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Zwitterionic polymer-modified silicon microring resonators for label-free biosensing in undiluted human plasma

James T. Kirk [a], Norman D. Brault [b], Tom Baehr-Jones [c], Michael Hochberg [c], Shaoyi Jiang [b], Daniel M. Ratner [a,*]

[a] Department of Bioengineering, University of Washington, Box 355061, Seattle, WA 98195, USA
[b] Department of Chemical Engineering, University of Washington, Box 351750, Seattle, WA 98195, USA
[c] Department of Electrical Engineering, University of Delaware, DuPont Hall, Newark, DE 19716, USA

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ABSTRACT

A widely acknowledged goal in personalized medicine is to radically reduce the costs of highly parallelized, small fluid volume, point-of-care and home-based diagnostics. Recently, there has been a surge of interest in using complementary metal-oxide-semiconductor (CMOS)-compatible silicon photonic circuits for biosensing, with the promise of producing chip-scale integrated devices containing thousands of orthogonal sensors, at minimal cost on a per-chip basis. A central challenge in biosensor translation is to engineer devices that are both sensitive and specific to a target analyte within unprocessed biological fluids. Despite advances in the sensitivity of silicon photonic biosensors, poor biological specificity at the sensor surface remains a significant factor limiting assay performance in complex media (i.e. whole blood, plasma, serum) due to the non-specific adsorption of proteins and other biomolecules. Here, we chemically modify the surface of silicon microring resonator biosensors for the label-free detection of an analyte in undiluted human plasma. This work highlights the first application of a non-fouling zwitterionic surface coating to enable silicon photonic-based label-free detection of a protein analyte at clinically relevant sensitivities in undiluted human plasma.

1. Introduction

For decades, the enzyme-linked immunosorbent assay (ELISA) served as the clinical standard for sensitive detection of diagnostic biomarkers in biological samples (i.e. blood, saliva, urine) (Lequin, 2005). Multiple surrogate methods, such as microarrays, enzyme-linked electrochemical immunosensors, and lateral flow immunoassays, have also been investigated and are gaining adoption in the clinic to perform assays with improved sensitivity and higher throughput. However, these assays are not without their limitations, as they require signal amplification of bound analyte by primary and secondary antibodies, substantially increasing both the cost and time of the diagnostic. In contrast, real-time label-free technologies for the detection of biomolecules—including plasmonic, photonic, electronic, and mechanical biosensors—are promising alternatives to ELISA by eliminating the need for signal amplification, thereby accelerating the time to diagnosis and reducing reagent costs (Qavi et al., 2009).

Within the last few years, silicon photonic resonant optical microcavities, such as microtoroids (Armani et al., 2007), microrings (Flueckiger et al., 2011; Washburn et al., 2009), and microspheres (Arnold et al., 2003), have demonstrated highly sensitive label-free detection of biological molecules. Microring resonators are exceedingly amenable to scalable fabrication using CMOS-compatible processes, setting them apart from most other resonant optical microcavity devices for high-throughput, multiplexed biosensing (Washburn and Bailey, 2010). SOI microring resonators, in particular, have been utilized for the detection of a diverse range of biological species, including antibodies (Luchansky and Bailey, 2010), proteins (Washburn et al., 2009), nucleic acids (Qavi and Bailey, 2010), and bacteria (Ramachandran et al., 2008), among others. While microcavity devices have proven to be very sensitive, their use has been largely limited to dilute biological samples, or required label-based signal amplification (Luchansky and Bailey, 2010, 2011; Luchansky et al., 2011). With the ultimate goal of performing label-free sensing in unmodified clinical samples, the field must address the challenge of non-specific protein adsorption in complex biological fluids.

Conventional label-free biosensors, including microring resonators, are poorly suited for label-free clinical biosensing due to the non-specific adsorption of protein, known as fouling, from complex biological samples. Protein fouling significantly decreases the sensitivity of biosensors due to a lack of biological specificity at the sensor

* Corresponding author. Tel.: +1 206 685 2840; fax: +1 206 685 3300.
E-mail addresses: jtk8@uw.edu (J.T. Kirk), ndb16@u.washington.edu (N.D. Brault), tbaehrjones@gmail.com (T. Baehr-Jones), hochberg@udel.edu (M. Hochberg), sjiang@u.washington.edu (S. Jiang), dratner@uw.edu (D.M. Ratner).

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surface, resulting in false positive signals (Jiang and Cao, 2010). Common strategies for passivating surfaces to non-specific biological interactions include adsorption of 'blocking' proteins (e.g. serum albumin) and grafting inert polymeric scaffolds (e.g. polyethylene glycol (PEG)) to the surface. These passivation approaches increase surface hydration through intermolecular hydrogen bonding. However, they are inadequate to fully resist protein fouling in undiluted complex biological samples (Jiang and Cao, 2010). Furthermore, PEG-grafted surfaces require extensive and complex chemical methods to covalently immobilize specific molecular capture elements.

Zwitterionic polymers, composed of sulfobetaine methacrylate (SBMA) or carboxybetaine methacrylate (CBMA) monomers, produce surfaces that are highly charged yet are overall net-neutral. Molecular simulations suggest that the zwitterionic nature of these materials electrostatically induces surface hydration as opposed to hydration by hydrogen bonding interactions, resulting in ultra-low protein fouling when exposed to human plasma and serum (Chen et al., 2005; He et al., 2008). The growth of zwitterionic surface coatings can be tuned using atom transfer radical polymerization (ATRP) for optimal resistance to protein fouling in complex biological solutions (Zhang et al., 2006). Previously, arrays of microring resonators have been utilized to monitor the in situ growth of SBMA coatings via surface initiated-ATRP to reduce non-specific protein adsorption in fetal bovine serum (Limpoco and Bailey, 2011). While pSBMA coatings resulted in low levels of protein fouling, they lacked reactive end groups to facilitate the immobilization of capture elements for specific analyte detection. CBMA-based polymers, however, have been shown to facilitate facile conjugation of biomolecules to plasmonic and mechanical biosensors (Jiang and Cao, 2010).

Surface-initiated, or "grow-from-surface", polymerization of zwitterionic polymers has been routinely performed via ATRP on biosensors to produce ultralow fouling coatings. This process requires substantial optimization of polymerization conditions, and personnel training to ensure ideal coating performance. In contrast to surface initiated-ATRP, solution phase polymerization of "graft-to-surface" zwitterionic polymer brushes does not require extensive chemical modification of the device to yield ultralow fouling surfaces and may be performed in an aqueous environment. This "graft-to" strategy has enabled the sensitive detection of analyte in human serum while minimizing protein fouling on silicon oxide-coated gold substrates (Brault et al., 2010) and silicon microcantilevers (Von Muhlen et al., 2010).

In this study, we implement a universal surface modification for silicon photonic biosensors that yields a sensor surface that is resistant to non-specific biomolecule interactions yet sensitive to the detection of analyte at clinically relevant concentrations. By conjugating CBMA polymer chains to the adhesive moiety 3,4-dihydroxy-L-phenylalanine (DOPA), we produce pre-grown zwitterionic polymer conjugates, DOPA-pCBMA (DpC), that readily graft to silicon oxide surfaces (Gao et al., 2010). To demonstrate the suitability of DpC coatings for biosensing, we optimize the functionalization and performance of DpC-coated sensors to interrogate protein–protein interactions in undiluted human plasma using streptavidin/anti-streptavidin as a model antigen/antibody pair. Our results represent a significant achievement for silicon photonic biosensors by demonstrating a label-free sensor surface that is both sensitive and remarkably specific for detecting biological interactions in human plasma.

2. Materials and methods

2.1. Materials

All chemical reagents were purchased from Sigma-Aldrich, Corp (St. Louis, MO) and used without further purification unless otherwise noted. Fraction V bovine serum albumin was purchased from EMD Chemicals (Gibbstown, NJ). Fibrinogen (Fb; Fraction I, bovine plasma) was purchased from Sigma-Aldrich. Human plasma and serum samples were provided as a gift by Dr. Jill Johnsen of the Puget Sound Blood Center (Seattle, WA). Murine monoclonal antibodies against streptavidin and monoclonal immunoglobulin (IgG1) control antibodies were purchased from Abcam, Inc (San Francisco, CA). Streptavidin and polycloncal anti-streptavidin antibodies were purchased from Vector Laboratories (Burlingame, CA). Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS) were purchased from Sigma-Aldrich.

2.2. Microring resonator biosensing platform

Silicon microring resonator biosensors and corresponding analysis instrumentation were manufactured by Genalyte, Inc. (San Diego, CA) (Iqbal et al., 2010). Each biosensor chip consists of an array of 72 individually addressable microring resonators (30 μm in diameter) suitable for real-time biosensing analysis. Sixty four of these microring resonators are exposed for biosensing and the remaining eight sensors are coated with a fluoropolymer-cladding to serve exclusively as temperature and vibration reference controls. Exposed microring resonators can be surface modified using chemistries that are compatible with the native oxide of the silicon waveguides. To minimize waveguide losses, the entire chip is coated with cladding with the exception of the exposed microring sensors, limiting all interactions with a biological sample to designated resonators. An external cavity diode laser with a center frequency of 1560 nm rapidly interrogates grating couplers of individual microring resonators (approximately 250 ms per ring), measuring the shift in resonance wavelength of the optical cavity as a function of time.

2.3. Polymer deposition on silicon microring resonator arrays

Methods for the synthesis of DpC conjugates and a description of the biosensor platform are described in the supplementary materials. To remove trace organic material prior to surface modification with DpC conjugates, biosensor chips were cleaned with piranha solution (1:1 30% H_2O_2:98% H_2SO_4) for 10 min with mild agitation to remove bubbles on the chip surface (*Caution*! *Piranha solution is extremely dangerous.*). Chips were washed with copious amounts of water prior to the deposition of DpC conjugates on the bare oxide surface of silicon microring resonators.

Solutions were introduced to sensors using two alternating 50 μL negative-pressure syringe pumps controlled by computer software. DpC conjugates were diluted to a concentration of 1 mg/ml in deposition buffer (10 mM Tris–HCl; pH 8.5). The biosensor chip was exposed to deposition buffer to establish a signal baseline prior to introduction of the polymer solution. An array of microring resonators was exposed to a sonicated DpC solution for 15 min, resulting in high-density deposition of DpC conjugates on the exposed oxide of the microring sensor surface. Microring resonators were washed with deposition buffer for 5 min, followed by an extensive wash in phosphate buffered saline (PBS; pH 7.4) to remove loosely bound DpC conjugates. As a control, a second array of microring resonators was exposed to a solution of 1 mg/ml BSA in parallel to DpC modification prior to performing protein fouling assays.

2.4. Protein fouling assays

The overall shift in resonance wavelength was used to compare the amount of protein fouling for DpC- and BSA-coated sensors. The ability of the surface modified sensors to resist protein fouling in complex biological solutions was assessed using

undiluted human plasma. After establishing a baseline in PBS, sensors were exposed to undiluted human plasma for 15 min. After returning to PBS, the overall shift in resonance wavelength was used to compare the amount of protein fouling for each surface modification strategy. The results were compared to the amount of protein fouling on unmodified (bare oxide) microring resonators following extended exposure to undiluted human plasma.

2.5. Immobilization of antibodies to DpC-modified microring resonator biosensors

The terminal carboxylic acid groups of DpC-coated microring resonators were activated using carbodiimide chemistry prior to antibody immobilization. A freshly prepared activation buffer (0.4 M EDC, 0.1 M NHS) was passed over the DpC-modified sensors twice for 5 min, separated by 1 min wash steps with ultrapure water. Activated DpC-coatings on microrings were exposed to either monoclonal anti-streptavidin (antiSA) or immunoglobulin control antibodies (IgGi, negative control). After antibody immobilization, activated coatings were quenched at elevated pH (10 mM HEPES, 300 nM NaCl, pH 8.2).

2.6. Detection of streptavidin in buffer and undiluted human plasma

Streptavidin (SA) was diluted in buffer at concentrations ranging from 50 ng/ml to 20 μg/ml. Concentration steps were separated by 5 min buffer (PBS) washes. The shift in resonance wavelength of antiSA-DpC microrings was compared to IgGi-DpC microrings to demonstrate specific streptavidin detection in buffer.

SA detection in undiluted plasma was confirmed by exposing sensors to a series of SA-spiked human plasma samples. SA-spiked plasma samples (10–10,000 ng/ml) were flowed over microrings for 5–10 min per sample (10 μL/min), and were separated by buffer washes for 5 min (30 μL/min). Specific SA binding was defined as the difference in sensor response between antiSA-DpC and IgGi-DpC microrings during buffer washes ($n \geq 30$).

3. Results and discussion

We evaluated the ability of the DpC strategy to prevent non-specific adsorption of protein to the oxide surface on the silicon microring resonator. As depicted schematically in Fig. 1a, arrays of microring resonator biosensors were exposed to solutions of DpC or bovine serum albumin (BSA) for surface passivation. The relative shift in the resonance wavelength of the microrings was monitored during deposition of DpC and BSA on a biosensor array (Fig. 1b). DpC and BSA coatings were characterized by X-ray photoelectron spectroscopy (XPS) and ellipsometry (see Tables S1 and S2). Microrings coated with BSA and DpC were exposed to solutions with varying concentrations of glucose (0.5 M to

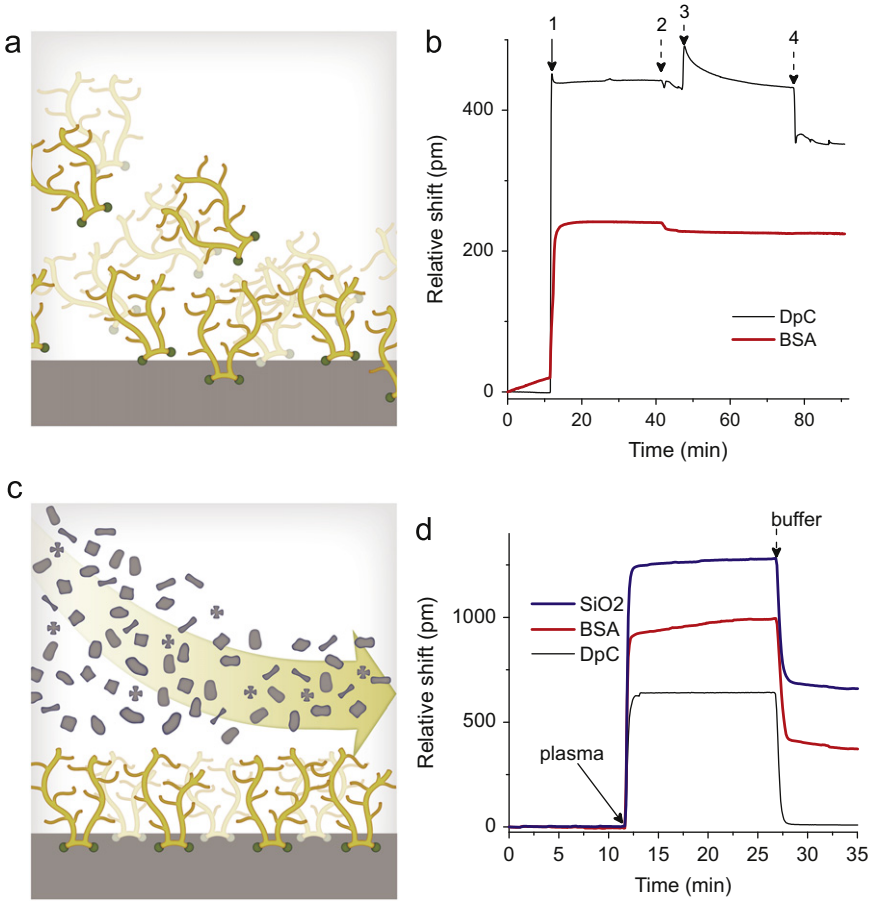

Fig. 1. (a) Schematic detailing the deposition of DpC polymer chains on the sensor's oxide surface. (b) The relative shift in resonance wavelength over time during surface modification. Microrings were exposed to (1) a solution of DpC or BSA and then returned to (2) deposition buffer. DpC-coated microring resonators were (3) washed with buffer to remove loosely bound polymer, and returned to (4) deposition buffer to quantify the adsorbate. (c) Schematic illustrating the resistance of DpC-coated surfaces to protein fouling in complex media. (d) Microring resonators were exposed to undiluted human plasma for 15 min prior to returning to buffer to determine the amount of non-specific adsorption based on the overall shift in resonance wavelength before and after exposure to plasma. Note: illustrations are not to scale.

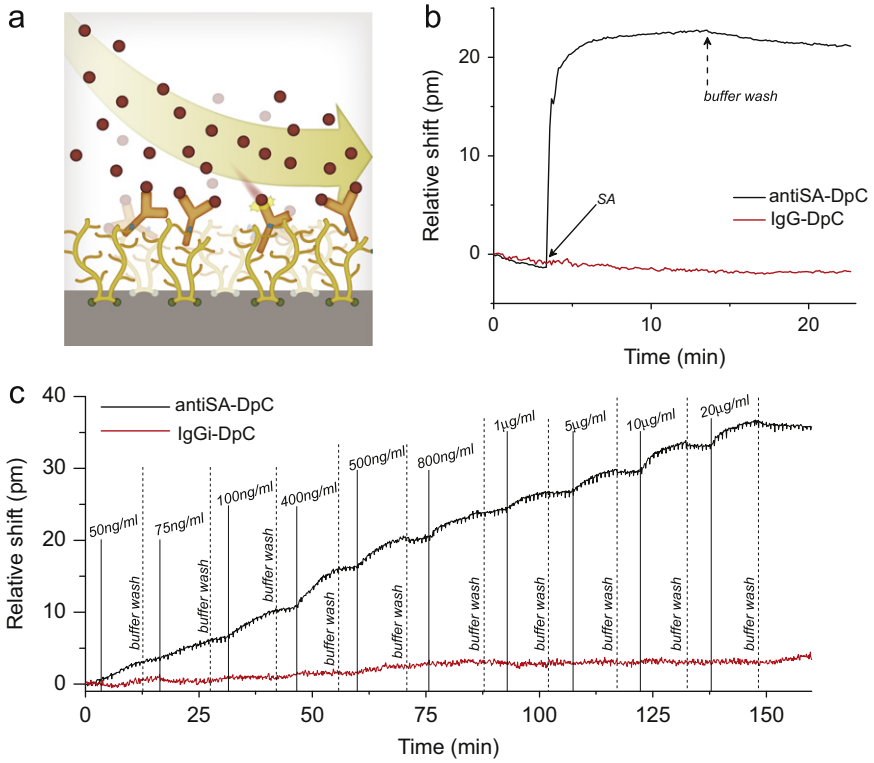

Fig. 2. (a) Specific binding of SA to DpC-immobilized antiSA in buffer. Note: illustrations are not to scale. (b) Upon exposure to a solution of SA in buffer, antiSA-DpC microrings demonstrate specific binding of SA as well as the appropriate dissociation response upon returning to buffer. As expected, IgGi-DpC microrings show no response to the buffer solution of SA. (c) AntiSA-DpC sensors exhibit concentration dependent binding of SA, with minimal non-specific binding to IgGi-DpC sensors.

62.5 mM, data not shown) to assess signal attenuation compared to the unmodified microrings. Coated sensors achieved the same responsivity when exposed to the refractive index standards, indicating that DpC surface modification did not substantially attenuate sensor performance.

To assess the ability of the biosensor surface coatings to decrease protein fouling (Fig. 1c), we exposed coated microring resonators to fibrinogen (supplementary materials Fig. S1) and undiluted human plasma (Fig. 1d). The overall shift in signal after exposing the sensors to 100% human plasma was used to assess the amount of protein fouling at the microring resonator surface. While BSA blocking of the sensor surface decreases the amount of protein fouling by 44.4% compared to bare microring (silicon oxide), the DpC coating achieves remarkably low fouling (98.6% decrease) in human plasma. This result demonstrates the significant ability of DpC coatings to yield biocompatible surfaces on silicon photonic devices.

In addition to effectively eliminating surface fouling, the DpC strategy enables facile conjugation of capture ligands that impart biological function to individual silicon photonic biosensors (Vaisocherová et al., 2009). The exposed carboxylic acid functionality of surface-grafted DpC is readily activated via standard bioconjugation chemistries to immobilize antibodies or other bioactive capture elements. For this study, we selected streptavidin/anti-streptavidin as a model antigen/antibody system to demonstrate specific and sensitive protein analyte detection in buffer and plasma samples. DpC coatings were activated via carbodiimide chemistry to immobilize a monoclonal antibody (antiSA) specific for the protein streptavidin (supplementary materials Fig. S2). An isotype control antibody (IgGi), sharing the same structure as antiSA, but with no binding specificity for SA, was immobilized to adjacent microring resonators to serve as a negative control during subsequent analyses. To demonstrate specific protein detection (Fig. 2a), SA was spiked in buffer (PBS). As expected, the antiSA-DpC microrings exhibited specific binding of SA, while control IgGi-DpC microrings had no significant sensor response (Fig. 2b). Furthermore, antiSA-DpC microrings exhibited concentration-dependent binding of SA while control IgGi-DpC microrings showed minimal non-specific SA adsorption (Fig. 2c). The relative resonance shift difference as a function of target analyte concentration can be expressed as:

$$d\lambda = A\alpha P/(1+\alpha P) \quad (1)$$

where P is the concentration of SA in solution, α is the binding coefficient, A is a constant of proportionality depending on the number of antiSA sites, and the amount of resonance shift per SA molecule, and finally $d\lambda$ is the relative resonance shift difference. A least-squares fit of Eq. (1) to the peak shift differences between the antiSA-DpC and IgGi-DpC microrings yields a best-fit binding coefficient α of 0.0034 $(ng/ml)^{-1}$and an observed K_d of 4.9 nM in buffer (supplementary materials Fig. S3). These results validate the ability of DpC-modified silicon devices to function as biocompatible sensors for specific biomolecule detection.

The primary goal of this study was to demonstrate the detection of analyte in undiluted biological fluids. In this case, human plasma was used as a clinically relevant sample. Undiluted human plasma was spiked with SA at concentrations ranging from 10 ng/ml to 10 μg/ml, encompassing a range of concentrations relevant to clinical diagnostics (Rifai et al., 2006). Sensors were exposed to increasing concentrations of SA-spiked human plasma, with buffer washes between samples (Fig. 3a). Large resonance shifts are seen on all rings, on the order of 650 pm, due to the difference in average refractive index between buffer and plasma. A clear relative shift difference is seen between the antiSA-DpC microrings and the IgGi-DpC control, indicating that SA is being specifically detected. It should be noted that the increase in fouling of the antibody-DpC functionalized microrings is likely due to nonspecific binding of plasma protein to the

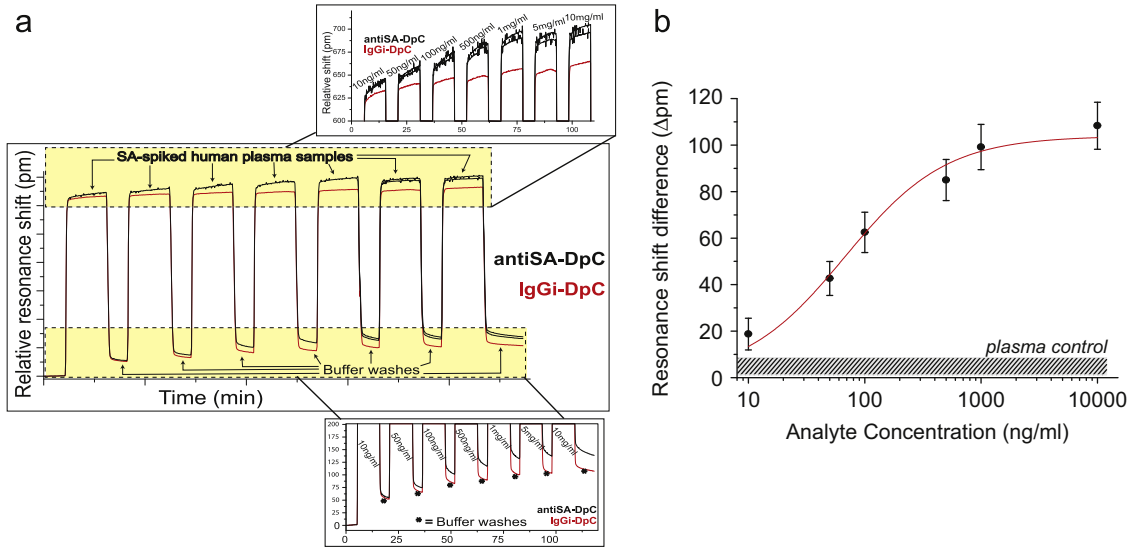

Fig. 3. (a) Sensor response to increasing concentrations of SA in undiluted human plasma separated by brief washes with buffer (inset, top). Specific SA binding was defined as the difference in signal between antiSA-DpC and IgGi-DpC microrings (inset, bottom). (b) A Langmuir best-fit binding curve for the differential binding response between antiSA-DpC microrings and IgGi-DpC negative control sensors ($n \geq 30$). The gray box represents the differential sensor response to an unspiked plasma control (mean ± SD).

immobilized antibody capture ligands. However, additional exposure of functionalized sensors to undiluted plasma resulted in little additional protein fouling. These results demonstrate that DpC coatings may be functionalized with biomolecules while largely retaining their non-fouling properties during extended exposure to undiluted human plasma.

To fully optimize sensor array performance in undiluted human plasma, we controlled the number of antibodies immobilized to DpC sensors. We achieved optimal sensor performance by immobilizing sensors with approximately 850,000 antibodies per microring (~165 pm relative shift; supplementary materials Fig. S2). The relative shift difference between antiSA-DpC and IgGi-DpC was monitored over time during buffer washes following each SA-spiked plasma sample. A least squares regression of the relative peak-shift differences between the antiSA-DpC and IgGi-DpC control microrings (Fig. 3b) yields a binding coefficient of 0.015 $(ng/ml)^{-1}$ and an observed K_d of 1.1 nM. The estimated number of SA binding events at the surface of each microring was determined to be 1.3E6 on average, in close agreement with the number of immobilized antibodies. Based on the approximate dimensions of the SA molecule ($5 \times 5 \times 5$ nm^3) (Darst et al., 1991), the observed response at saturation corresponds to 40% surface coverage of the microring. It is worth noting that we observe a difference in the binding coefficients when characterizing antiSA-DpC/SA association in buffer versus undiluted plasma. This variation in binding coefficients was anticipated due to solution composition (plasma vs. buffer), and the results are comparable to past literature observations (Morgan et al., 1998).

A control experiment was performed by exposing antiSA-DpC and IgGi-DpC sensor arrays ($n \geq 30$) to undiluted human plasma with no SA spiked into the sample in order to determine any differential non-specific adsorption of plasma protein to immobilized antibodies (Fig. 3b, gray box represents the mean ± SD). Assuming a noise floor of 3σ, the functional biosensors exhibit sensitivities of approximately 10 ng/ml of SA in undiluted human plasma. The achieved limit of detection is an order of magnitude more sensitive than the basic commercial colorimetric ELISA used for protein detection in clinical assays (supplementary materials Fig. S4).

Our results demonstrate a concentration-dependent response of functionalized sensors to SA-spiked plasma samples with a limit of detection of 10 ng/ml. This study establishes an important accomplishment for silicon photonic biosensors by demonstrating specific detection in undiluted plasma at ELISA-like sensitivities. The specific binding of SA was confirmed through signal amplification by flowing a secondary polyclonal antiSA antibody over the sensor array (supplementary materials Fig. S5). As expected due to their relative molecular weights (Darst et al., 1991; Weisenhorn et al., 1992), there is good agreement between the number of SA molecules (57 kDa) bound from plasma samples and the number of polyclonal antiSA antibodies (150 kDa) bound during amplification. These results indicate that the DpC strategy is amenable to signal amplification, which can enable even further improvements on the limit of detection in complex media. Similar amplification strategies have been previously employed via antibody- and sub-micron microsphere-mediated mass tags, enabling ultralow limits of detection on microring resonators (Luchansky et al., 2011).

4. Conclusions

To fully exploit the potential of silicon photonic-based sensing platforms, robust chemical surface modification is necessary for label-free device performance in complex biological samples. This study highlights a rapid and versatile chemical surface modification for silicon photonic biosensors via a DpC polymer strategy. We have shown that DpC polymer-coated silicon photonic biosensors can provide ELISA-like sensitivity with extraordinary selectivity in undiluted human plasma, without the need for signal amplification. This development in biocompatible silicon photonics represents a significant step toward the application of these devices in clinical diagnostics and the biomedical sciences. Future efforts will focus on employing the DpC surface modification strategy for the development of robust assays for multiplexed detection of clinically relevant biomarkers.

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Appendix A. Supplementary materials

Supplementary materials associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bios.2012.10.079.

References

Armani, A.M., Kulkarni, R.P., Fraser, S.E., Flagan, R.C., Vahala, K.J., 2007. Science 317 (5839), 783.
Arnold, S., Khoshsima, M., Teraoka, I., Holler, S., Vollmer, F., 2003. Optics Letters 28 (4), 272–274.
Brault, N.D., Gao, C., Xue, H., Piliarik, M., Homola, J., Jiang, S., Yu, Q., 2010. Biosensors and Bioelectronics 25 (10), 2276–2282.
Chen, S., Zheng, J., Li, L., Jiang, S., 2005. Journal of the American Chemical Society 127 (41), 14473–14478.
Darst, S.A., Ahlers, M., Meller, P., Kubalek, E., Blankenburg, R., Ribi, H., Ringsdorf, H., Kornberg, R., 1991. Biophysical Journal 59 (2), 387–396.
Flueckiger, J., Grist, S.M., Bisra, G., Chrostowski, L., Cheung, K.C., 2011. Proceedings of SPIE 7929, 79290I-1–79290I-10.
Gao, C., Li, G., Xue, H., Yang, W., Zhang, F., Jiang, S., 2010. Biomaterials 31 (7), 1486–1492.
He, Y., Hower, J., Chen, S., Bernards, M.T., Chang, Y., Jiang, S., 2008. Langmuir 24 (18), 10358–10364.
Iqbal, M., Gleeson, M.A., Spaugh, B., Tybor, F., Gunn, W.G., Hochberg, M., Baehr-Jones, T., Bailey, R.C., Gunn, L.C., 2010. IEEE Journal of Selected Topics in Quantum Electronics 16 (3), 654–661.
Jiang, S., Cao, Z., 2010. Advanced Materials 22 (9), 920–932.
Lequin, R.M., 2005. Clinical Chemistry 51 (12), 2415–2418.
Limpoco, F.T., Bailey, R.C., 2011. Journal of the American Chemical Society 133 (38), 14864–14867.
Luchansky, M.S., Bailey, R.C., 2010. Analytical Chemistry 82 (5), 1975–1981.
Luchansky, M.S., Bailey, R.C., 2011. Journal of the American Chemical Society 133 (50), 20500–20506.
Luchansky, M.S., Washburn, A.L., McClellan, M.S., Bailey, R.C., 2011. Lab on a Chip 11 (12), 2042–2044.
Morgan, C.L., Newman, D.J., M Burrin, J., Price, C.P., 1998. Journal of Immunological Methods 217 (1–2), 51–60.
Qavi, A.J., Bailey, R.C., 2010. Angewandte Chemie—International Edition 49 (27), 4608–4611.
Qavi, A.J., Washburn, A.L., Byeon, J.Y., Bailey, R.C., 2009. Analytical and Bioanalytical Chemistry 394 (1), 121–135.
Ramachandran, A., Wang, S., Clarke, J., Ja, S., Goad, D., Wald, L., Flood, E., Knobbe, E., Hryniewicz, J., Chu, S., 2008. Biosensors and Bioelectronics 23 (7), 939–944.
Rifai, N., Gillette, M.A., Carr, S.A., 2006. Nature Biotechnology 24 (8), 971–983.
Vaisocherová, H., Zhang, Z., Yang, W., Cao, Z., Cheng, G., Taylor, A.D., Piliarik, M., Homola, J., Jiang, S., 2009. Biosensors and Bioelectronics 24 (7), 1924–1930.
Von Muhlen, M.G., Brault, N.D., Knudsen, S.M., Jiang, S., Manalis, S.R., 2010. Analytical Chemistry 82 (5), 1905–1910.
Washburn, A.L., Bailey, R.C., 2010. Analyst 136 (2), 227–236.
Washburn, A.L., Luchansky, M.S., Bowman, A.L., Bailey, R.C., 2009. Analytical Chemistry 82 (1), 69–72.
Weisenhorn, A., Schmitt, F.J., Knoll, W., Hansma, P., 1992. Ultramicroscopy 42, 1125–1132.
Zhang, Z., Chen, S., Chang, Y., Jiang, S., 2006. Journal of Physical Chemistry B 110 (22), 10799–10804.