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Affinity based glucose measurement using fiber optic surface plasmon resonance sensor with surface modification by borate polymer

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ABSTRACT

An affinity based method of glucose measurement using a fiber optic surface plasmon resonance (FO-SPR) sensor with surface modification by a borate polymer was proposed. In this method, the sensor is able to obtain the glucose concentration by detecting the surface refractive index of the sensor, which could avoid the impact of bioelectricity from viable tissues when applied for implantable measurement. A biocompatible borate polymer, PAA-ran-PAAPBA, which is capable of associating and dissociating with glucose molecules dynamically, performed non-consumption measurement of glucose, thereby enabling the possibility of glucose detection in hypoglycemic situations. Numerical simulation was performed based on the FO-SPR theory, and an online-transmission FO-SPR sensor with optimized structural parameters was fabricated. PAA-ran-PAAPBA was synthesized and immobilized onto the surface of the FO-SPR sensor using layer-by-layer self-assembly technique. An experimental system was built, and contrast-measurement experiment for 1–10 and 10–300 mg/dL glucose solutions was performed; the FO-SPR sensor bonded with the borate polymer exhibited higher accuracy, especially for low-concentration detection. This study laid a technical foundation for further exploration of implantable measurement systems for blood glucose.

1. Introduction

Diabetes mellitus is a common disease that threatens human health, and it is important to monitor the blood glucose of diabetics continuously for diagnostics and treatment [1–5]. To date, the method for continuous monitoring of blood glucose that has been used in clinical treatment essentially comprises biosensors based on enzyme electrode [6–9], and the most representative products include SEVEN? *R* Plus (DexCom, Inc.) [10], Paradigm? *R* REAL-Time (Medtronic, Inc.) [11] and FreeStyle Navigator? *R* (Abbott Laboratories) [12]. These devices determine the concentration of blood glucose by detecting the glucose molecule in the interstitial fluid (ISF), which is minimally invasive, practical and provides a quick response. However, these implantable biosensors based on enzyme electrode work by detecting the electric current of the glucose oxidation catalyzed by the oxidase immobilized on the sensor. Thus, they are susceptible to the bioelectricity in the viable tissues, which can cause a significant drift in the measuring signal, making them inappropriate for long-term monitoring. The glucose concentration of diabetics provided by these biosensors is always inaccurate, and it is necessary to calibrate them periodically using finger-prick blood extraction, which brings sufferings to the patients. Additionally, the glucose will be consumed irreversibly [13–15] because of the oxidation, resulting in an inaccuracy at low glucose concentration. Consequently, it is almost impossible to find hypoglycemic states in the clinical treatment of diabetes.

The sensing technique based on fiber optic provides an excellent approach to fabricate miniaturized sensors, which enables the possibility of implanting the sensor into subcutaneous tissues. In recent years, the optical glucose sensing is emerging and some fiber optic sensors have been used for glucose detection, such as the fluorescence sensors [16,17] and fiber optic attenuation total reflection (FO-ATR) sensors [18]. Fluorescence sensing is a sophisticated technology, however, the compound that could produce fluorescence effect is limited and the response speed of these sensors is relatively low, which is unsuitable for the continuous monitoring of diabetics. The FO-ATR sensor has a rapid response but the performance of this sensor is positively correlated to the optical length [19]. However, the size of the sensor for implantable measurement restricts the optical length, thus limiting the performance of the sensor. In our

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study, a method of glucose measurement based on fiber optic surface plasmon resonance (FO-SPR) sensor is presented. The sensor measured glucose concentration by detecting the surface refractive index of the interstitial fluid instead of the electric current. Thus, it could avoid the impact of bioelectricity from viable tissues and the signal would be more reliable when applied for implantable measurement.

As the component of the interstitial fluid is complex, any component could cause the variation of the refractive index. Thus, the implantable FO-SPR sensors need to immobilize specific biomolecules that could selectively absorb the glucose to implement the detection. The representative biomolecules are concanavalin (ConA) [20,21] and D-galactose/D-glucose binding protein (GGBP) [22–24]. They have good affinity to the glucose molecules, which have been used to realize the specific measurement of glucose. However, ConA is toxic, and it is easy to trigger immune response. GGBP is nontoxic but difficult to synthesize. Additionally, it is physically and chemically instable. There are also reports showing that boronic acid is a biocompatible group with low cytotoxicity and low immunogenicity, especially for the 3-acrylamidophenylboronic acid (AAPBA) [25–27]. However, the poor solubility limits its application. Recently, Li et al. developed poly(acrylamide-*ran*-3-acrylamidophenylboronic acid) (PAA-PAAPBA), the introduction of biocompatible hydrophilic PAA segments can improve the water solubility, and this copolymer has been used for the glucose detection. The experiment performed by Li et al. also confirmed that this polymer just specifically absorbed glucose molecules, but insusceptible of other compounds or solvents [28]. In this study, the borate polymer, PAA-*ran*-PAAPBA [29], was used for the first time to modify the surface of the FO-SPR sensor and realized the specific measurement of the glucose. The borate polymer was synthesized, and then immobilized onto the surface of the FO-SPR sensor using a layer-by-layer self-assembly technique [30]. The immobilized polymer exists in a solid state on the surface of the sensor and it is able to associate and disassociate with the glucose molecules dynamically. It did not consume glucose and provided a more accurate measurement, which enabled the possibility of glucose detection in the hypoglycemic situations. Compared with conventional SPR sensors modified by ConA and GGBP, the FO-SPR sensor modified by PAA-ran-PAAPBA has excellent stability, remarkable affinity to glucose and high sensitivity. This study established a technical foundation for implantable glucose measurement by FO-SPR sensor in clinical applications.

2. Method of glucose measurement by FO-SPR sensor with affinity based surface modification

2.1. Sensing principle of the FO-SPR sensor

As shown in Fig. 1(a), after a white light source is coupled into the core of fiber optic, it produces internal total reflection with various reflection angles θ, and the evanescent wave is generated [31] simultaneously, the electric field intensity of which decays exponentially at the interface of the core of fiber optic and the metal film. The evanescent wave then excites the collective oscillation of free electrons on the surface of the gold film, generating a surface plasmon wave (SPW). The wave vector of the SPW is given by the following relation:

$$k_{sp} = k_0\left(\frac{\varepsilon_m \varepsilon_s}{\varepsilon_m + \varepsilon_s}\right)^{1/2} \tag{1}$$

where k_0 is the wave vector of light in free space, ε_m and ε_s are the dielectric constants of the metal and the dielectric medium, respectively. The wave vector of the incident light is given by the following relation

$$k_{fo} = \frac{\omega}{c}\sqrt{\varepsilon_{fo}} \tag{2}$$

where k_{fo} is the wave vector of the incident light in the fiber optic with dielectric constant ε_{fo}, ω the angular frequency and c is the speed of light in free space. When the horizontal component of the incident light wave vector ($k_x = k_{fo}\sin\theta$) is equal to the SPW vector (k_{sp}) at the interface of gold film and glucose solution, or the following relation is satisfied:

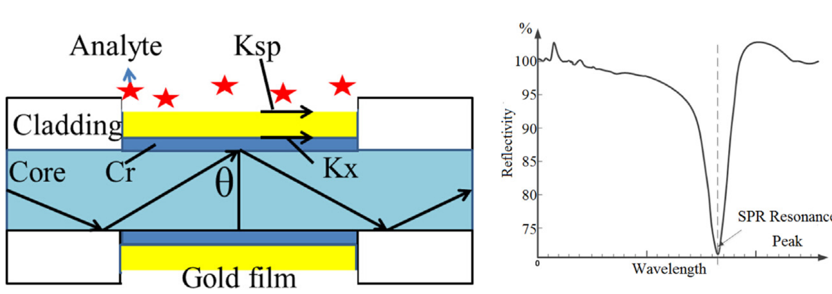
$$\frac{\omega}{c}\sqrt{\varepsilon_{fo}}\sin\theta = k_0\left(\frac{\varepsilon_m \varepsilon_s}{\varepsilon_m + \varepsilon_s}\right)^{1/2} \tag{3}$$

the complete transfer of energy from the incident light to the surface plasmon takes place. This phenomenon is termed as SPR [32].

FO-SPR can be equivalent to the superposition of multiple prism SPR reflection. As the wave vector of the incident light is related to the wavelength, when an incident light at particular wavelength meets the condition of exciting SPR, the total reflection coefficient (reflectivity) of incident light reaches the minimum (shown in Fig. 1(b)) where the wavelength is called the resonance wavelength [33]. It is extremely sensitive to the variation of the optical refractive index on the surface of the gold film. Thus, glucose solutions with various concentrations can be characterized by detecting the refractive index fluctuation and the corresponding resonance wavelengths, which avoids the impact of bioelectricity when used for implantable glucose detection.

2.2. Principle of reaction between boric acid and glucose

In general, the boric acid possesses functional hydroxyl groups that are capable of strongly combining glucose molecules. As shown in Fig. 2(a), boric acid exists in equilibrium between the normal, uncharged state and a dissociative, negatively charged state in an aqueous solution. The reaction of boric acid and glucose is shown in Fig. 2(b): it is a condensation reaction between the hydroxyls of the boric acid and the glucose molecule. When the concentration of the glucose is high, the glucose molecules could be adsorbed by the



(a) (b)

Fig. 1. Sensing principle of FO-SPR sensor.