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Biosensing using surface electromagnetic waves in photonic band gap multilayers

Adam Farmer[a], Andrienne C. Friedli[b], Stephen M. Wright[c], William M. Robertson[a,*]

[a] Department of Physics and Astronomy, Middle Tennessee State University, Murfreesboro, TN 37132, USA
[b] Department of Chemistry, Middle Tennessee State University, Murfreesboro, TN 37132, USA
[c] Biology Department, Middle Tennessee State University, Murfreesboro, TN 37132, USA

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ABSTRACT

A biosensor based on the excitation of surface electromagnetic waves in photonic band gap multilayer films is demonstrated. The operating principle of this device is similar to surface plasmon biosensors with the key difference that a photonic band gap film replaces the metal film as the medium in which surface electromagnetic waves are excited. The use of photonic band gap films offers a number of advantages. First, the surface wave resonance is much sharper leading to the potential of greatly enhanced sensitivity. Second, the properties of the photonic band gap material can be engineered to make a sensor that operates at any wavelength. The experiments reported here are conducted with a surface wave resonance at 470 nm, a wavelength not generally accessible with surface plasmon sensing. Finally, the photonic band gap films are more mechanically robust than metal films and they offer new substrates for surface chemistry. The paper describes the design of the photonic band gap films, the surface chemistry and biology to create sensing chips, and the spectroscopic experimental configuration used to observe and track the surface mode resonance. Experimental results are presented on refractive index sensing, antibody–antigen reactions, and DNA binding.

1. Introduction

This paper describes the design, implementation, and testing of a spectroscopic optical biosensor based on surface electromagnetic waves (also known as Bloch surface waves or surface optical waves) in photonic band gap (PBG) films. The sensor belongs to the class of affinity binding sensors which function by detecting the mass loading at a surface due to the formation of thin overlayers typically as a result of antibody–antigen or DNA-probe reactions. The operating principle of this sensor is similar to that of surface plasmon sensors that have a long and commercially successful history [1–4]. The key difference is that the active sensing material consists of a photonic band gap (PBG) multilayer in place of the metal film used in conventional surface plasmon sensors. This substitution offers a number of significant advantages. First, the wavelength of operation and the sensitivity of the surface mode resonance to overlayers can be engineered by a suitable design of the PBG material. Second the surface optical wave resonance in PBG films is roughly two orders of magnitude sharper than coupling to surface plasmons in metal films. In general terms sharp resonances translate to enhanced sensitivity, although the full relationship is complex [4,5]. Finally, the PBG films are mechanically and chemically more robust than the metal films (typically gold or silver) used in surface plasmon sensors, offering the possibility of new sensing chemistries and the possibility to use this sensing method in harsh environments. A number of works have already explored aspects of the use of surface electromagnetic waves in PBG's for gas sensing [6], for near-field imaging [7], and for biological sensing via surface wave enhanced diffraction [8–11].

Surface electromagnetic waves in PBGs and surface plasmons in metal films are both non-radiative modes meaning that they cannot couple directly to light in vacuum because of phase matching restrictions [1,12]. In each case coupling of light to the surface modes can be accomplished using an evanescent-wave prism arrangement that effectively increases the parallel wave vector of the incident light [13]. In previous work on surface electromagnetic wave coupling in PBG multilayer films [14–16], a single wavelength laser source was used and the angle of incidence of the light into the prism was varied using computer-controlled precision rotation stages. Coupling of incident light into surface electromagnetic waves was indicated by a sharp drop in reflectivity at the phase matching angle. In the work described here, we use a collimated broad bandwidth optical source incident at a fixed angle of incidence and a compact spectroscopic detection method that eliminates the need for any moving parts.

In order to sense particular targeted chemical or biological targets, the PBG multilayer is coated with a sensing layer. The sensing layer is designed to interact with a specific entity leading either to a mass loading and/or to an index change in the sensing layer. This change in surface conditions results in a change in the optical

* Corresponding author.
E-mail address: William.Robertson@mtsu.edu (W.M. Robertson).

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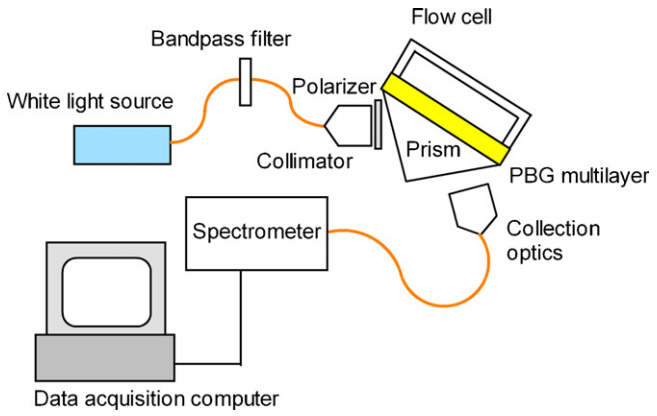

Fig. 1. Schematic diagram of the experimental configuration. A 30 nm band of light centered at 470 nm is collimated and incident at an angle of about 67°. The reflected light is collected and fed to a compact fiber-coupled spectrometer.

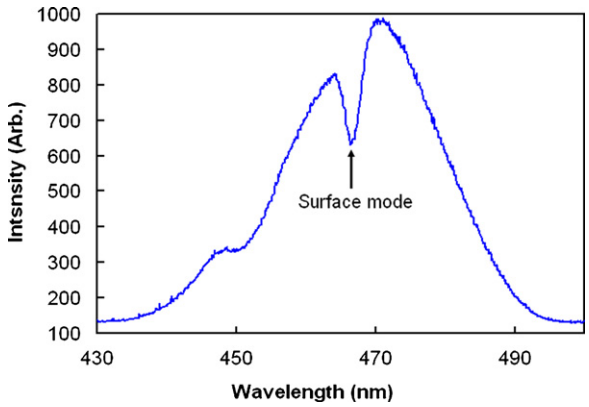

Fig. 2. The spectrum of the reflected light shows an intensity drop at 467 nm indicating light lost due to coupling to a surface optical mode.

coupling to the surface electromagnetic waves in the underlying multilayer. Detecting a change in coupling conditions due to a surface interaction in the sensing layer is the basis of sensor action. The form of the sensing layer can have many variations. In a simple gas sensor the sensing layer consists of a thin terminating material that reacts when exposed to a specific chemical species to create a layer with altered optical characteristics; for example, the optical properties of Teflon AF 1600 are affected by exposure to organic vapors such as methyl ethyl ketone or acetone [17]. For the detection of biological entities such as proteins (antibody–antigen) or DNA (DNA–DNA or DNA-probe), the sensing layer consists of an attachment layer onto which a probe for a specific species can be anchored. Examples of attachment layers are amine-terminated groups in the case of proteins or aldehyde-terminated groups in the case of DNA.

To demonstrate the use of PBG multilayers as surface electromagnetic wave sensors the results of three experiments are presented: (i) sensitivity of the surface mode to bulk refractive index changes using various water–ethanol mixtures, (ii) BSA protein-antibody binding, and (iii) DNA-probe binding.

2. Experimental configuration

2.1. Optical system

The experimental configuration used in the work described here is shown in Fig. 1. The output of a tungsten white light source (Ocean Optics HL2000) was coupled into a multimode fiber (62.5 μm core) and directed to a variable bandpass filter (Ocean Optics LVF-HL). The variable filter was adjusted to pass a 30 nm band of wavelengths centered around 470 nm approximating the output of a blue light emitting diode. The filtered light was guided by a 125 μm core optical fiber to a collimator. The parallel light beam was passed through a polarizer oriented so as to make the light incident on the PBG multilayer s-polarized. The collimated light was incident at an angle of 67°—above the angle for total-internal-reflection between the prism and water in the flow cell.

Fig. 1 shows a detailed view of the prism, PBG multilayer, and the flow cell. The PBG multilayer was deposited onto a glass slide by a commercial thin film fabrication company. Details of the design of the multilayer are provided in a subsequent section. The glass slide is optically attached to the prism using ethylene glycol as an index-matching fluid. A flow cell is formed from a neoprene gasket that is pressed against the multilayer-coated side of the glass slide by a machined Plexiglas holder. The holder has input and output connectors to facilitate the injection of fluids through the flow cell.

In the experiments described here, the coupling of light to surface electromagnetic waves is indicated by a drop in the reflectivity of a particular wavelength from within the incident band of wavelengths. The collimator ensures that all of the light is incident at a well-defined angle of incidence. Only one specific wavelength satisfies the phase matching condition that allows coupling to the surface electromagnetic waves. This narrow wavelength band generates surface electromagnetic waves at the multilayer-flow cell interface and is thus missing from the reflected light. A lens collects the light reflected from the prism and focuses it into a 500-μm diameter fiber optic cable that is fed to the input of a compact high-resolution spectrometer (Ocean Optics HR2000). Fig. 2 shows a spectrum of the light reflected from the prism coupled multilayer system for s-polarized incident light. The coupling to the surface mode is clearly evident in the s-polarized spectrum by the drop in the reflected light at 467 nm.

In a sensing experiment an affinity binding reaction takes place at the multilayer-water interface. The dielectric loading caused by the specific binding event at the surface alters the conditions for surface optical wave resonance such that a different wavelength is coupled to the surface optical waves. The progress of a binding reaction is monitored by the shift in the wavelength of the reflectivity minimum.

2.2. Multilayer design

A central element of the sensor described here is an optical multilayer structure that supports the generation of surface electromagnetic waves. The multilayer is deposited on an optically transparent substrate (a glass microscope slide in the experiments described here). The multilayer consists of alternating layers of high refractive index and low refractive index materials (specifically TiO_2 and SiO_2 respectively). For the experiments described here, the multilayers were fabricated from our design by a commercial thin film fabrication facility.

The layer thickness values are selected so that the multilayer structure exhibits a photonic band gap at the operation wavelength and at the angle of incidence of light on the sensor slide. Although there are other layer parameters that can result in a photonic band gap, the most straightforward is to select thickness values, d_i, for the ith layer based on the relation

$$d_i = \frac{\lambda}{4n_i \cos\theta_i} \quad (1)$$

where λ is the center wavelength of operation of the sensor, and n_i and θ_i are respectively the refractive index and the angle of propagation of the light in the ith layer.

The terminating layer of the multilayer is used to adjust the position of the surface electromagnetic wave mode within the photonic band gap. The terminating layer, which can be either a high or low refractive index layer, does not typically have the same thickness as the other layers of its type in the multilayer. The thickness required to set the mode at any position within the gap depends on the parameters of the multilayer (refractive indices and number of pairs of high and low index layers); however, the optical response of the multilayer can be accurately calculated using Fresnel's equations. Locating the mode close to the center of the photonic band gap leads to a surface electromagnetic wave mode that is strongly confined to the surface. For the experiments described here, the multilayer consisted of 4 bilayers (TiO_2/SiO_2) with the first 3 bilayers having alternating thicknesses of 108.9 nm/170.5 nm. The final two layers had thicknesses of 108.9 nm/290 nm.

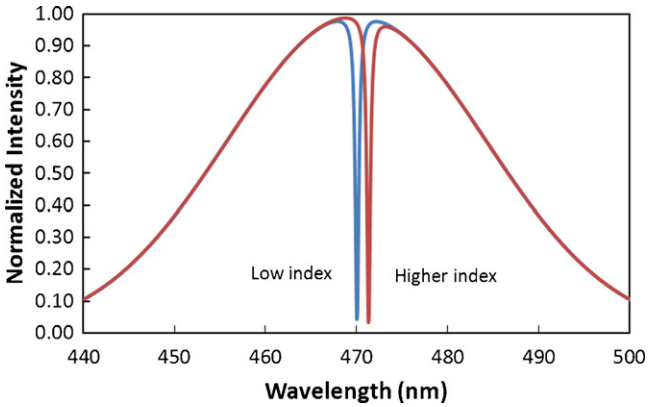

Fig. 3. Theoretical calculation of wavelength shift of the surface mode with a refractive index chance of $\Delta n = 0.001$. The mode shifts to longer wavelengths with increasing refractive index.

2.3. Interfacial binding layer preparation

The surface mode shifts when species are physisorbed or chemisorbed at the air/surface interface. Since SiO_2 and TiO_2 surfaces are relatively unreactive, an interfacial layer is required to chemically bind biological or chemical recognition elements to the multilayer surface. For the affinity binding examples discussed here, we chose to use organosilane coupling agents [18] to form organosiloxane thin interfacial films.

Organosiloxane film formation. Organosilane precursors 3-aminopropyl triethoxysilane (APTES), 3-aminopropyl trimethoxysilane (APTMS) and 11-triethoxysilyl undecanal (TESU) were purchased from Gelest, Inc. and distilled immediately before use. Anhydrous toluene was purchased from Sigma–Aldrich and used as received. All water used in film preparation was ultrapure (17 MΩ). Glassware was base-washed, rinsed with water, and dried in an oven before use. Silicon wafers (2″, 011, Wafer World) were cleaved into quarters and used to determine optimum film formation conditions using ellipsometry (J. A. Woollam, Inc. M-44 Spectroscopic Ellipsometer) or water contact angle goniometry (Ramé-Hart 100 Goniometer) measurements. PBG multilayers were prepared by chemical vapor deposition (Thin Films Labs). To remove any surface contaminants, substrates were thoroughly cleaned using a modified literature procedure [19]: ozone treatment (Jelight UV-O Ozone Cleaner) for 2 min, followed by 30 min in 1:1 methanol:HCl solution, rinsed with water, immersed in H_2SO_4 for 30 min, thoroughly rinsed, and dried in a stream of nitrogen. The clean substrates were transferred to a glove box and immersed in a 0.1–1% (by volume) solution of silane precursor in anhydrous toluene. The optimum immersion times and silane concentrations required for monolayer films from each precursor were determined from a plot of ellipsometric thickness or contact angle vs. immersion time. After immersion, the coated substrates were rinsed twice in anhydrous toluene, dried in a stream of nitrogen, and baked on a hotplate at 110 °C for 10 min, and stored in Fluoroware® containers until used. Advancing and receding water contact angles (θ_{adv} and θ_{rec}) in films tend to plateau once they reach monolayer thickness, whereas ellipsometric thicknesses continue to increase. Dilute solutions formed more controlled monolayers – a 0.3% solution of APTES formed a monolayer in 150 min with a thickness of 7 ± 2 Å and $\theta_{adv} = 55 \pm 5°$; $\theta_{rec} = 50 \pm 5°$ whereas a 1% solution of APTES formed a monolayer in 15 min with a thickness of 8 ± 2 Å and $\theta_{adv} = 41 \pm 6°$; $\theta_{rec} = 35 \pm 7°$ The film properties are consistent with literature [20] and similar to those of APTMS, except that films form faster with the APTES precursor. A 1% solution of long-chain aldehyde TESU formed a monolayer in 4 h with a thickness of 16 ± 2 Å and $\theta_{adv} = 69 \pm 3°$; $\theta_{rec} = 64 \pm 1°$. Monolayer films from 1% APTES or 1% APTMS solutions were deposited on PBG slides for 15 min for surface binding to BSA protein and DNA binding experiments were accomplished with monolayers from 1% APTMS or 1% TESU on PBG substrates.

3. Results and discussion

3.1. Refractive index sensing

Although the ultimate purpose of the sensor was to detect affinity binding of biological entities, we performed an initial test of the sensitivity of the device to small changes in refractive index using water/ethanol mixtures. The change in refractive index leads to a change in the optical conditions that results in a shift in the wavelength of the surface mode coupling. This process can be modeled accurately using Fresnel's equations [14,16]. Fig. 3 shows a numerically calculated plot of the surface mode coupling for pure water ($n = 1.334$) and for a water-ethanol mix ($n = 1.335$). There are two notable features that can be taken from this plot. First, the shift in mode position is towards longer wavelength with increasing index and the value of the theoretical shift is 0.6 nm for an index change of 0.001 implying a sensitivity to refractive index of 600 nm/RIU. Second, the theoretically calculated mode is clearly much narrower and deeper than the mode measured experimentally (see Fig. 2 for a typical experimental spectrum). This difference is a result of the optical limitation on realizing collimated light from a broadband source. The relatively large core fiber used to relay light from the optical source means that there is a spread of angles in the light exiting from the collimator and a concomitant broadening in the wavelength spread of the mode coupling angle. The mode coupling angle can be made narrower through the use of a smaller core fiber but at the loss of light intensity coupled into the fiber. We compromised on a relatively large fiber core because it did not in any way limit the resolution of the biological affinity binding events that we were investigating.

Experimental results of the wavelength shift of the mode position with the addition of small amounts of ethanol to pure water are shown in Fig. 4. As expected theoretically, the mode shifts to successively longer wavelengths as the index of the solution increases. The volume of the flow cell was 11 ml and the traces in the figure with mode minima moving from left to right are pure water, 0.2 ml, 0.3 ml, and 0.4 ml of ethanol added respectively. The index of ethanol/water mixtures in this ratio were measured independently using an Otago hand held refractometer which gave refractive indices of 1.3329, 1.3347, 1.3356, and 1.3368 for water and the three ethanol–water mixtures respectively. Fig. 5 plots the theoretical wavelength shift of the multilayer as a function of refractive index (solid line) calculated using Fresnesl's equations. Superimposed on the theoretical plot are the four experimental

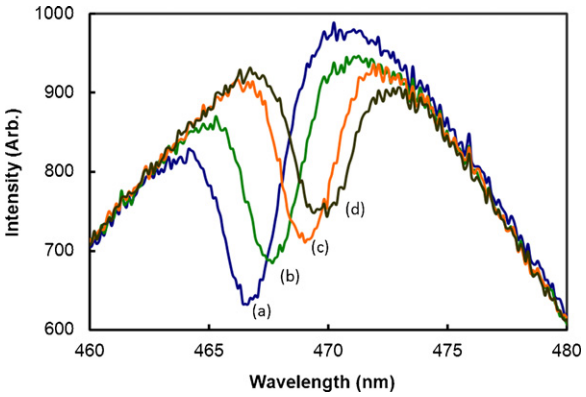

Fig. 4. Shift of surface electromagnetic mode resonance as ethanol is added to water. (a) Pure water, (b) 0.2 ml ethanol, (c) 0.3 ml ethanol and (d) 0.4 ml ethanol.

ethanol–water measurements (squares). Our measured sensitivity of 600 nm/RIU cannot be compared directly to surface plasmon sensitivity because there are no results, to our knowledge, for surface plasmons at our wavelength range of 470 nm. The accepted values for gold are 970 nm/RIU at 630 nm and 13,800 nm/RIU at 850 nm [21]. The high surface plasmon sensitivity, and its large change from the infrared to the visible, is due to the strong dispersion in the complex optical constants of gold over this wavelength range. In contrast, the properties of SiO_2 and TiO_2 vary slowly over the optical spectrum leading to a generally smaller shift but one that is more consistent in magnitude over the visible and infrared.

3.2. Protein-antibody binding

The protein binding experiment involved the reaction of Bovine Serum Albumin (BSA) with an antibody to BSA. In order to attach the BSA protein to the multilayer slide, the outermost glass layer of the multilayer was first functionalized with either an amine or aldehyde coating. This process is a standard approach to attaching biomolecules for use in array studies [22]. A volume of 10 μl of BSA at 100 μg/ml (ArrayIt Micro Spotting Solution) was hand-applied using a pipette. The slide was dried, heated to 95 °C for 30 min, fixed with UV (6500 μJ/cm^2) and washed to remove excess salts. The slide was also exposed to a protein solution to block any remaining binding sites on the slide (ArrayIt Blockit Blocking Buffer). The prepared slide was assembled in the flow cell and filled with water.

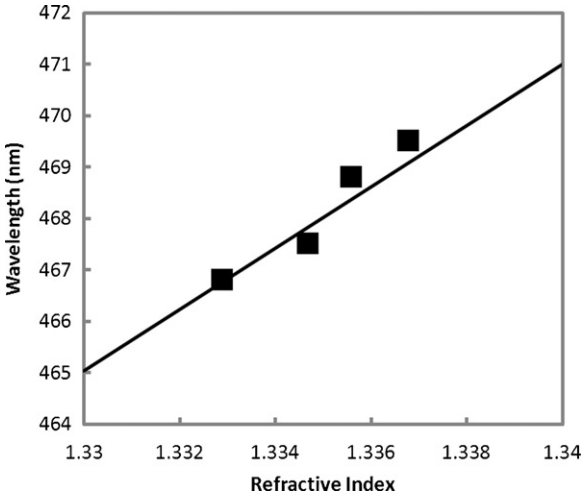

Fig. 5. Theory plot of wavelength shift vs. index change of solution (solid line) indicating a sensitivity of 600 nm/RIU. The four points on the plot correspond to the experimental wavelength shift with index shown in Fig. 4.

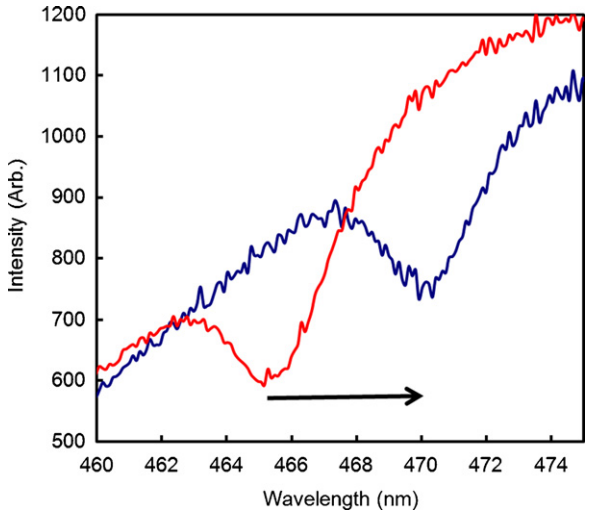

Fig. 6. Mode shift to longer wavelength due to BSA anti-BSA binding.

The linear filter was set with its peak at around 470 nm, the angle of incidence was varied until a good surface mode was obtained, and a baseline spectrum recorded. After this baseline spectrum was established, the angle of incidence was not varied at any time during the remainder of the experiment. To observe the affinity binding reaction, 5 ml of anti-BSA antibody diluted to 50 μg/ml in water (Bethyl Laboratories) was injected into the flow cell. Spectra were recorded just after injection and at 5 min intervals for 45 min to permit real time tracking of the antibody–antigen reaction. After the 45 min had elapsed, the flow cell was washed with 50 ml of water to remove any unbound antibody and a final spectrum recorded. Comparison of the initial and final mode positions permitted the determination of whether binding had occurred free from any shifts that might be due to differences in the refractive index of the solutions. As shown in Fig. 6, the shift in mode position due to antibody-antigen binding in this case was about 5 nm.

3.3. DNA binding

The DNA binding experiment was performed using a DNA probe (Integrated DNA Technologies) for a conserved region of the Non Structural gene from influenza virus. The target DNA in these experiments was obtained from *Escherichia coli* that had been transformed with a pGEM-T plasmid containing the reverse transcribed NS gene from influenza MAL/NY/6750/78, (890 base pairs in length). DNA was extracted from the *E. coli* and then amplified to useable levels via Polymerase Chain Reaction.

The experiment proceeded in a fashion similar to the protein reaction described previously. The probe was attached to the functionalized multilayer slide, dried, heated, fixed, washed, and blocked. The slide was assembled in the flow cell. The surface mode was located and baseline spectrum recorded. The DNA, in water, was first heated to 95 °C before being injected into the flow cell to ensure that the DNA was single stranded and therefore available to react with the covalently bound probe. Upon injection the progress of the reaction was monitored as a function of time. Finally, the flow cell was flushed with water and the baseline spectrum was recorded. By comparing the initial and final spectra, the shift due to DNA binding was established as indicated by the results shown in Fig. 7.

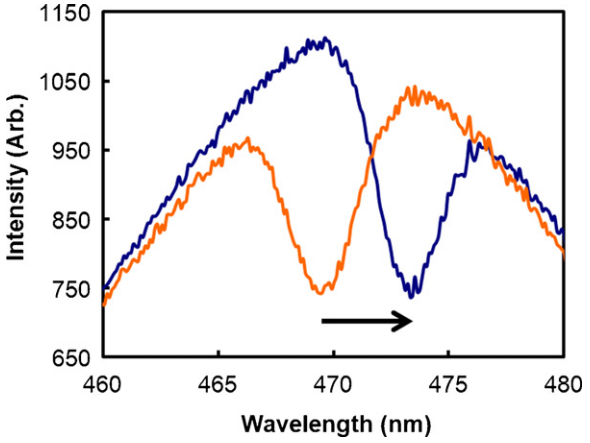

Fig. 7. Surface mode position before (left minimum) and after (right minimum) DNA probe binding.

4. Conclusion

This work demonstrates the feasibility of sensing affinity-binding reactions using the surface electromagnetic wave excitation in multilayer films that exhibit a photonic band gap. The surface wave resonance in these systems is considerably narrower than surface plasmon resonance in metal films whereas the shift with dielectric loading is comparable. This fact means that this system is capable of high sensitivity. In addition, the films are mechanically robust, and the surface functionalization options leading to selective biosensors are plentiful. Many examples of sensing layers have been developed for surface plasmon sensors. Some of these systems are specifically for the metal substrates (usually gold); however, most can be adapted for use with the multilayer sensor described here.

The wavelength of operation of the multilayer was selected to be at 470 nm in order to demonstrate operation at a wavelength not easily accessible to surface plasmon sensors using gold films. The only advantage to using the short 470 nm radiation in this label-free sensing configuration is that the surface wave radiation is tightly bound to the interface. However, this short wavelength may have more significant application for enhanced fluorescence sensing from labeled biomolecules [23,24] because the confinement of the radiation to the surface can lead to orders of magnitude increase in the electromagnetic field at the multilayer interface.

In this work we chose to use a broadband source. Although we used a lamp and band pass filter, the spectrum we used is essentially similar to a blue light emitting diode. This sensing system could be made very compact and relatively inexpensive through the use of a fiber-coupled blue LED and compact spectrometer. Because the optical properties of the PBG multilayer can be engineered such a system can be configured to operate at essentially any wavelength. In conclusion, the results presented here demonstrate that this system holds the promise of improved detection of biomolecules and could be applied for diagnostics, and for food and water quality testing.

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Biographies

Adam F. Farmer graduated from Middle Tennessee State University in 2004 with a triple major in biology, chemistry and physics. He graduated from the Medical Physics program at Vanderbilt University and he is currently a physicist at Jackson-Madison County General Hospital.

Andrienne C. Friedli obtained a B.A. in Chemistry at Rice University in 1984. She earned an M.S. in organic chemistry at Yale University in 1986, followed by a Ph.D. in physical organic chemistry at the University of Texas, Austin, awarded in 1992. After a postdoctoral stint at the California Institute of Technology, Pasadena, California, she took a tenure-track position at Middle Tennessee State University in Murfreesboro, Tennessee, in 1993. A Professor since 2005, she has held a part-time appointment in the Office of Research at MTSU since 2006.

Stephen M. Wright holds a B.A. from Northwestern College, Watertown, Wisconsin, in 1978 and B.S. from the University of North Dakota in Grand Forks, North Dakota in 1983. He earned his M.S. and Ph.D. degrees in microbiology in 1985 and 1990 from

the University of North Dakota School of Medicine. He worked at St. Jude Children's Research Hospital in Memphis prior to becoming a professor of biology at Middle Tennessee State University in 1992.

William M. Robertson graduated with a B.Sc. degree in physics from Imperial College of Science and Technology, London, UK in 1980. He received his M.S. and Ph.D. degrees in 1982 and 1987 respectively from Purdue University, West Lafayette, Indiana. Both degrees were in physics. He worked at Argonne National Laboratory, in Argonne Illinois, IBM's Watson Research Center in Yorktown Heights, New York, and the National Research Council Canada in Ottawa before becoming a professor of physics at Middle Tennessee State University.