal was to fabricate electrodes that closely mimicked human taste buds to detect the basic five tastes: bitter, sour, sweet, salty, and umami. Each of 8 electrodes was outfitted with a unique biomimetic lipid bilayer species, each of which reacted differently upon exposure to the same “flavour” profile—creating a unique fingerprint that was readily identifiable.⁷² Since Toko's device, other potentiometric sensors have been created to identify ions such as ammonium,^{64,65} potassium,⁶⁵ and nitrite,⁶⁶ and to analyze components of some beverages such as tea⁶⁸ and wine.⁶⁹ Some limitations of the potentiometric sensors include a narrow range of detectable ions, electronic noise, and adsorption of ions to the electrodes, causing interference.^{74,86}

A second type of electrochemical tongue uses voltammetric sensors—which records the relationship of potential and current over series of pulses. For voltammetric sensors, there are three electrodes: working, auxiliary, and reference. The reference electrode remains at a constant potential, while current is generated between the working and auxiliary electrodes. The earliest voltammetric tongue was created by Winquist, et. al. in 1997 to analyze the aging process of milk and orange juice over time.⁷⁴ The setup involved 2 working electrodes, gold and platinum, and a potentiostat enabled the system to change between electrodes for detection of different compounds as shown in Figure 10. Two types of pulse voltammetry were used: large amplitude pulse voltammetry (LAPV), and small amplitude pulse voltammetry (SAPV). Both voltammetry methods induce a series of potential pulses to the electrodes, and track the resultant current response over time. Each electroactive compound in the solution responds differently to the pulses, creating a unique “map” of current response for each compound, shown in Figure 11.

One disadvantage of voltammetric sensors is that there are thousands of data points to be processed from the I/V curves generated. This demands the necessity of data processing techniques that can handle and make sense of this large amount of information.^{67,71,74} *Winquist et. al.* used principle component analysis (PCA) to process the obtained data; more recently, others have used both multifrequency LAPV⁷¹ and data compression methods⁶⁷ to more easily and quickly distinguish between overlapping frequencies created by solutions with multiple components.

4.3. Optical Sensors

In addition to vapour analysis with optical sensors, *Walt et. al.* and *Suslick et. al.* have also contributed to the development of optical sensors for electronic tongue devices. The principles in vapour sensing are much the same as in liquid sensing. In 2005, *Walt et. al.* incorporated the optical fibres with microbead arrays in a microfluidic chamber to detect DNA via fluorescence of the sensors, shown in Figure 12.⁷⁵ Using colorimetric methods, *Suslick et. al.* developed an electronic tongue device that holds chemisensitive dyes in a sol-gel as solution are run over them. This system has been used successfully for a variety of liquid analyses, including soft drinks⁷⁸ and protein identification.⁷⁶ Still another group has used spectrophotometric analysis to detect inorganic bromide in water using bromide reactive dyes.⁷⁷

5. Technological Advances and Applications: Barcoded Resin Technology

5.1. Sensor Technology: Spectroscopic Barcoding

Electronic noses and tongues can be more finely tuned and broadly selective using new materials such as barcoded resins (BCRs) and principles such as surface enhanced Raman scattering (SERS). Each BCR has a unique Raman and infrared spectra, arising from its composition, which is transformed into a barcode for identification. Example barcodes are shown in Figure 13. Upon interaction with an analyte, the vibrational signatures of the polymer array change, resulting in slight but detectable spectral variations for each BCR. The collective response (or disease-specific patterns) can then be quantified using multivariate data analysis. The spectral changes reflected in each BCR—ca. 700 BCRs

available thus far⁸⁷—can then be used as a data point for pattern recognition, increasing the accuracy of symptom specific and disease-specific response for the e-nose device.^{87–93}

To synthesize the BCRs, sub-library copolymers is created via various combinations of the five main alkylated styrene monomers. A six digit binary code is assigned to each BCR, one digit for each monomer. For example, BCR12's code is 001010, indicating that it is made up of equal parts of monomers 001000 and 000010. The sub-library of copolymers can then be resynthesized to include one of the fluorinated monomers (A-I) to produce hundreds of different copolymers. The library of currently available monomers is shown in Figure 14. Each copolymer can then be scanned via Raman spectroscopy or Fourier Transform Infrared (FTIR) spectroscopy and a spectrum generated that is unique to each composition. Following preprocessing steps such as baseline subtraction and normalization, spectra can then be converted into barcodes; each wavelength maximum peak corresponds to a line in the barcode. The barcode identification method has made it possible to distinguish between as many as *ca.* 700 unique copolymers, offering a significant selectivity improvement to those currently used.

5.2. BCR Sensor Array Fabrication

BCR sensor arrays can be fabricated either using bulk copolymers or beaded copolymers. Both are deposited into etched, patterned silicon wells. Both methods preserve spectroscopic barcodes of the BCRs, and provide a facile, reproducible and reusable array that can be implemented in an e-nose device.⁸⁷

To create the etched silicon substrates, a combination of lithography and anisotropic dry reactive ion etching (RIE) was used on silicon substrates for micro-well formation as follows: the silicon substrates were piranha cleaned, HMDS primed and spin-coated with AZ P46 20 photoresists. Areas of the silicon were exposed by irradiating the film ($\lambda = 400$ nm) through a lithography mask built in-house. RIE using a combination of SF₆/C₂F₄, at pressures of 125 and 75 sccm, respectively, was used to etch the exposed silicon of the wafer. In this way, 10, 100, and 200 nm-deep wells were obtained SEM images of patterned wafers are shown in Figure 15A. The patterned wafer was then coated with a 200 nm thick copper film by RF sputtering. For deeper wells, a combination 504 photoresist SiO₂ hard mask was used. In this approach, 4 μ m oxide films were deposited by plasma enhanced chemical vapour deposition (PECVD) and the resulting oxide patterned with conventional 504 photoresist. The exposed oxide areas were etched with buffer oxide etch (BOE). The same RIE conditions were used to etch the oxide.^{94,95}

For sensor arrays that used bulk copolymers, each of the polymer resins was dissolved in chloroform (*ca.* 10 % W/W). One drop of the homogeneous solution was dispersed into a well on the patterned substrate using a capillary tube. The procedure was repeated for each polymer in the library producing an 8×8 array. The coated substrate was heated to 50°C for *ca.* 2 h on a hot plate to evaporate residual chloroform from the polymer films. The polymer samples in each well were identified by a number (representing a row) and a letter (representing a column).⁹⁵

For the sensor arrays that used beaded copolymers, beads were deposited onto the micro-patterned silicon substrates by dusting an amount of beads on the surface of the silicon chip. A rubberized spatula was used to spread the powder in a circular motion over the chip to ensure the filling of the holes. SEM of the BCR arrays are shown in Figure 15B, it clearly shows that by selecting the right bead/well size combination, an ideal ensemble could be achieved. Excess beads were removed by wiping with a kimwipe or under a stream of nitrogen.⁹⁴

5.3. Application Using BCRs as an E-nose

The BCRs can be used for both vapour and liquid sensing without loss of their identifying barcodes; this offers facile array fabrication because spatial orientation of each copolymer in an array does not need to be controlled. Though the copolymer types can be randomly mixed throughout an array, ordered arrangement of the polymer beads into rows and columns is desirable for fast spectroscopic imaging.

As an analyte-containing vapour is passed over the sensor array (Figure 15C), analytes interact with the polymers in a variety of ways, including being absorbed into the polymer network, polymer swelling, or adsorbing to the polymer surface. This, in turn, changes the chemical make-up of the polymer network, which then causes slight changes in the FTIR and Raman spectra. The changes are very subtle, such that the microbead is still identifiable by its barcode after a partial least square regression (PLS). Spectra for each of the polymers in the microwell are taken before and after analyte exposure, and the resultant spectral change is represented by an angle, θ calculated by PLS. Angle maps and histogram graphs representing the resultant changes in the composition matrix provide a response “fingerprint” for each of the copolymers in the sensor array. Each polymer reacts uniquely to each analyte, and it is therefore possible to collect an individual response pattern for analyte identification in vapours for which the analyte is not known. Because these polymers are non-selective in vapours containing multiple analytes (such as exhaled breath) the global response pattern of the sensor must be considered when comparing trends in sample composition.

The polymer sensor array was put inside a gas flow cell and screened by FT-IR and Raman spectroscopy prior to analyte vapour exposure. Saturated analyte vapour, generated by slowly bubbling nitrogen through a vial containing the liquid of interest, was then passed through the gas flow cell containing the sensor arrays as shown in Figure 15C.⁹⁵ After analyte vapour exposure, the sensing system was allowed to reach equilibrium before the spectrum or image acquisition; equilibrium was verified to be the absence of changes in measured spectra. Prior to the acquisition of the FTIR spectra, several pre-processing steps were taken. To account for the atmospheric or analyte vapour (in air) effects, a background measured for each trial was subtracted from the response. Histograms and angle response maps are shown in Figure 16.

BCRs have also been used as biosensors in liquids for both antibody-antigen binding⁹⁶ and pathogen detection.⁹⁷ Both of these methods use a fluorescent sandwich immunoassay antibody detection method: the microspheres were conjugated with an antibody, and the corresponding antigen was captured between the microsphere antibody conjugate and a

second fluorescently labelled antibody. Upon binding, the beads became fluorescent, and identification of the bound antibody was possible by cross-referencing the Raman barcode of the microsphere (Figure 17).^{96,97}

5.4. SERS Active Particles for Signal Enhancement

There is also much potential for the incorporation of SERS active particles for use in electronic nose and tongue systems. The use of SERS greatly enhances the optical properties of the original material, which in turn increases accuracy of analyte detection.⁹⁸ Fenniri, et. al. have explored different nanoparticles, such as gold octahedra,⁹⁹ gold and silver bimetallic particles on a silicon substrate,¹⁰⁰ and silver fractals¹⁰¹ to induce SERS for molecule identification. These SERS active materials have also been combined with polymer microspheres, including silver nanoparticle cross-linked polymer microspheres¹⁰² and gold polystyrene/polyethylene glycol microbeads, shown in Figure 18.¹⁰³ The use of SERS active particles and/or barcoded resins in electronic nose and tongue systems can greatly enhance selectivity and sensitivity—two parameters that are essential for accurate and early medical diagnosis.

Conclusions

As advances in electronics, image processing, and material design continue, the electronic nose and tongue devices have adapted to become smaller, more selective, and more sensitive, with fast data processing time and facile readout of vapour and liquid analysis.^{104–107} Each of the sensor types have various advantages and disadvantages; thus, it is important to consider the ultimate aim of analysis and type of sample to be characterized. Both mass and electrical/electrochemical sensors both provide sensitivity and selectivity in vapour and liquid analysis; however, these devices have a delicate setup, are unfortunately prone to drift due to changes in environment such as temperature and humidity, and require complex data analysis to extract the de-convolute the sensor response signal from the background noise. Optical sensors provide a cost-effective, facile fabrication method while maintaining high throughput sample analysis; however, they also may require complex data analysis and provide more of a qualitative characterization than quantitative. While these systems have been used in a wide variety of applications from food and drinks, to explosives vapours, some of the most promising work has been done in medical diagnostics. These devices have already been implemented to detect diseases such as lung cancer,^{1,79,81,82,108–111} asthma,¹¹² and other diseases known to produce specific VOCs in exhaled breath.⁸⁰ Bacteria presence and growth phase identification has also been possible.^{113,114} In addition to exhaled breath, disease biomarkers have also recently been identified through multiple “omics” studies in saliva,^{115–117} sweat,^{105,106,118–120} and urine;^{121–123} As the technology for more expansive and selective sensors continues, devices may further be developed to create unique patient profiles for a variety of diseases via analysis of the various body vapours and fluids.

In the future, electronic noses and tongues may also prove to be a useful tool in unravelling the pathophysiology of mental illnesses. Several studies have shown that anxiety and depression lead to changes in salivary cortisol levels.^{124–129} In addition, alterations in the

sympathetic nervous system in response to emotional stress produce noticeable changes in saliva,¹²⁸ such as secretion of chromagranin A,^{129–131} salivary alpha amylase,^{130–136} and pro-inflammatory cytokines.^{131,137} Mental illnesses such as Alzheimer's disease and Post Traumatic Stress Disorder can also be signified by changes in skin odour and urine.^{138,139}

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Fig. 1.
Schematic diagram of the experimental setup²⁴.

Fig. 2. Histogram indicating sensitivities of different coatings: HSt (1), ODA (2), CuSt₂ (3), Cu(ODA)₂St₂ (4), Cu(ODA)₄St₂ (5), Cu(ODA)₆St₂ (6), Cu(AcAc)₂ on SiO₂ (7), towards different analytes: methanol (1), ethanol (2), acetone (3), diethyl ether (4), ethyl acetate (5), benzene (6), chloroform (7), n-hexane (8), toluene (9).²⁴

Fig. 3. Frequency shift (drift removed) for a microcantilever resonating at 16.9 kHz with a sensitive coating thickness of 21 μm , exposed to ethanol at different concentrations²⁶.

Fig. 4. (A) Schematic of a sensor array showing an enlargement of one of the modified ceramic capacitors used as sensing elements. The response patterns generated by the sensor array are displayed for acetone (B), benzene (C), and ethanol (D).³⁴

Fig. 5.

(A) Conceptual illustration of a carbon nanotube network connecting source (S) and drain (D) electrodes of a FET. SWNTs are decorated with metal nanoparticles (silver dots) for selective detection of analyte gases (red dots). (B) Electronic measurements, such as source-drain conductance (G_{SD}), as a function of gate voltage (V_G) before (bare) and after thermal evaporation of discontinuous layer of gold (Au evap).³⁹

Fig. 6.

Response of bare NTFET device to (A) NH_3 and (B) NO_2 gases; response of Pd-decorated NTFET device to (C) H_2 and (D) H_2S gas. Left: A single gas exposure consisted of (i-ii) a five-minute settling period, (ii-iii) five-minute exposure to gas followed by (iii-iv) a ten-minute recovery period. NTFET conductance (G at $V_G = 0$, blue curve) is derived from the G - V_G curves measured during the test. Right: G - V_G curves recorded before and after gas introduction.³⁹

Fig. 7. Schematic depiction of the self-encoded bead array (SEBA) concept. A mixture of sensor beads is prepared by combining aliquots from three stock solutions each containing a different type of polymer/dye sensor suspended in a Nanopure water/0.01% Tween solution. A drop of the final mixture is then placed onto the distal tip of an etched imaging fibre.⁴⁹

Fig. 8. CCD images of each imaging fibre bundle. Bundle A-C (top) and bundle D-F (bottom) showing the fitted ROIs corresponding to each addressable bead sensor. A total of 2683 sensors were analyzed: (A) 814, (B) 286, (C) 301, (D) 692, (E) 294, and (F) 296 beads. The ROIs were automatically generated using Labview and IMAQ Vision software. Each imaging fibre's face is 1 mm^2 . Images were acquired with 100-ms exposure time, and excitation/emission filters were 560 (bp 40) and 630 (bp 20) nm, respectively.⁴⁵

Fig. 9. Miniaturized array. The metalloporphyrines were dissolved in a polymer film (dibutylphthalate in polystyrene) and deposited on Teflon (A, showing metals only for clarity). The array before vapour exposure (B) and colour change profile after exposure to n-butylamine (C, 1 min, 9.3% in N_2).⁵³

Fig. 10. Schematic diagram of the voltammetric electronic tongue setup.⁷⁴

Fig. 11.

Recordings from experiments carried out on various samples using the application measurement sequence. In this, LAPV followed by SAPV is carried out at the gold working electrode, where after the sequence is repeated at the platinum working electrode. The samples investigated were: (A) Phosphate buffer; (B) Citrate buffer; (C) Milk.⁷⁴

Fig. 12. Schematic diagram showing the microfluidic T-junction layout (A) and the optical imaging fibre bundle showing DNA hybridization in the microfluidic manifold (B)⁷⁵

Fig. 13. Raman (left) and infrared (right) spectroscopic barcodes of BCRs.⁹¹

Fig. 14. Styrene monomers used to generate a library of 630 spectroscopically encoded polymers.⁸⁷

Fig. 15. (A, left to right) RIE etching and SEM images of micropatterned silicon chips⁹⁴. (B, left to right) beads deposited in microwells and close-up view of bead in well.⁹⁴ (C) Setup for scanning sensor arrays after vapour exposure.

Fig. 16.

Raman (upper left) and FTIR (upper right) angle maps (before versus after analyte vapour exposure) and histograms of the individual Raman (lower left) and FTIR (lower right) responses (angle value) of 64 BCRs (sensors) to hexane (analyte).⁹⁵ The values in the histogram correspond to the values along the diagonal in the angle map.

Fig. 17.

(A) Electronic absorption and emission spectra of Cy3 (upper spectra) and Cy2 (lower spectra) dyes. Excitation laser lines at 532 nm (green arrow) and at 780 nm (red arrow) are shown. (B) From top to bottom are the electronic emission spectra of Ab1 and Ag1, the Raman spectra of BCR2 before and after conjugation with Ab1 (75 μg), and exposure to Ag1 (15 μg/mL). (C) From top to bottom are the Raman spectra acquired with the 780 nm laser line of BCR2 before and after conjugation with Ab1, and exposure to Ag1. (D) Optical image of a mixture of BCR1, BCR3, BCR4, and Ab1-BCR2 after exposure to Ag1. (E) Raman mapping at 500 cm⁻¹ (λ_{ex})532 nm) showing the fluorescent Ab1-BCR2 conjugates. (F) Raman classification of all the BCRs (λ_{ex}) 780 nm).⁹⁶

Fig. 18. SEM images of (A) Au nanoparticle/bead and (B) close-up showing Au nanostructures attached to the surface. (C) Cross-sectional TEM with XRD pattern of the bead crust.¹⁰²

Table 1
Overview of electronic nose and tongue sensor types

Sensor type	Signal Transduction Mechanism	Common Materials
Mass	Change in resonant frequency upon analyte adsorption	Piezoelectric crystals (quartz), thin films, microcantilevers
Electrical and Electrochemical	Electrical response from sensor sensor upon analyte adsorption (e.g. change in resistance, impedance, current, electrical potential)	Metal oxide semiconductors, conductive polymers, single walled carbon nanotubes, lipid bilayer, metal electrodes
Optical	Sensors display a shift in emission or absorption of different types of radiations (e.g. photons or electrons) upon binding with a desired analyte.	Dye-coated fibre optic polymers, microbeads, thin films, barcoded resin polymer microbeads, sol-gels