Journal of Biosensors & Bioelectronics

Magnusson, J Biosens Bioelectron 2013, 4:2
DOI: 10.4172/2155-6210.1000e120

Research Article Open Access

The Complete Biosensor

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Design and fabrication of nanostructured sensors based on optical, electrical, or mechanical principles has advanced tremendously in the last decade. This is due in part to progress in numerical design tools, computational power and nanofabrication capability. Across the globe, there is growing interest in advanced sensor technologies for diverse applications in homeland security, biomedicine, drug development, food safety and environmental monitoring. These sensor systems must be portable and cost-effective, while providing rapid response with high sensitivity, reliability and minimal false-reading counts. Most biosensor technologies currently available employ fluorescent or absorption labeling to register a specific biomolecular reaction. For reasons of expense and expediency, there is increasing demand for improved sensor techniques that do not require labeling. In this editorial, we briefly discuss advanced guided-mode resonance (GMR) biosensor technology meeting these demands. Since these sensors can be designed to resonate in multiple modes, complete information about a bioreaction can be extracted, including the biolayer thickness, biolayer refractive index, and the change in the background solution refractive index. Thus, justifiably, we refer to this sensor as the complete biosensor.

The resonance frequency of the GMR device varies as any of its structural parameters change. In a biomolecular binding event, an attaching biolayer alters the effective thickness of the resonant layer affecting the resonance wavelength. This is shown schematically in figure 1. The wavelength change can be monitored with a spectrum analyzer in real time to quantify the binding dynamics. A wide variety of sensor geometries, materials and system architectures can be implemented.

To provide a historical perspective, in 1992, Magnusson and Wang [1] suggested application of the GMR effect to sensors and disclosed GMR filters that were tunable on variation in resonance structure parameters, including thickness and refractive index [2]. Wawro et al. [3] presented new GMR biosensor embodiments, as well as new applications of these sensors when integrated with optical fibers. The use of modal and polarization diversity for multi parametric biosensors is a particularly interesting aspect of this technology [4].

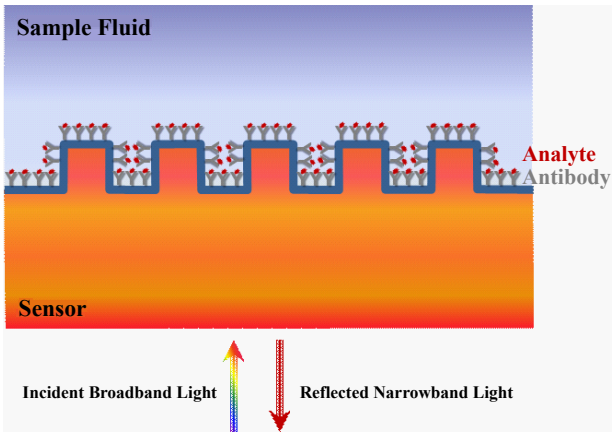

Figure 1: A guided-mode resonance sensor schematic.

Applying the GMR concept, we have developed and verified a new foundational methodology for biosensing that is robust against false readings. We employ modal and polarization-based parametric discrimination. Our resonant sensors are designed to support two or more leaky optical modes in the spectral band of interest. These modes can be directly excited with a beam of unpolarized light as they resonate in their respective polarization states. This property provides enriched data sets that can be used to calibrate simultaneously for variations such as temperature or sample background density, in the same sensor element, thus increasing detection accuracy and reducing probability of false readings. Concurrent, co-localized data acquisition *via* such polarization and modal diversity eliminates errors associated with the use of separate reference sites. Our sensors can be arrayed into high-density (~ 10,000 sensors/cm^2) platforms that are easily interrogated with a single beam of light. They are extremely economic in fabrication and amenable to mass production. This important sensor technology will find increasing application, for example, in medical diagnostics and drug development.

Applying this concept, figure 2 shows an example set of resonance peaks for a typical sensor. All four peaks can be monitored conveniently in real time using a spectrum analyzer.

In an example experiment, we monitor the TE_0 and TM_0 peaks at an identical physical location on the sensor surface. The objective is

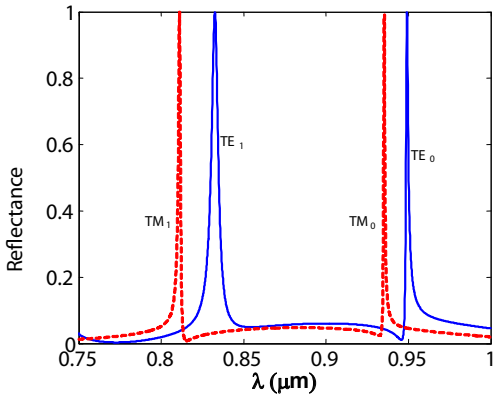

Figure 2: Computed resonance spectra for a representative dielectric GMR sensor operating in an aqueous environment. Two resonance peaks associated with the lowest waveguide modes for each polarization state appear.

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Received May 20, 2013; **Accepted** May 21, 2013; **Published** May 22, 2013

Citation: Magnusson R (2013) The Complete Biosensor. J Biosens Bioelectron 4: e120. doi:10.4172/2155-6210.1000e120

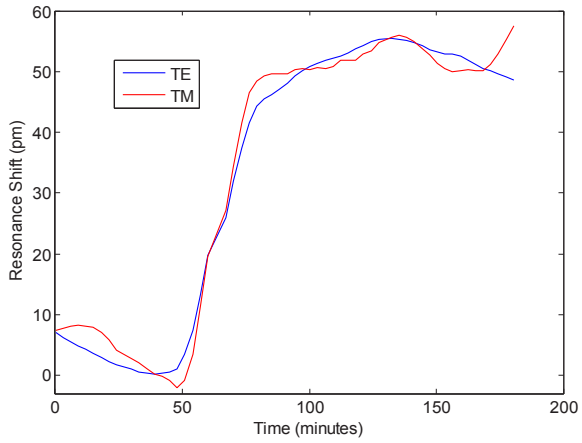

Figure 3: Measured biolayer temporal dynamics for a 68 nM solution of calreticulin binding to anti-calreticulin in a PBS solution. We record both polarization states for the lowest waveguide modes.

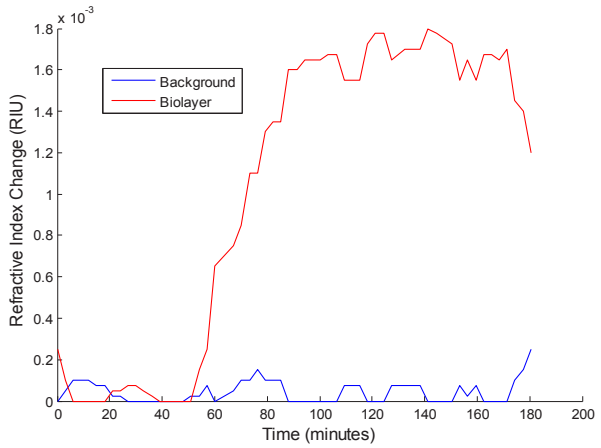

Figure 4: Refractive indices of the biolayer and background determined by backfitting the results in figure 3 to a numerical model. The background refractive index remains constant during this particular reaction.

to determine the refractive index of the biolayer and background in a single measurement. We assume the thickness of the biolayer is ~ 20 nm, based on knowledge of the binding molecular species. Figure 3 shows the measured spectral shifts for both polarization states as a function of time for the detection of the biomarker protein calreticulin. The capture layer is a specific monoclonal IgG antibody (anti-calreticulin) that is covalently bound to the sensor surface. By back fitting this dual-peak response into our rigorous electromagnetic analysis codes, we distinguish the resonance shift contributions due to the targeted bioreaction from the background bulk-index changes (which occur, for example, due to thermal drift). This is accomplished by calculating and mapping the TE and TM resonance peak shifts over a range of added biolayer and background refractive indices. The resulting numerical look-up table is applied to match the corresponding detection layer and background index when the two resonance peak shifts are known. Figure 4 illustrates the resulting resonance shift contributions due to surface changes and background variations.

In conclusion, the guided-mode resonance biosensor is complete in the sense that it can be used to find all unknowns in a bioreaction as a function of time. The example provided demonstrates determination of two parameters for calreticulin binding to a matched antibody. By fitting to a model of the known sensor with rigorous electromagnetic computations, we quantify the variations in the layer refractive index and show that the background is stable. By monitoring an additional peak due to a third resonating mode, the biolayer thickness could also be found.

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