Title : Web Based Photonic Crystal Biosensors for Drug Discovery & Diagnostics
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Extended Abstract

SRU Biosystems Inc. manufactures photonic crystal based biosensors, for drug discovery and diagnostic applications, in roll-to-roll format. Employing web based processing techniques results in advantageous consumable cost structure that enables new and important applications. For example, SRUs BIND label free sensor platform gives scientists engaged in drug discovery the means to screen for binding between candidate proteins, small molecules, or molecular fragments and target proteins or cell receptors without the use of conventional fluorescent or radioactive molecular tags (labels).

Sub-wavelength periodicity in refractive index, typically across a planar surface, specifies the structure of a photonic crystal. Such a structure has allowed resonance modes defined sharply by the angle, wavelength, and polarization of incident light. An excited resonance mode yields high electromagnetic field strength confined closely to the plane of periodicity. The photonic crystal biosensor application takes advantage of the resonance condition, by localizing biochemical or cell based assay interactions within the high field region i.e. on the surface of the photonic crystal. SRU's sensor technology takes advantage of the interaction between the confined resonance field and assay material through two distinct sensing modes; label free detection and fluorescence amplification.

SRU's BIND® sensing technology enables the label free sensing mode of photonic crystals. Binding between biological materials on the surface of the sensor increases the total mass of material localized within the resonance field. This increase in optical density, on top of the photonic crystal, changes the resonance frequency, similar to the response of a quartz crystal oscillator. One can directly convert the extent of resonance wavelength change to an increase in surface mass density thus quantifying the biological binding event. Many drug development programs begin with a search or "screen" of a large drug candidate library testing for binding to a known target protein, where the target protein has a role in disease. Label free assays greatly simplify and speed the screening of potential drug compounds because label molecules, attached to test species like sidecars, can interfere with a natural interaction with the target compound. Also, the label free method can easily quantify and normalize multiple binding step assays because each step simply adds more detectable mass.

One can also design a photonic crystal to increase signal from a fluorescently labeled molecule that has attached to target species on the sensor surface. In this case, a resonance mode coincides with the fluorescent excitation source, frequently a laser. The photonic crystal intensifies the incoming excitation field and thus amplifies the signal from fluorescent tags immobilized by the assay within the crystal plane. Fluorescent amplification, also known as evanescent resonance, increases the lower limit of detection for some already highly sensitive fluorescent assays. This enhanced sensitivity permits detection of species at very low concentration, an important capability in diagnostic applications. For example, the discipline of pharmacogenomics seeks to test patients for gene presence determined to affect drug efficacy or dosing sensitivity. Recently, the FDA approved a labeling change for a common blood thinner, Warfarin, notifying that dose modification in response to a gene determination can prevent a serious reaction. These types of tests benefit from enhanced fluorescence biosensors.

SRU manufactures photonic crystal biosensors in a roll to roll format and attaches them to industry standard supports making a highly sensitive detection platform available in the form of familiar consumable labware. The process achieves sub wavelength refractive index periodicity by transferring a grating like structure from a master to the web surface and then over coating the structure with a thin film of high refractive index material. The thin film follows the structures periodic contours resulting in highly regular refractive index periodicity. These structures resonate, with appropriately polarized light, in highly predictable and controllable modes.

With liquid over the sensor, one frequently interrogates the sensor by directing polarized light through the substrate. The substrate material should not affect the polarization of light

passing to or from the photonic crystal surface. This requirement favors non birefringent web materials.

The replication process makes use of UV curable materials to transfer the periodic structure from a sub-wavelength patterned master to the web. A UV source solidifies such a material after a rolling process has sandwiched it between the web substrate and the master. Once cured, the UV curable transfer material maintains the photonic crystal form molded by the master and remains adhered to the web when peeled from the master surface. The optical properties of the cured transfer material affect the performance of the photonic crystal. Depending on sensor design, a significant portion of the optical field resides within this material as it bounds the high refractive index coating on one side. Low absorption and low refractive index transfer materials favor biosensor performance.

The uniformity and process control achievable with reactive sputtering make it a preferred deposition method for photonic crystal production. The various forms of the photonic crystal biosensor call for optical grade coatings ranging from 100 to 300 nm. These sensors have coating uniformity requirements similar to multi-layer wide band anti reflection coatings though the number of film layers rarely exceeds two. The vacuum coating process must maintain low optical absorption at the wavelengths of operation, particularly in the case of amplified fluorescence. The high field generated by resonance will interact most strongly with the vacuum deposited layers. High optical absorption in these layers will subdue or extinguish resonance. Low amounts of absorption can reradiate as background fluorescence or photoluminescence and have a severe effect on the dynamic range of fluorescence amplification sensors.

Following application of the high refractive index thin film, the photonic crystals patterned on the roll can function as sensors. To make them conveniently useful, SRU cuts sensor coupons from the web and bonds them to various supports commonly found in life science labs. The web-sensor coupon typically becomes the bottom surface of a multi well, liquid containing vessel such as a microplate or the top surface of a microarray (microscope) slide. The coupon cutting process should leave the biosensor surface free from damage and contamination. The bonding process employs either pressure sensitive adhesive cut to fit the coupon and support or flow-able, reactively cured adhesives such as UV curable polymers. Because the adhesive comes into contact with assay test solutions, it should not release water soluble materials even during long soak periods. Such extractable materials can interfere with biological processes as well as produce misleading sensor readings.

SRU applies reactive coatings to the surface of the photonic crystal biosensor to selectively immobilize target proteins or cells on the surface of biosensor. These “surface chemistry” coatings typically bind to the plethora of primary amines available on proteins. The anticipated assay type including target size and number of steps determines the type of surface chemistry applied. Thus, with a range of surface chemistry processes, one can further customize a biosensor design to specifically address the end user’s needs. Covalent protein attachment of proteins to the surface produces a more stable assay with less background binding than does, for example, charge based binding. To reduce cost, the application process for selectively reactive surface chemistry coatings would preferably migrate to a roll-to-roll process such as vacuum deposition. Downstream handling and process compatibility currently inhibit this transition.

Following application of surface chemistry, the packaged biosensor product should have a shelf life of one year. Some highly reactive surfaces require storage at reduced temperature. The packaging, similar to all the biosensor components, should not outgas contaminants onto the sensor surface. Labeling should ensure product trace-ability.

In conclusion, the processes exist to produce a wide range of consumable sensing products based on photonic crystal oscillators. Many opportunities also exist to further the utility and performance of these products.