

Solution-Based Analysis of Multiple Analytes by a Sensor Array: Toward the Development of an "Electronic Tongue"

Steve Savoy,^a John J. Lavigne,^a J. Seung-Jin Yoo,^b John Wright,^a Marc Rodriguez,^a Adrian Goodey,^a
Bridget McDoniel,^a John T. McDevitt,^a Eric V. Anslyn,^a Jason B. Shear,^a Andrew Ellington,^a and Dean
P. Neikirk,^b

The University of Texas at Austin

^aDepartment of Chemistry and Biochemistry

^bDepartment of Electrical and Computer Engineering

Austin, TX 78712

ABSTRACT

A micromachined sensor array has been developed for the rapid characterization of multi-component mixtures in aqueous media. The sensor functions in a manner analogous to that of the mammalian tongue, using an array composed of individually immobilized polystyrene-polyethylene glycol composite microspheres selectively arranged in micromachined etch cavities localized on silicon wafers. Sensing occurs via colorimetric or fluorometric changes to indicator molecules that are covalently bound to amine termination sites on the polymeric microspheres. The hybrid micromachined structure has been interfaced directly to a charged-coupled-device (CCD) that is used for the simultaneous acquisition of the optical data from the individually addressable "taste bud" elements. With the miniature sensor array, acquisition of data streams composed of red, green, and blue (RGB) color patterns distinctive for the analytes in the solution are rapidly acquired. The unique combination of carefully chosen reporter molecules with water permeable microspheres allows for the simultaneous detection and quantification of a variety of analytes. The fabrication of the sensor structure and the initial colorimetric and fluorescent responses for pH, Ca⁺², Ce⁺³, and sugar are reported. Interface to microfluidic components should also be possible, producing a complete sampling/sensing system.

Keywords: Micromachined aqueous chemical sensor

1. INTRODUCTION

Recently, sensors capable of complex chemical analyses have seen increasing levels of development. A number of array-based sensors have been demonstrated for gas phase sensing; however, many of these sensors are unsuitable for solution phase analysis. In addition, there are increasing demands for sensors having biologically relevant response to materials that are solution-born. Current DNA- and antibody-based sensors are sensitive and specific, but they lack the capacity to give reliable real-time analyses due to their slow response times, and difficulty in mass production. Furthermore, many sensors capable of high sensitivity and high selectivity detection have been fashioned for single analyte detection (i.e. small molecule detection and immunological assays for toxins and pathogens), but only in a few selected cases have array sensors been prepared which display multi-analyte detection capabilities.

Here we report work that could lead to the development of such a new class of sensors. We present results on a device that allows for the simultaneous, real-time detection and quantification of multiple analytes in solution. The sensor suite consists of chemical sensors immobilized in micromachined platforms, and is therefore miniaturized and potentially inexpensive to mass produce. The array has the capacity to incorporate significant redundancies, so that "false" signals can be recognized in comparison to "real" signals. Our group has also assembled new molecular and polymeric reagents capable of binding with a number of target analyte species. These receptors have been shown to have the capacity to bind to distinct biological agents with affinities similar to those found in nature. New oligomeric receptors based upon thioureas and guanidiniums have also been developed. Incorporation of these novel function groups into peptide libraries yields enormous molecular diversity for creating chemical libraries and sensors.

2. OTHER SENSING TECHNOLOGIES

2.1 Electronic noses

As an example of the success expected from array based sensors, we first outline how the sense of smell has been mimicked allowing for the identification and quantification of complex mixtures of vapors. We fully expect that with the new

system discussed in this paper, it will be possible to create powerful sensor technologies suitable for solution phase analyses of a wide range of samples.

Array based sensors displaying the capacity to sense and identify complex vapors have been demonstrated recently using a number of distinct transduction schemes. For example, functional sensors based on Surface Acoustic Wave (SAW), tin oxide, conductive organic polymers and carbon black/polymer composite sensors have been fashioned¹⁻⁵. All these sensors display the capacity to identify and discriminate between a variety of organic vapors by virtue of small site-to-site differences in response characteristics. When these sensors are exposed to volatile compounds, some of the components adsorb onto the surface of the different elements, leading either to small changes in the electrical resistance or mass of the composite layers. It is these small differences in the behavior of the various sites that allows for a discrimination, identification and quantification of the vapors. Pattern recognition of the overall "finger print" response for the array serves as the basis for an olfaction-like detection of the analyte species. Although SAW sensors yield extremely sensitive responses to vapor, engineering challenges have prevented the creation of large arrays having multiple sensor sites; the largest SAW device reported to date possesses 12 sensor elements.

Importantly, although the individual sensor elements respond only in a slightly different manner than do the neighboring sites, the selectivity and discrimination capabilities are brought out from a comparison of the "fingerprint" signal of the entire array. What makes the system particularly powerful is the ability to "teach" the array to respond to new stimuli. For this purpose, the fingerprint signal for known and/or unknown analytes is recorded into a data base for future use in the identification of the same or similar species. This notion of a pattern is of paramount importance for the electronic nose, and is also a key feature in the development of an "electronic sense of taste."

2.2 Other polymer supported chemical/biochemical sensors

Historically, one of the most commonly employed sensing techniques has exploited colloidal polymer microspheres for latex agglutination tests (LATs) in clinical analyses. Commercially available LATs for more than 60 analytes are used routinely for the detection of infectious disease, illegal drugs, and early pregnancy tests. The vast majority of these types of sensors operate on the principle of agglutination of latex particles (polymer microspheres) which occurs when the antibody-derivatized microspheres become effectively 'cross-linked' by a foreign antigen resulting in the attachment to, or the inability to pass through a filter. The dye-doped microspheres are then detected colorimetrically upon removal of the antigen carrying solution. However, LATs lack the ability to be utilized for multiple, real time analyte detection schemes as the nature of the response intrinsically depends on a cooperative effect of the entire collection of microspheres.

New advances in localized analyte recognition have been developed by Walt and coworkers⁶. This group has covalently attached polymeric "cones," which are grown via photopolymerization, onto the distal face of fiber optic bundles. These sensor probes are designed with the goal of obtaining unique, continuous, and reproducible responses from small localized regions of dye-doped polymer. Here, the polymer serves as a solid support for 'indicator' molecules that provide information about test solutions through changes in their optical properties. These polymer supported sensors have been used for the detection of analytes such as pH, metals, and specific biological entities.

While impressive as the developments are in this area, the methods for manufacturing large numbers of reproducible sensors have yet to be developed. Moreover, no methods for acquisition of data streams in a simultaneous manner are currently available with these approaches. Optical alignment issues also appear to be problematic. The methods proposed herein possess a number of strategically important advantages related to manufacturing, sensor reproducibility, and enhanced sensitivity. Many of these advantages are brought about using the highly reproducible micromachining methods.

3. RECEPTOR DEVELOPMENT

3.1 The combinatorial library approach

Critical to the fabrication of sensor arrays is the creation of a large number of chemically diverse receptors. Many researchers in academia, government, biotechnology firms, and pharmaceutical companies are assembling teams of scientists to tackle a number of important problems using combinatorial approaches. Although combinatorial chemistry is only about twelve years old, the area has revolutionized the way new biologically relevant reagents are developed and tested.

Robust chemical receptors can be created using functional groups that are heat resistant and not amenable to degradation by natural enzymes. For instance, we have pursued the synthesis of oligomeric receptors based upon the thiourea and guanidinium chemical functional groups, as shown below⁷. The three coupling strategies used to form the respective

functional groups are completely compatible with each other. The capability to mix linking groups (amides, thioureas, and guanidiniums) as well as the side chains (hydrophobic, cationic, anionic, and hydrogen bonding) gives us the ability to create diversity in the oligomers that is greater than any diversity yet developed in the field of molecular recognition and artificial receptors. In fact, the use of these monomers affords diversity above and beyond that found with natural biological receptors.

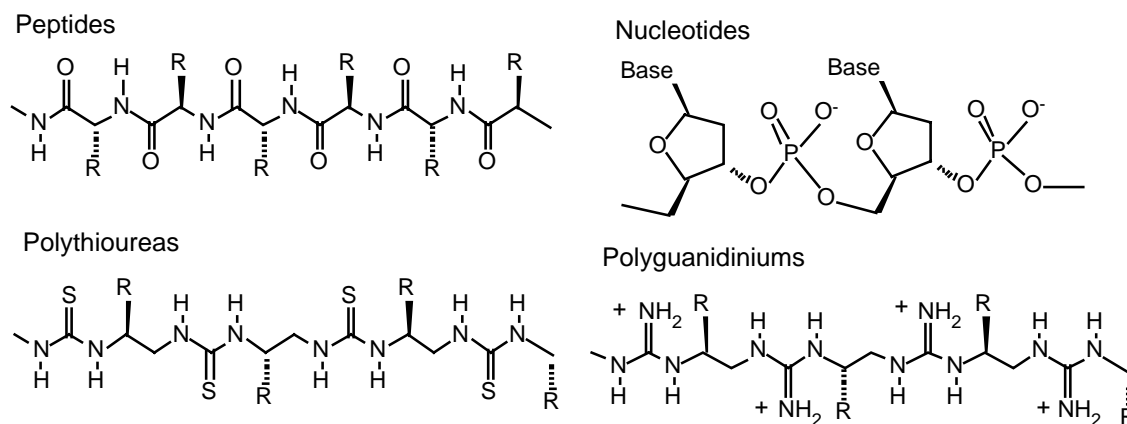


Figure 1: Alternative solid-state oligomer preparation methods using thiourea- and guanidinium-based reagents.

These linkages are readily adapted to the most common method for the development of chemical libraries, known as split synthesis, in which the compounds are assembled in a step wise manner using a bead or resin particle. The method involves the sequential addition of monomers to each bead, but the order of addition is completely random. New building blocks (monomers) are added and the process is continued until the desired library has been created. Such libraries are characterized by "one bead = one compound". Even a relatively short sequence can lead to the creation of a chemically diverse set of compounds that are localized at the surfaces of the polymer beads. For example, ten synthetic steps using the three monomers yields, 3^{10} or 59,049 different bead types. Hence, each single bead to be used in our sensing strategy will have its own distinct recognition specificity, independent and different than all its neighbors.

3.2 Signaling protocols – developing “smart dyes”

We have also shown that the microenvironment at the surface and interior of the resin beads can be conveniently monitored using spectroscopy when simple pH sensitive dyes or solvachromic dyes are imbedded in the beads. As a guest binds, the local pH and dielectric constants of the beads change, and the dyes respond in a predictable fashion. The strategy has been found to be successful for small molecules such as citrate and alkali metals. The binding of much larger analytes with larger charges and hydrophobic surfaces, such as DNA, and proteins, should induce even larger changes in local microenvironment, thus leading to large and reproducible spectral changes. This means that most any receptor can be attached to a resin bead that already has a dye attached, and that the bead becomes a sensor for the particular analyte; a “smart dye”.

Aptamers and unnatural biopolymers that are developed by our combinatorial methods can be used immediately in a sensing mode simply by attaching the receptors to a bead that is already derivatized with a dye sensitive to its microenvironment. This is an extremely powerful method for sensor development, because the signaling protocol becomes routine and does not have to be engineered each and every time, only the receptors need to be engineered. The ability to use several different dyes with the same receptor, and the ability to have more than one dye on each bead, builds a signaling protocol that is second to none in the sensing arena.

3.3 Screening

Essential to the design of receptors is the ability to bind the analyte molecules/pathogenic species. In an array setting, the receptors/sensors created from the library techniques are required to have differential responses to the analytes; none of the receptors need have a mutually exclusive response. Thus, the pattern created from the cumulative response of the various sensor sites in the array allows for the identification of the analytes. It is the overall collective response of many beads, rather than a single highly specific interaction that allows for the identification. It is this important design factor that alleviates much of the difficulty associated with the identification of the analyte receptor sites.

Our sensing platforms consist of 10 x 10 (or larger) array of beads. While the number of beads is significantly less than that originally present in the unscreened library, the number of utilized beads is indeed significantly larger than that used in most current (i.e. single analyte) sensor systems. However, because the number is smaller than the number of beads that result from a combinatorial chemistry procedure, it will be useful to screen in an intelligent manner the libraries so as to isolate the strategically important beads (i.e. those that yield significant responses to the analytes of interest). As mentioned above, it will not be necessary to develop highly specific binding sites as is normally done in most combinatorial methods, but rather target binding sites which display only moderate selectivity. For example, the *in vitro* selection screen relies upon affinity chromatography and repeated cycles of selection/amplification. We will not need to winnow down the populations to a select few, but instead to a few hundred to fill our arrays. This feature greatly simplifies the process compared to conventional *in vitro* selection. Similarly, with the unnatural biopolymer work, the screening only needs to identify a few hundred compounds with differential responses to the targeted analytes.

Similarly, we do not have to isolate the receptors that are specific and have the highest affinities to the targeted analytes since due to the screening procedure the highly specific aptamers and unnatural biopolymer receptors will automatically be in the pool of sensors used. Importantly, so will several other receptors with less specific and lower affinities. This feature leads to another advantage to our proposed method; the array can be taught to recognize new analytes that the libraries have not been screened against. Since we do not winnow the libraries down to a few specific receptors, but instead use a hundred or more selective and differential receptors, it is assured that several of these receptors will also have some affinity for new analytes similar to those used in the original screen that generated the library. In other words, a new analyte of a family similar to that used in the original screen should still be detectable. The standard methods that create highly specific receptors would miss these new analytes.

4. TECHNICAL APPROACH

4.1 The sense of taste

The mammalian sense of taste occurs as a result of complex chemical analyses which are completed in parallel fashion at a series of chemical active sites called "taste buds". The taste buds are located within a depression in the tongue where the molecular and ionic reagents become restricted to allow time for their identification^{8, 9}. Here, the four primary tastes are sensed: sweet (carbohydrate based molecules), sour (acidic concentration), salty (sodium chloride), and bitter (quinine and other basic functionalities). Likewise, it is the magnitude of these four signals that creates a pattern distinctive for each food.

One of the most important aspects of a mammals sense of taste, as well as sense of smell, is the combination of specific and nonspecific receptors sites. In the sense of smell, there are receptors that have evolved to be quite specific, for example, those targeted to pheromones. However, the sense of smell and taste also respond to completely new analytes for which there was no evolutionary pressure to develop a receptor. Although the identification of new tastants/odorants is rooted in molecular recognition events, in nature these species are assayed with nonspecific receptors. The pattern and the intensity of signals created by the array of nonspecific sensors is deconvoluted by the brain, remembered, and recognized later as a specific tastant or odorant. A successful sensor arrays should have the same ability to be exposed to new analytes and "learn" what the patterns represent, store them, and recall them for future reference.

4.2 Micromachined sensor platform

Our solution-phase multi-analyte sensor array has been inspired by the mammalian tongue. In our artificial tongue, synthetic beads which possess receptors on their surfaces serve the role of "taste buds". For the taste pores, micro-machined substrates are used to localize these beads as well as to serve as a microenvironment into which the chemical assays can be completed. A high sensitivity CCD array is exploited to measure changes in optical characteristics which occur upon binding of the biological/chemical agents. Finally, pattern recognition algorithms completed on a computer platform serve as the intelligence factor for the analysis. Like the human tongue, the "fingerprint" response evoked from the simultaneous interactions occurring at multiple sites will be used to identify the species present in unknown samples.

Shown in Figure 2 are schematic diagrams which detail the features of our array sensors. (A) First, illustrated are the important electrical components that allow for acquisition of the optical signal. A blue light emitting diode (LED) is shown here as is used for systems relying on changes in fluorescence signals. For colorimetric (i.e. absorbance) based systems, a white light is used in place of the high energy excitation source. For fluorescence measurements, filtering agent is exploited to remove the excitation wavelength. A charge-coupled device (CCD) positioned below the micromachined stage allows for data acquisition. (B) Second, top and side perspective views showing the bead array are provided. Here, micromachined pits in a Si wafer act to spatially confine the individual beads to their respective locations. The etch process is controlled so that it

is terminated at a transparent membrane which is located at the bottom of the well. Light modulated by the bead passes through the bottom opening and onto the CCD detector. Fluid delivery for both sample and reference samples can be provided. Evaluation of the optical changes is completed using the described CCD detector and associated computer readout system.

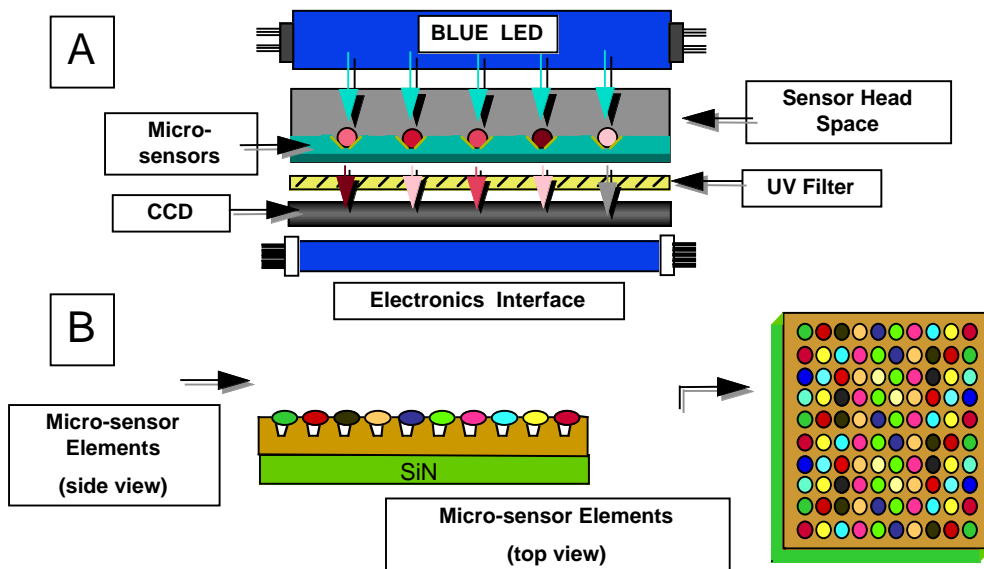


Figure 2: An overview of the proposed sensor array. See text for description of the system.

One of the critical issues for the practical application of microelectronic fabrication techniques to microsensors is the scale limitation (in all three dimensions) for both minimum and maximum feature sizes. For the chemical agent sensor arrays discussed here, the need for structures with significant size in the third dimension is acute. The beads used for synthesis are typically 50 - 100 microns in diameter, and change size (e.g., swell or shrink) when the chemical environment changes. Unlike prior fiber optic analysis of remotely acquired optical information, (i.e. fluorescence and reflected light) which require elaborate optical filtration schemes, direct determination of changes in the absorption and emission properties provides the ability to make parallel analyses for analyte determination and quantification.

To analyze these changes we are fabricating "micro test-tubes" using a combination of bulk and surface micromachining to provide the necessary confinement of our sensing beads. As illustrated in Figure 3, a conventional bulk micromachining step is used to form a pyramidal pit in a silicon substrate, sized to allow a sensing bead to rest inside it, and a transparent cover plate placed on top to keep the bead in place. Illumination can then be applied to one side, while a photodetector is placed on the other. To hold the sensing beads in place, monolithically fabricated transparent "sliders" can also be fabricated, as well as color filters to aid in colorimetric/fluorometric detection. Figure 4 shows a 5 x 6 bead sensor array, and a scanning electron microscope image of a single dry bead in a micromachined storage well.

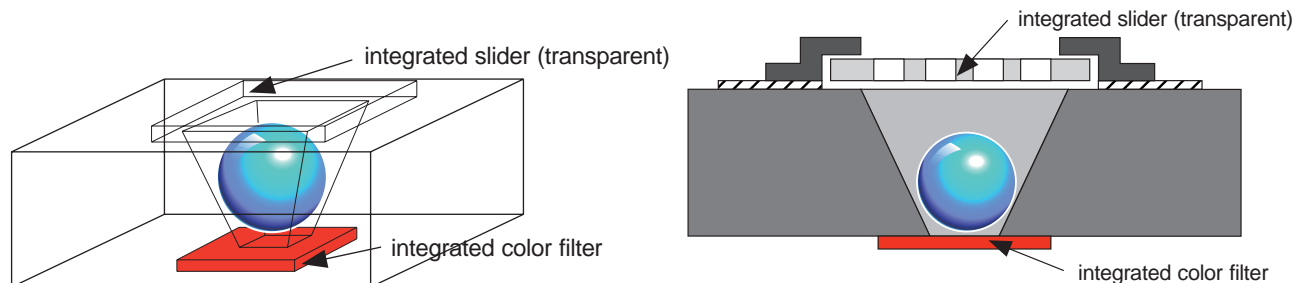


Figure 3: Illustration of microbead storage well with micromachined sliding cover plate and integrated optical filter.

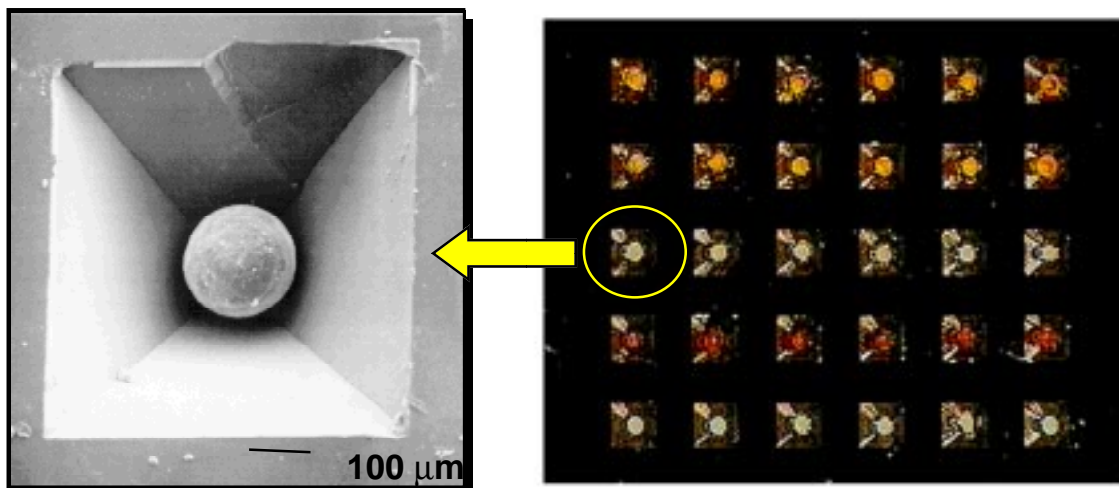


Figure 4: Shown here is an electron micrograph of a functional sensor, which in this case can be used to assay for Ca^{2+} ions.

The fabrication of micromachined “test-tubes” allows us to immobilize the sensing beads, and to provide optical access, proper illumination, wavelength filtering, and optical detection. In our current sensor we use simple optics to image the micromachined bead array directly onto a commercially available charge coupled device (CCD) array. This hybrid assembly is relatively simple, while allowing separate optimization of the analyte sensing and photodetection sections of the system. The colorimetric data can be collected using a color CCD, with each well illuminating many RGB pixels in the CCD, as has been done in our preliminary demonstrations. It is also possible to integrate color filters into the storage wells allowing the use of mono-chrome CCDs. In this approach multiple wells would each be loaded with an identical sensing bead, but each well would have a different integrated optical filter. The data streams from the multiple wells would then yield the desired colorimetric analysis. Here it will be necessary to carefully consider the various performance trade-offs between monolithic and hybrid assemblies. Figure 5 shows our strategy to interface to microfluidic components, producing a complete sampling/sensing system.

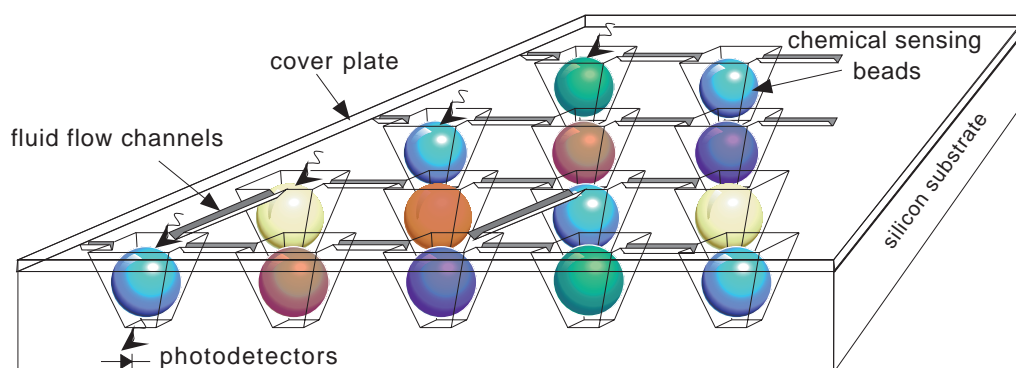


Figure 5: Illustration of a micromachined bead array combined with fluid flow channels for analyte analysis. By selecting appropriate flow channel routing and incorporating micro-valves, a reconfigurable sensing array would be possible.

Recent advances in the development of efficient and inexpensive charge-coupled devices (CCD) made the choice of such array detectors for optical sensing applications quite appropriate. Indeed, the commercialization of a number of products which use CCD as the active optical sensors: video cameras, laser printers, electronic cameras and a variety of scientific instruments, bodes well for their use in our field applications. Furthermore, CCD detectors have begun to transform the field of optical spectroscopy and optical imaging applications¹⁰. These systems have been produced with excellent spatial resolution, ultra-high sensitivity and large dynamic ranges. For example, CCDs have the capacity to detect gray scales of one

part in 256,000, compared with one part in 256 for the human eye, while the high sensitivity characteristics of scientific CCD's have allowed researchers to study the fluorescence behavior of single molecules.

In the context of our application, commercially available CCD arrays are interfaced with filters, light sources, fluid delivery and micromachined bead receptacles, so as to create a functional sensor array. Data acquisition and handling issues are largely completed with the existing CCD technology. Data streams (red, green, and blue for colorimetric assays and gray intensity for fluorescence assays) will be transferred from the CCD to a computer via a data acquisition board. Current CCD's allow for read-out rates of 10^5 pixels per second. Thus, the entire array of beads can be evaluated hundreds of times per second allowing for studies of the dynamics of the various host-guest interaction rates as well as the analyte/polymer diffusional characteristics. Evaluation of the transient data allows for an alternative way to identify and quantify the chemical/biological composition of the test samples.

4.3 Proof of principle for the "electronic tongue"

To demonstrate the capabilities of the sensor arrays, a number of examples are discussed here. For example, when *o*-cresolphthalein is attached to a bead, the dye serves a dual role of binding site as well as reporter molecule. It should be noted that in most cases separate reagents will be attached to the beads to serve the two distinct roles. This particular dye shows a characteristic purple color when Ca^{2+} is present in solutions of high pH (Figure 6), exhibiting a characteristic strong absorption at green wavelengths (absorbance max. at ~ 550 nm). When immobilized on a PS-PEG resin bead, the reversible response to Ca^{2+} occurs in seconds. Shown in Figure 6 is the magnitude of the optical signal transmitted through a single polymer bead derivatized with *o*-cresolphthalein^{11, 12}. Data is provided for the bead as the pH is cycled between acid and basic environments. In the acid media, the bead is clear and the system yields large signals at the optical detector. On the other hand, upon raising the pH the bead turns purple in color and the transmitted green light is greatly diminished. Large signal reductions are recorded under such circumstances. The evolution of the signal changes show that the response time is quite rapid, on the order of 10 seconds (Figure 7). Furthermore, the behavior is highly reproducible. Collectively, these results demonstrate the capacity of a CCD detector to complete in a simple and efficient manner color analyses which are indicative and which can be traced back to modifications in chemical environments.

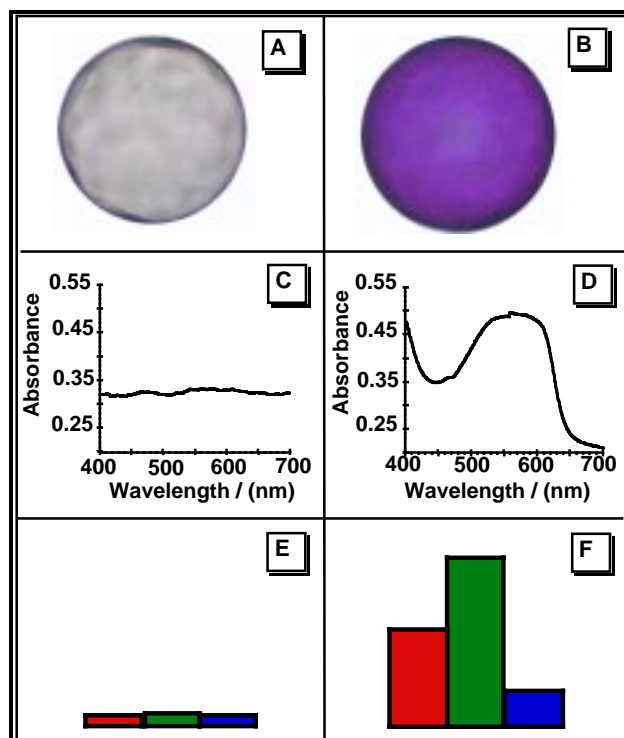


Figure 6: Optical images of an *o*-cresolphthalein complexed derivatized microsphere ($130 \mu\text{m}$ diameter) with (A) no Ca^{+2} present and (B) 0.1 M Ca^{+2} present. The absorbance spectra recorded for the *o*-cresolphthalein complexed derivatized microspheres with (C) no Ca^{+2} and (D) 0.1 M Ca^{+2} present are also shown using aqueous solution as background. The final two panels show the RGB color attenuation values for *o*-cresolphthalein complexed derivatized microspheres with (E) no Ca^{+2} present and (F) 0.1 M Ca^{+2} present.

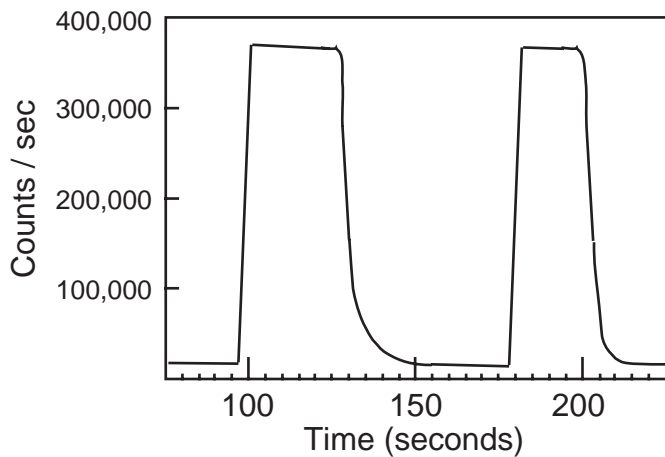
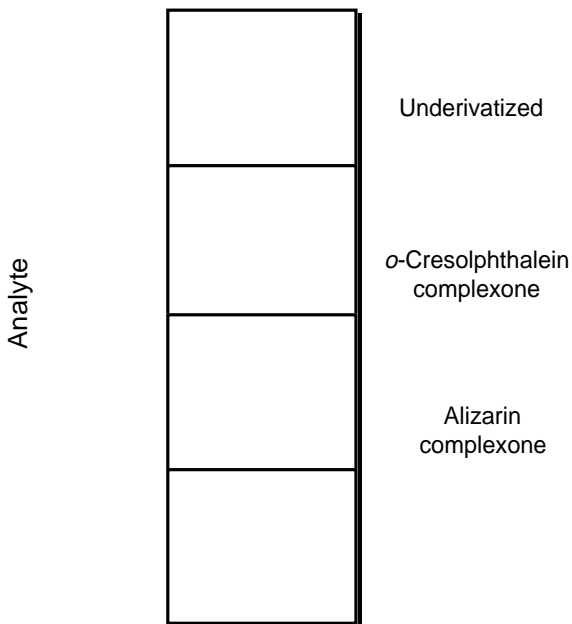


Figure 7: Optical signals recorded for green light transmitted through a single o-cresolphthalein derivatized bead are shown. Here the solution pH is cycled between acid and basic environments with concomitant change in the transmitted light intensity. The data here shows that large and reproducible signals can be acquired with the bead detector system. Moreover, rapid response times are noted for the structure.

Perhaps the most powerful attribute of the described electronic tongue sensor array is the capacity to simultaneously analyze the chemical composition of complex mixtures of analytes. Figure 8 shows the composite changes to different analytes for four different environments including no analyte, Ca^{+2} , Ce^{+3} , a mixture of Ca^{+2} and Ce^{+3} for microspheres tagged with: (A) underivatized, (B) o-cresolphthalein complexone, (C) alizarin complexone, and (D) fluorescein, at five representative pHs (3,5,7,9,11). The patterns are found to be distinctive for the different mixes of analytes. The corresponding RGB signatures are shown in Figure 9.



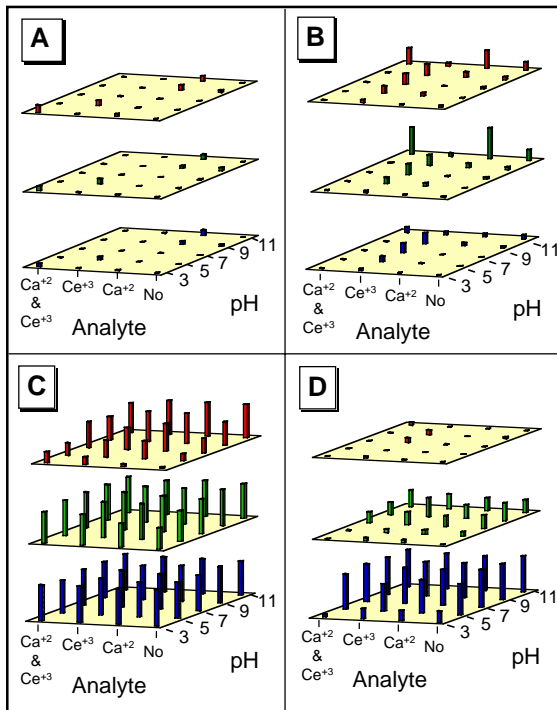


Figure 9: RGB color intensities analyses for four unique chemical sensor microspheres including (A) underivatized (acetylated), (B) fluorescein isothiocyanate, (C) alizarin complexone and (D) *o*-cresolphthalein complexone for environments of no analyte, Ca^{+2} only, Ce^{+3} only, and a mixture of Ca^{+2} and Ce^{+3} . All microsphere sensors were analyzed at 5 different pH's of 3, 5, 7, 9, 11. The height of each bar represents the relative absorbance for each indicator molecule. These data show the capacity of the array technology to evaluate complex mixtures of analyte species.

Optical photo-micrographs of a simple test bed are shown in Figure 10. Light originating from the bottom side of the silicon wafer passes through the colored bead and provides the illumination source to visualize the bead structure. The etched substrate and bead combination provide an assembly whose optical properties are well matched for spectral analyses. Here shown is only a small portion of the larger array. Some etch pit are purposely left empty to serve as reference channels.

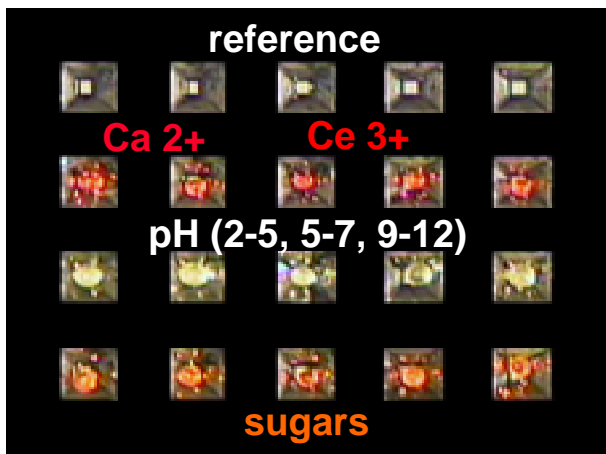


Figure 10: Photomicrographs of polymer beads localized into the micromachined cavities. Shown here is a 5 by 4 region of the array which is loaded with a variety of fluorescent beads. The complete array in this case is 10 by 10.

5. CONCLUSIONS

In summary, we have demonstrated that a combination of novel photochemical sensing schemes, micromachining methods, and molecular engineering of receptor sites has resulted in the development of a new type of array which functions as an "electronic tongue". Already demonstrated has been the functionality of a test bed array in which simple receptor sites have been utilized. Basic data acquisition methods, sensor fabrication techniques, rapid response time characteristics, and reversible binding of analyte species have all been demonstrated in the context of this new type of sensor. Further increase in the power and diversity of the electronic tongues will occur following the optimization of the receptors for analytes and pathogens using powerful combinatorial library approaches along with refinement of the microencapsulation, microfluidic delivery system, and electronic component integration. The success of such systems, however, will depend on the application of more sophisticated pattern learning and recognition protocols.

6. ACKNOWLEDGEMENTS

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