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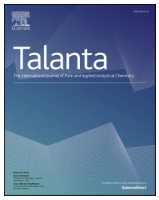

Bio-inspired polydopamine layer as a versatile functionalisation protocol for silicon-based photonic biosensors

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ABSTRACT

Photonic biosensors have made major advances in recent years, achieving very high sensitivity, and progressing towards point-of-care deployment. By using photonic resonances, sensors can be label-free, which is particularly attractive for a low-cost technological realisation. A key remaining issue is the biological interface and the efficient and reliable immobilisation of binder molecules such as antibodies; many protocols are currently in use that have led to widely varying sensor performance. Here, we study a very simple and robust surface functionalisation protocol for silicon photonics, which is based on polydopamine, and we demonstrate both its simplicity and its high performance. The use of polydopamine (PDA) is inspired by molluscs, especially mussels, that employ dopamine to adhere to virtually any surface, especially in an aqueous environment. We studied the versatility of the PDA protocol by showing compatibility with 5 different disease biomarkers (Immunoglobulin (IgG), C-reactive protein (CRP), Tumour Necrosis factor-α (TNF-α), Interleukin-6 (IL-6), Matrix metalloproteinase (MMP-9) and show that the protocol is resistant to hydrolysis during incubation; the loss of functionality due to hydrolysis is a major issue for many of the functionalisation protocols commonly used for silicon-based sensors. The study using guided mode resonance-based sensors highlights the wide dynamic range of the protocol (0.01 ng/mL to 1 μg/mL), using IgG, CRP and MMP-9 protein biomarkers as exemplars. In addition, we show that the surface chemistry allows performing measurements in 10% human serum with a sensitivity as low as 10 ng/mL for IgG. We suggest that adopting this protocol will make it easier for researchers to achieve biofunctionalisation and that the biosensor community will be able to achieve more consistent results.

1. Introduction

The continued improvement of label-free biosensors is essential for the development of the personalised and precision medicine paradigm, as well as for environmental and food safety monitoring [1,2]. Many transduction methods have been developed that convert biomolecular interactions into electrical and acoustic signals [3,4]. Amongst different modalities developed and studied, silicon-based photonic biosensors offer particularly interesting properties such as high sensitivity, label-free operation, contact-free readout, and multiplexed detection. The high refractive index sensitivity of these structures enables biomarker detection down to very low concentrations (fg/ml-pg/ml) which is competitive with established and much more expensive laboratory-based techniques [5].

A key issue with such biosensors is the wide variability of the reported detection limits. Even when comparing the same protein being detected with the same photonic modality, for example with silicon micro rings, researchers report widely varying performance (Table S1). One possible reason could be due to variations in the functionalisation protocol, some of which can be very complex, require multiple steps and may not return consistent results. For example, we show, in Table S1, that the limits of detection obtained for the protein biomarkers CRP and IgG may vary widely, even when using the same sensing modality but different biofunctionalisation protocols. One of the key requirements for the scalability of biosensors, however, is a robust and easy-to-implement surface chemistry for the immobilisation of the bioreceptors of interest; therefore, such wide variability is not acceptable.

In this context, it is instructive to consider the historical development of surface functionalisation protocols; initially, a non-covalent approach, i.e. simple physical adsorption, was widely used, but this suffers from many drawbacks such as the random orientation of biomolecules, irreproducibility, long reaction times and risk of structural

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damage of biomolecules [6]. In response to these drawbacks, a range of covalent approaches were developed which, for silicon-based photonic biosensors, are largely based on silanisation of the sensor surface to introduce functional chemical groups such as amino moieties [7,8], epoxy, carboxylic acid or thiol groups [7,9]. Even though silanisation is a well-explored process [10], polymerisation of silanes can result in multi-layer formation and aggregation which reduces the surface sensitivity [11]. Additionally, crosslinkers are subsequently required to covalently couple chemical groups introduced at the surface to functional moieties on the antibody surface. However, the functional groups of these crosslinkers, such as N-hydroxysuccinimide (NHS)-ester, are susceptible to hydrolysis [12]. For the immobilisation of biomolecules, which inevitably needs to be performed in aqueous solvents, this can lead to low efficiency of surface bioconjugation [13] and lack of reproducibility [14].

Thus, there is a clear need to develop a more robust approach for modifying the surface of photonic sensors that allows for the direct (i.e., without the need for additional crosslinkers) covalent attachment of bioreceptors while maintaining their functionality. Moreover, the approach should not reduce the refractive index sensitivity of the photonic sensor and ideally should exploit low-cost and readily available materials and require a minimum of reaction steps that are simple to perform for large-scale fabrication.

Here, we study a functionalisation protocol for silicon photonics that is based on polydopamine (PDA) and show that it meets the above requirements. PDA films have been used for a wide range of applications, including coatings for scaffolds and implants to promote cell adhesion [15] that are stable and biocompatible in vivo [16]. The use of PDA films to derivatize surfaces for protein immobilisation was first demonstrated in 2007 [17] and has since been demonstrated with electrochemical [18,19], surface plasmon resonance (SPR) [20], and interferometric biosensors [21]. Catechol and amino groups associated with the dopamine molecular structure are used by mussels to allow them to attach to virtually any surface in an aqueous environment (Fig. 1a–c). Under alkaline conditions, dopamine polymerizes spontaneously on surfaces to create a conformal and robust PDA film. Subsequent covalent attachment of biomolecules to the PDA surface proceeds in aqueous solutions directly, i.e., without the need for additional reagents or crosslinkers, via Schiff-based and Michael-addition reactions [22,23].

We study PDA films assembled on silicon-based photonic sensors for the covalent attachment of antibodies to the sensor surface. As an exemplar, we used silicon nitride chirped guided mode resonance (GMR) biosensors due to their high performance and ease of use (Fig. 1d–g) [24]. Specifically, we demonstrate that PDA films are compatible with a wide range of antibodies and that the resulting functionalised sensors outperform comparable sensors prepared using a commonly used approach based on silane with an NHS linker. In addition, we study the use of PDA coatings for the protection of silicon-based sensors exposed to cell culture media; cell culture media have previously been shown to degrade silicon-based sensors upon extended (several hours) exposure due to their alkaline nature [25] and we show that PDA films provide added protection and thus allowing to perform measurements for longer times. While we focus here on silicon nitride, we also show the application of PDA to silicon and silicon dioxide to illustrate their broad applicability across silicon photonics.

2. Experimental section

2.1 Materials (Supplementary information S2)
2.2 Fabrication of guided mode resonance sensors and microfluidics (Supplementary information S3 and S4)
2.3 PDA surface functionalisation protocol

We performed both quartz crystal microbalance (QCM-D, QSense Analyzer, Biolin Scientific) and GMR studies to characterise the PDA protocol. The sensors were placed horizontally into a petri dish containing 2 mg/mL dopamine solution in tris buffer of pH 8.5 for 30 min to aid the formation of a polydopamine film. We chose an incubation time of 30 min, which results in a typical film thickness of ~2–3 nm [26]. We note that thicker PDA films can be created by extending the incubation period but that a thicker film is detrimental to the photonic biosensor performance, as it reduces the overlap between the optical mode and the surface molecular layer, thereby reducing the sensitivity of the sensor; it is worth recalling that the photonic sensor uses an evanescent field to

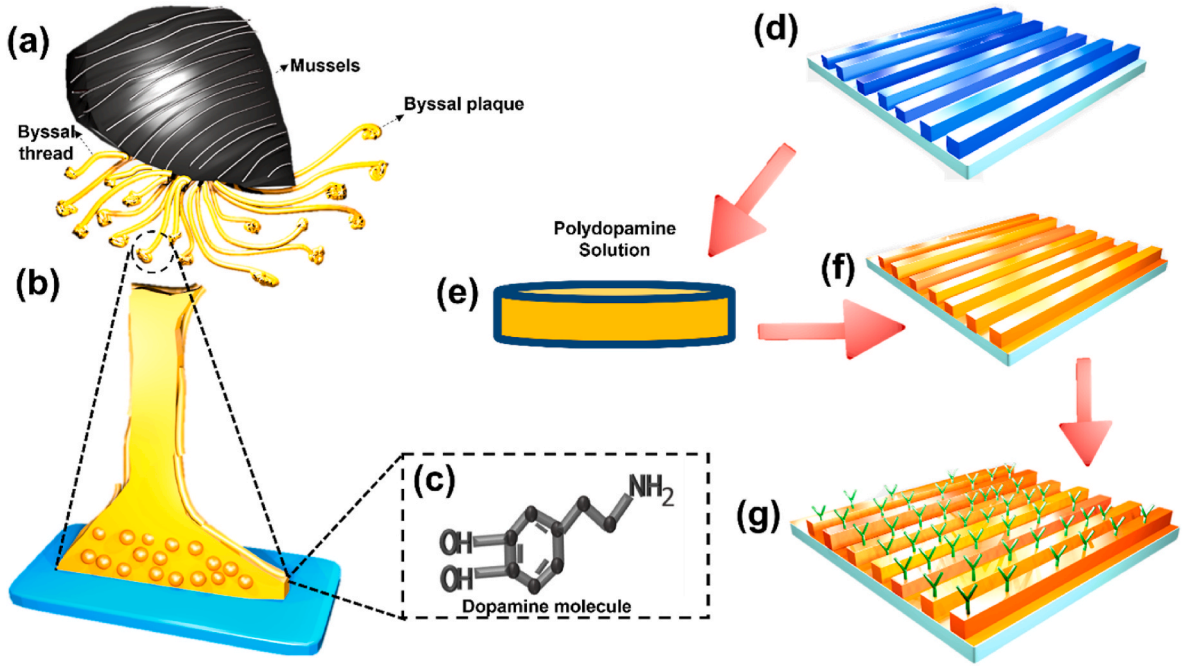

Fig. 1. (a) Mussels with adhesive fibres; (b) enlarged image of secreted byssal; (c) chemical structure of the dopamine molecule; (d) sensing surface (here: silicon nitride grating); (e) polydopamine solution applied to surface; (f) sensor coated with the polydopamine solution; (g) direct antibody attachment to the polydopamine coated sensing surface.

interact with the biomolecules, and that the evanescent field only extends 50–100 nm into the analyte. We highlight the limited spatial extent of the optical mode in Fig. 3c to illustrate this point.

Following PDA film formation, the sensors were rinsed with tris buffer followed by distilled water before being dried with nitrogen. Both the QCM-D and GMR experiments were performed at 20°C and with a constant flow rate of 75 μl/mL controlled by a peristaltic pump for QCM-D and a syringe pump for GMR setup. PBS (pH 7.4) was first flowed over the sensor surfaces to establish a stable baseline. Following stabilization, antibodies were introduced at a concentration of 50 μg/mL in PBS, followed by a PBS washing step to remove unbound antibodies. A 1% solution of casein in PBS was then used to block unreacted regions of the PDA surface, again followed by a PBS washing step. Finally, the antigen solutions (in PBS) were introduced into the fluidic channels at a range of concentrations before the surface was again rinsed with PBS.

3. Results and discussion

3.1. Quartz crystal microbalance analysis

The optimisation and characterisation of the PDA protocol were initially performed with a commercial QCM-D system using silicon dioxide-coated quartz sensors. The results were compared to sensors functionalised with silane in combination with a heterobifunctional chemical crosslinker maleimide-PEG-NHS as described in the reference [24]. As shown in Fig. 2a, upon exposure of the PDA modified sensor surface to a solution of anti-IgG, we observe a shift in resonant frequency which, after rinsing with PBS, decreases by ~ 68 Hz. The resonant frequency of the QCM-D is associated with the mass attached to the quartz sensor, where a decrease in frequency corresponds to an increase in mass bound to the sensor surface. We observe an increase in antibody density on PDA films compared to that observed for surfaces functionalised via silane - NHS (Fig. 2c)), leading to a corresponding increase in the binding of the antigen to the antibody functionalised surface (Fig. 2d)), ultimately enhancing the limit of detection.

The process was repeated for a total of 5 different antibody-antigen pairs (IgG, TNF-α, CRP, IL-6, MMP-9) (Fig. 2c and (d)) to study the compatibility of the functionalisation protocol with a range of antibodies and antigens. We observed that the protocol worked consistently well for all the antibodies tested, which suggests the broad applicability of protocol.

Comparing the frequency shift observed with PDA compared to silane - NHS chemistry also shows a consistently higher shift, both in terms of immobilised antibodies and captured antigens. We attribute this increase to the higher stability of the PDA process, which is not prone to hydrolysis; even when exercising careful control, hydrolysis is always a risk for the silane –NHS based chemistry. In addition to the improved performance, the PDA process is significantly simpler and quicker to use than the silane - NHS chemistry. In fact, since introducing the PDA-based protocol into our laboratory, we have seen a significant improvement in yield; while we used to observe a yield of 30–50 % for successful sensor experiments with silane - NHS chemistry and significant variations between different users, the yield has now increased to near 100 % and consistency between different users, which we attribute

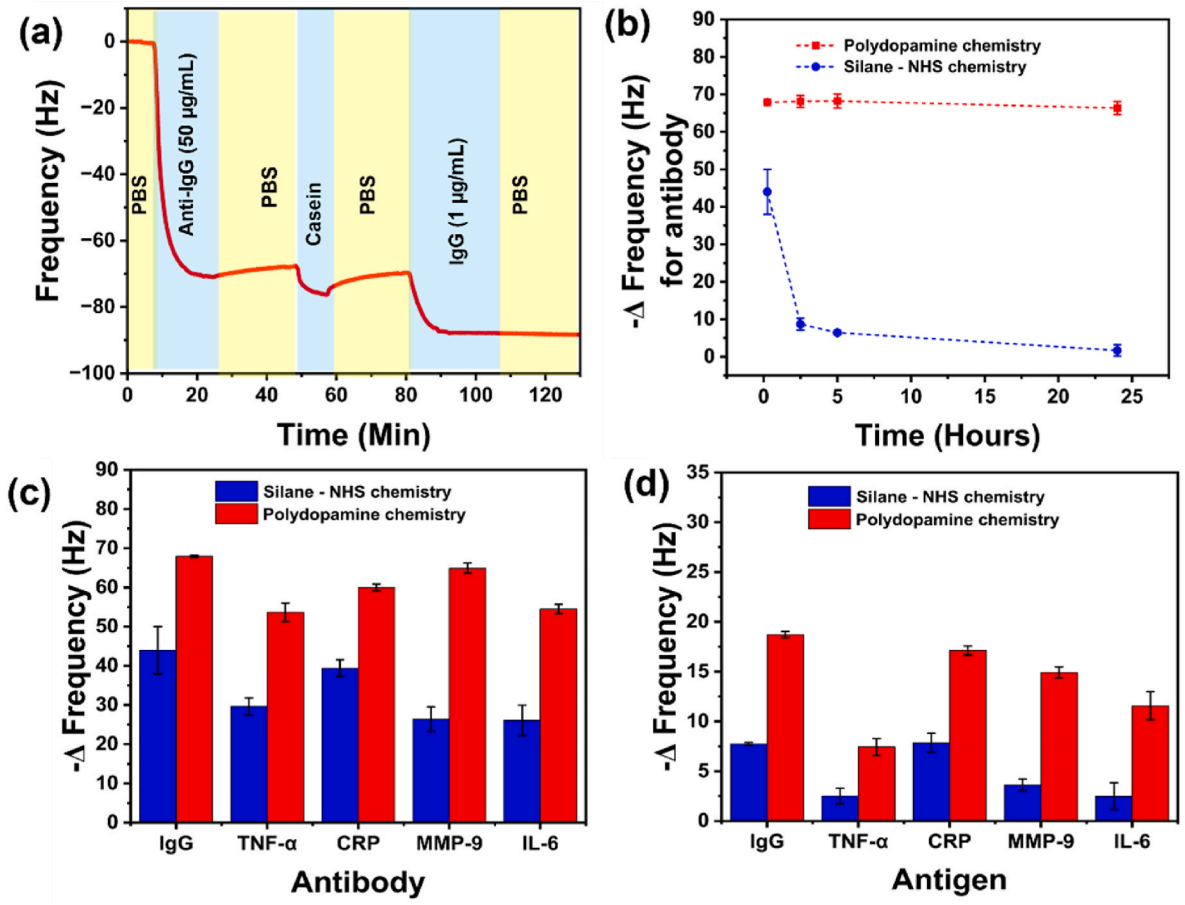

Fig. 2. (a) IgG immunoassay on a PDA-functionalised silicon dioxide QCM sensor; (b) comparison of chemical reactivity of polydopamine and MPTES + NHS-$(PEG)_6$-maleimide functionalised surfaces after preincubation for up to 24 h in PBS (pH-7.4). The drop in the activity of MPTES + NHS-$(PEG)_6$-maleimide chemistry is observed because of hydrolysis of the NHS ester; (c, d) comparison of the observed frequency shifts for five clinically relevant antibodies (50 μg/mL) (c) and associated antigens (1 μg/mL) (d) for both polydopamine and silane-NHS functionalised sensors (n = 3 ± Standard Deviation (SD)).

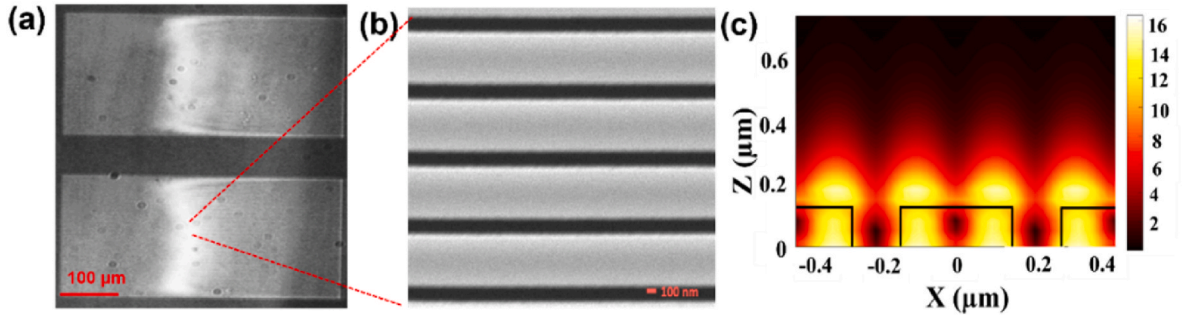

Fig. 3. a) Optical micrograph of the resonance on the chirped GMR grating, taken in reflection. The image shows the resonances observed in reflection from two chirped GMRs as a typical example; (b) scanning electron micrograph of the grating. The period is varied between 432 and 440 nm and the filling factor is 0.7. The gratings are designed for a resonance wavelength around 650 nm; (c) E-field of the GMR on resonance (TM mode), highlighting that the evanescent field of the mode decays exponentially from the surface of the Si_3N_4 and the penetration depth is less than 200 nm, with the optical field concentrated within the first 50 nm from the surface.

to the simplicity and improved robustness of this protocol.

To demonstrate the stability of the PDA protocol against hydrolysis, silicon dioxide QCM-D sensors functionalised with polydopamine, and silane-NHS chemistry were pre-incubated in PBS buffer (pH 7.4) for different time intervals, between 0.25 h and 24 h, and were subsequently functionalised with anti-IgG and tested by QCM-D to study the effect of pre-incubation on antibody immobilisation efficiency. The analysis indicated that the reactivity of polydopamine towards antibody bioconjugation did not change significantly during this period such that the chemical reactivity of the surface did not diminish even after 24 h (Fig. 2b). In contrast, a clear and rapid decrease in the activity of the silane - NHS chemistry functionalised sensors were observed because of hydrolysis of the NHS ester. The experiment highlights that polydopamine based surface chemistry is highly resistant to hydrolysis and more robust than other chemistries which one of the important requirements for large scale fabrication of photonic biosensors i.e., robust bioreceptor immobilisation chemistry.

3.2. Chirped guided mode resonance analysis of the sensor

Finally, we applied the protocol to silicon nitride based GMR sensors. GMR sensors exhibit an upward (red-) shift in resonance wavelength with the binding of proteins to the sensor surface, as the bound material increases the local refractive index of the cladding and thereby the effective index of the mode (Fig. 3). In the chirped GMR, the grating period is varied in one direction, which enables the spectral shift to be translated into a shift in the spatial location at which the grating is resonant (see Fig. 3 (a)). Using this chirped approach eliminates the need for a spectrometer by translating the spectral information into spatial information, hence the readout can be performed using a simple CMOS camera [27]. By monitoring the resonance position against time, the adsorption kinetics of the capture antibody onto the PDA-coated sensor surface is revealed, as is the binding kinetics of the antigen to the antibody.

A full binding curve for anti-IgG (50 µg/mL) and IgG (0.01 ng/mL), using casein (1%) as the blocking agent is shown in Fig. 4a as a function of time. Fig. 4b shows the range data for different IgG concentrations. Here, the IgG concentration was varied from 0.01 ng/mL to 10000 ng/mL and the resonance position reached a steady state after 15–20 min. We note that the maximum shift was observed for an IgG concentration of 1000 ng/mL. At the lower end, the shift observed for a 0.01 ng/mL IgG concentration was approx. 3 µm, which is well above the 3σ (mean $3\sigma = 1.39\ \mu m \pm 0.5\ \mu m$ (n = 30 ± SD)) value of the system.

We also compared the immobilisation of antibodies (50 µg/mL) and antigen (10 pg/mL) on polydopamine and silane-NHS functionalised GMR chips (Fig. S5) and noted, as expected from the QCM-D study (Fig. 2), that the resonance shift is higher for the PDA surface chemistry that ultimately can play an important role in improving the limit of detection. In this context, it is noteworthy that the experiment was conducted with similar parameters as in Ref. [24] and the silane - NHS result shown here matches that of [24] closely. We also evaluated the specificity of the PDA protocol on the GMR sensor (Fig. 4c and d). An anti-IgG (50 µg/mL) functionalised GMR sensor was challenged with a high concentration of CRP (10 µg/mL). As can be seen in Fig. 4c, negligible binding was observed. In contrast, we observe a very strong resonance shift when the sensor is challenged with the target antigen IgG at the same concentration (10 µg/mL). Similarly, we observed a negligible change for the non-specific antigen (TNF-α) for anti IgG-functionalised sensor and a good binding curve for 100 pg/mL IgG. In addition to that dynamic range study for two other biomarkers CRP and MMP-9 was also performed on GMR sensors (Fig. 4e and f).The concentration of the biomarkers was varied from 0.01 ng/mL to 10000 ng/mL and saturation was observed at around 1000 ng/mL for both the biomarkers. We also studied the stability of polydopamine films by storing the PDA functionalised sensor in air for 0.15 h and for 24 h (Fig. S6a). Following functionalisation, the resonance shift observed for the antibody binding was very similar for both films, indicating good stability and lack of degradation of the PDA film. Another aspect is to better understand the immobilisation mechanism between the antibody and the PDA surface. To this end, we used 10% solution (v/v) amine-functionalised silica nanoparticles (Fig. S6b). This binding curve indicates that the covalent immobilisation of biomolecules on the PDA surface takes places via the amine functional group directing towards Michael addition and Schiff base reaction.

3.3. Detection of rabbit IgG in human serum

We further evaluated the potential applicability of a PDA functionalised GMR biosensor for detection in complex biofluids. Different concentrations of rabbit IgG in 10 % (by volume) human serum samples (serum samples were diluted by PBS buffer) were measured. We used a signal and a reference channel, the reference channel being functionalised with an isotype control antibody that helps to differentiate the non-specific background signal from the specific antibody signal, because it has no specificity to the target antigen. When exposing both channels to the spiked serum, the specific binding of IgG remains clearly detectable from the difference between the two signals. We used concentrations between 10 ng/mL and 1000 ng/mL (Fig. 5b). As expected, the detection limit is higher than in PBS buffer, but sufficient for detecting clinically relevant concentrations.

3.4. Sensor stability in alkaline solutions

We note that a common problem with silicon-based photonic biosensors is the slow etching of the photonic nanostructure in alkaline solutions such as cell culture media. This can be seen in Fig. S7 where the

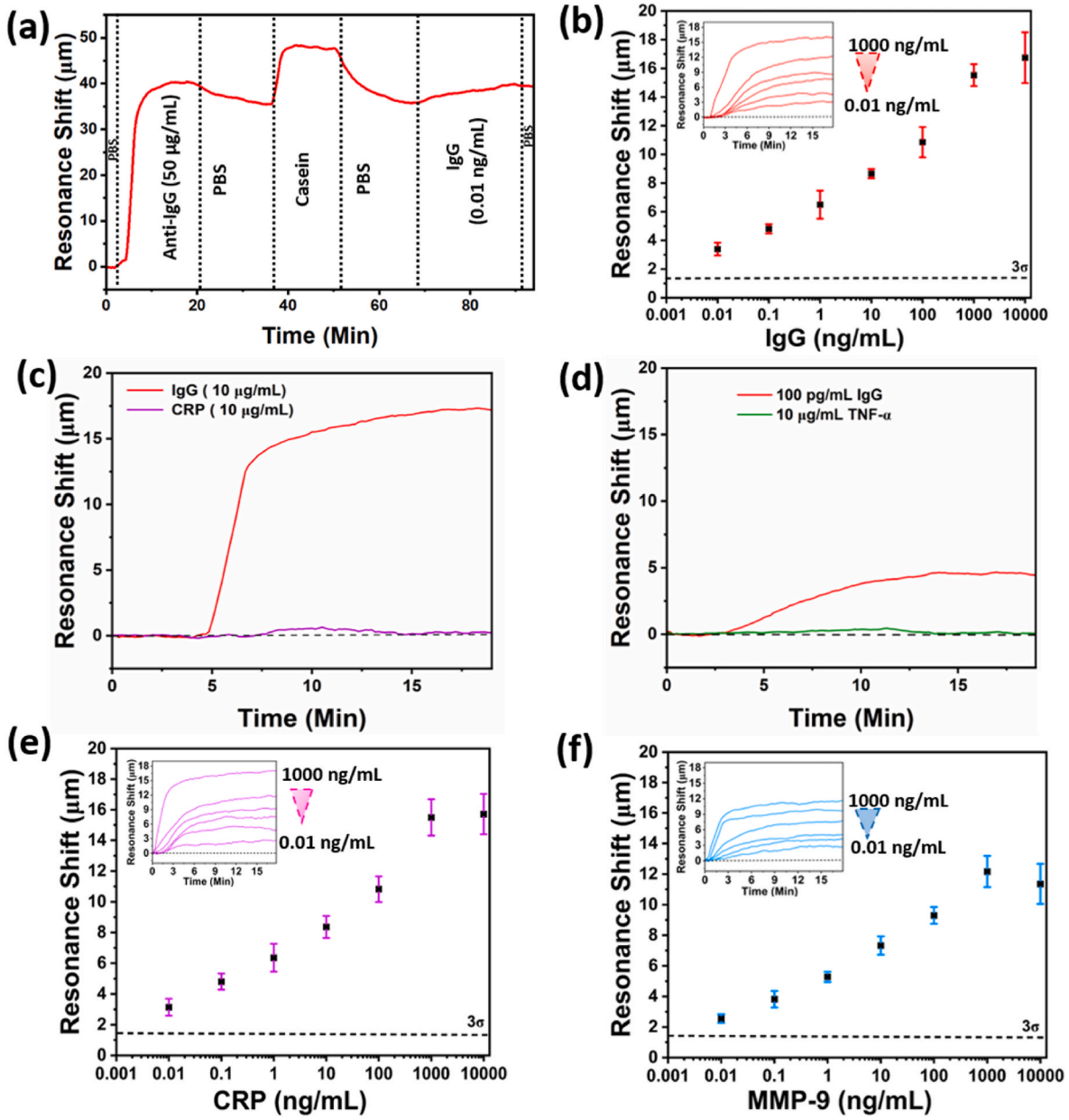

Fig. 4. (a) IgG immunoassay on PDA-functionalised silicon nitride guided mode resonance grating sensors; b) Resonance shifts observed for an IgG concentration in the range from 0.01 ng/mL to 10,000 ng/mL (n = 3 ± SD). The inset shows the respective binding curves for an IgG concentration ranging from 0.01 ng/mL to 1000 ng/mL; c, d) Selectivity test performed on polydopamine coated silicon nitride GMR grating; c) binding curve for 10 μg/mL of IgG and 10 μg/mL of CRP for a grating functionalised with anti-IgG (50 μg/mL). For 10 μg/mL IgG, a good shift in the resonance position is observed, while for the same concentration of CRP, only negligible non-specific binding is observed; (d) In the second selectivity test, the sensor was functionalised with anti-IgG (50 μg/mL), exposed to 100 pg/mL IgG and 10 μg/mL TNF-α. Again, the specific binding is strong while the non-specific binding is negligible; e and f) Resonance shifts observed for CRP and MMP-9 concentrations in the range from 0.01 ng/mL to 10,000 ng/mL respectively (n = 3 ± SD). The inset shows the respective binding curves for the protein concentrations ranging from 0.01 ng/mL to 1000 ng/mL.

degradation of a bare silicon grating is observed after around 10 h following immersion in PBS (pH 7.4) and after only 4 h when exposed to a cell culture medium. When repeating the same experiment with PDA-coated samples, the onset of degradation was seen to be delayed (Fig. S7, solid lines). This observation highlights the ability of PDA coatings to protect silicon-based sensors and points towards using either modified PDA coatings or composites of PDA coatings with other polymers to form more robust protection of the silicon surfaces in alkaline media enabling measurements such as cell imaging for extended periods [28].

4. Conclusions

We have studied a bio-inspired polydopamine (PDA)-based surface functionalisation protocol for silicon-based sensors and have shown that it can be used as a simple, single-step method for the immobilisation of functional bioreceptors on the sensor surface. The polydopamine based protocol provides a higher surface density of immobilised biomolecules when compared to more familiar surface chemistries based on surface silanisation and NHS crosslinkers and bioreceptor conjugation using crosslinkers. We believe that this improvement is partially due to the insensitivity of the PDA film to hydrolysis but also to its simplicity and the brevity of the process. Further, when tested on GMR biosensors, we

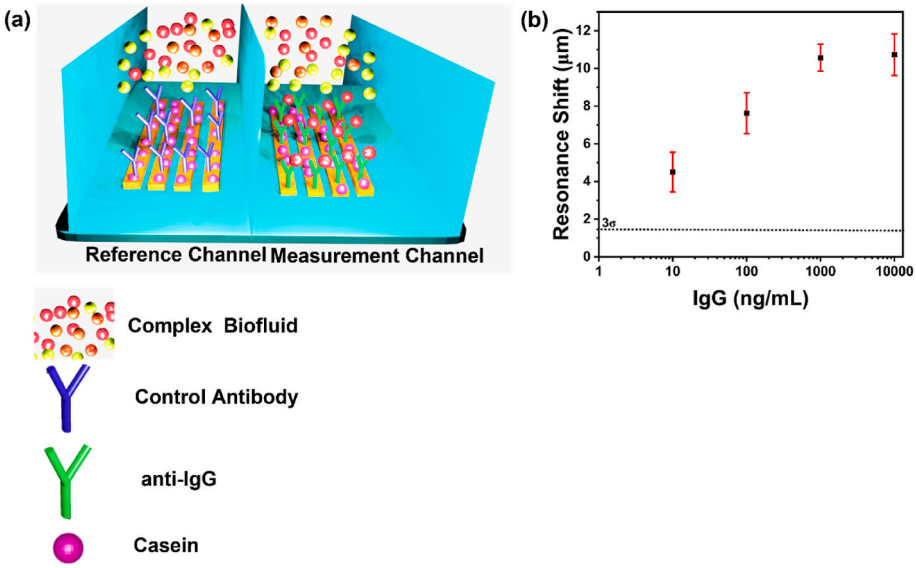

Fig. 5. (a) Working principle of referencing approach to perform measurements in a complex biofluid. The measurement utilises a reference channel immobilised with IgG isotype antibodies and a measurement channel functionalised with specific antibodies (anti-IgG). The spiked human serum is flown through both channels. To remove the matrix effect, the resonance shift in the reference channel is subtracted from the resonance shift in the measurement channel which results in the shift shown in (b). (b) Resonance shift observed for an IgG concentration in the range from 10 ng/mL to 10,000 ng/mL following subtraction of the matrix effect.

observe a wide dynamic range for the detection of IgG, CRP and MMP-9 biomarkers. In addition, we also verified the compatibility of the protocol with complex biofluids (diluted human serum) and were able to successfully perform measurements to ng/mL sensitivity. We also tested the integrity of the film by exposing coated and uncoated sensors to alkaline media and observed a delay in the onset of degradation, thus highlighting the high quality of the film and its ability to provide additional functionality by protecting the sensor surface. Overall, we suggest that the wider adoption of this protocol should improve the consistency of photonic immunoassays and that its simplicity will encourage researchers to engage more widely with surface functionalisation and the addition of biorecognition elements to their experiments.

Credit author statement

Shrishty Bakshi: Experimental design, investigation, data collection and analysis, writing - original draft; **Kezheng Li**: Sensor fabrication; **Pin Dong**: Investigation, formal analysis; **Isabel Barth** - Investigation, Formal analysis; **Casper Kunstmann-Olsen**: Microfluidic fabrication; **Steven Johnson**: Original idea, supervision, review and editing; **Thomas F. Krauss**: Supervision, review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.talanta.2023.125300.

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