Biotechnology Advances, Volume 39, March–April 2020, Article number 107398
DOI:10.1016/j.biotechadv.2019.05.004

# Soft and flexible material-based affinity sensors

Lingyin Meng[1], Anthony P.F. Turner[2,*], Wing Cheung Mak[1,*]

[1] Biosensors and Bioelectronics Centre, Department of Physics, Chemistry and Biology, Linköping University, SE-581 83 Linköping, Sweden

[2] SATM, Cranfield University, Bedfordshire, MK430AL, UK

[*]Corresponding authors

## Abstract

Recent advances in biosensors and point-of-care (PoC) devices are poised to change and expand the delivery of diagnostics from conventional lateral-flow assays and test strips that dominate the market currently, to newly emerging wearable and implantable devices that can provide continuous monitoring. Soft and flexible materials are playing a key role in propelling these trends towards real-time and remote health monitoring. Affinity biosensors have the capability to provide for diagnosis and monitoring of cancerous, cardiovascular, infectious and genetic diseases by the detection of biomarkers using affinity interactions. This review tracks the evolution of affinity sensors from conventional lateral-flow test strips to wearable/implantable devices enabled by soft and flexible materials. Initially, we highlight conventional affinity sensors exploiting membrane and paper materials which have been so successfully applied in point-of-care tests, such as lateral-flow immunoassay strips and emerging microfluidic paper-based devices. We then turn our attention to the multifarious polymer designs that provide both the base materials for sensor designs, such as PDMS, and more advanced functionalised materials that are capable of both recognition and transduction, such as conducting and molecularly imprinted polymers. The subsequent content discusses wearable soft and flexible material-based affinity sensors, classified as flexible and skin-mountable, textile materials-based and contact lens-based affinity sensors. In the final sections, we explore the possibilities for implantable/injectable soft and flexible affinity sensors, including hydrogels, microencapsulated sensors and optical fibers. This area is truly a work in progress and we trust that this review will help pull together the many technological streams that are contributing to the field.

**Keywords:** affinity sensors; point-of-care; wearable; implantable; papers; conducting polymers; molecular imprinted polymers; skin patches; contact lenses; hydrogels



Published by Elsevier. This is the Author Accepted Manuscript issued with: Creative Commons Attribution Non-Commercial No Derivatives License (CC:BY:NC:ND 4.0).
The final published version (version of record) is available online at DOI:10.1016/j.biotechadv.2019.05.004. Please refer to any applicable publisher terms of use.

## 1. Introduction

Predictions from the co-chair of the World Economic Forum's Future Council, Melanie Walker, suggest that hospitals could largely be a thing of the past within little over a decade, replaced by mobile and wearable technologies delivering healthcare in decentralised locations in a far more cost-effective manner (Walker, 2016). Whether or not we subscribe to the predicted timescale, it is clear that such a theranostic revolution would herald a period of far-reaching social, economic and political upheaval. The sheer numbers of people affected, structural reorganisation and financial implications, present an extremely complex landscape that is challenging to navigate. At the heart of all this, however, lies the sensing, processing and transducing capabilities of biointerfaced devices, such as biosensors.

Biosensors, as classically defined, incorporate biological or biologically derived sensing elements that harness the exquisite specificity and sensitivity of living systems in conjunction with electronic transducers and processors, to either provide data directly or to actuate an appropriate response (Turner, 2013). Such devices provide a key element in a frictionless approach to health management, which potentially empowers users with the data and information they require to efficiently manage their health anywhere and anytime, while providing them with confidence in the integrity of data and the security of any automated actions. Based on the biorecognition principle, biosensors are categorised as: (i) catalytic biosensors, typical examples are enzyme biosensors; and (ii) affinity biosensors, typical examples are immunosensors and nucleic acid biosensors. Catalytic biosensors use catalysts as biorecognition elements, such as enzymes, biomimetic/synthetic catalysts, cells and microorganisms etc., where the sensing principle is based on the detection of biocatalytic reactions in the presence of an analyte. In contrast, affinity biosensors use affinity molecules as biorecognition elements, such as antibodies, nucleic acids, receptors, and synthetic affinity polymers, where the sensing principle is based on detection of affinity interactions between the biorecognition element and the analyte. Affinity sensors are highly important for the detection of the majority of biomarkers in disease diagnosis and continuous monitoring and offer some advantages over catalytic biosensors, most notably the lack of consumption of the analyte. The addition of affinity elements enables selective and specific binding for their target species at low concentrations of analyte in complex samples, and the binding interactions can be monitored in real time (Turner, 2013).

Advances in material science, manufacturing and device integration are propelling the development of new affinity sensors. A major trend is the move from conventional invasive point-of-care tests towards minimally-invasive and non-invasive wearable and implantable

devices for continuous, real-time and remote monitoring. The development of wearable and implantable devices for long-term monitoring is now a key goal. The recent boom in wearable sensors has highlighted the potential of continuous measurement and the appetite amongst users for personalised information, such as biosensor patches and printed electronics, is now well established. Arguably, the major bottleneck at the current time is the availability of reliable sensors that directly measure key biochemical parameters consistently in real situations. Most current wearable devices have ingeniously exploited physical sensors that were already readily available and used these to infer relevant secondary information. Chemical sensors and biosensors, affinity sensors in particular, present greater challenges, but the direct molecular information that they can deliver is essential to higher level algorithms for personalised management of health, artificial intelligence and control of biochemical systems.

Recently, several excellent review articles have been published on flexible and wearable sensing devices (Huang et al., 2014; Liu et al., 2017; Ray et al., 2019; Trung and Lee, 2016; Wang et al., 2016a; Xu et al., 2018a). However, these reviews mainly focused on power supplies (Li et al., 2018), electronic design (Liu et al., 2017; Zhao et al., 2017), physical sensors for measurements of temperature, heart rate, body motion and strain (Huang et al., 2014; Trung and Lee, 2016), chemical sensors (pH, ions and humidity) and catalytic biosensor (glucose, lactate and dopamine etc.) (Ray et al., 2019; Wang et al., 2016a; Xu et al., 2018a). Most of these review articles focus on catalytic biosensors or chemical sensors, while there is little coverage of soft and flexible material-based wearable and implantable affinity sensors. In this review, we aim to cover the research & development trends from convention to advanced soft and flexible materials utilised for the development of state-of-the-art affinity biosensors towards emerging wearable and implantable affinity biosensors. Hence, the review commences with membrane-based lateral-flow affinity test strips and microfluidic paper-based tests. We then move to the multifarious polymer designs that form a key component of affinity sensors (i.e. PDMS polymers for microfluidics and flexible affinity sensing platforms, functional conducting polymers as bio-affinity transducer interfaces, and molecularly imprinted polymers (MIPs) used as advanced synthetic affinity biorecognition elements) and their role in portable *in vitro* diagnostic (IVD) devices. Finally, we review the emerging field of wearable and implantable affinity sensors (that go beyond IVD devices). We aim to provide a comprehensive review covering the concept of using soft and flexible materials for the development of IVD affinity sensors, and chart the route towards wearable sensors and other advanced applications of implantable affinity sensors. We present a multidisciplinary approach that we hope will inspire and benefit a broad scientific audience working on various formats of affinity sensors.

Figure 1 summarises some examples of soft and flexible materials that we use to illustrate the potential development of affinity biosensors.

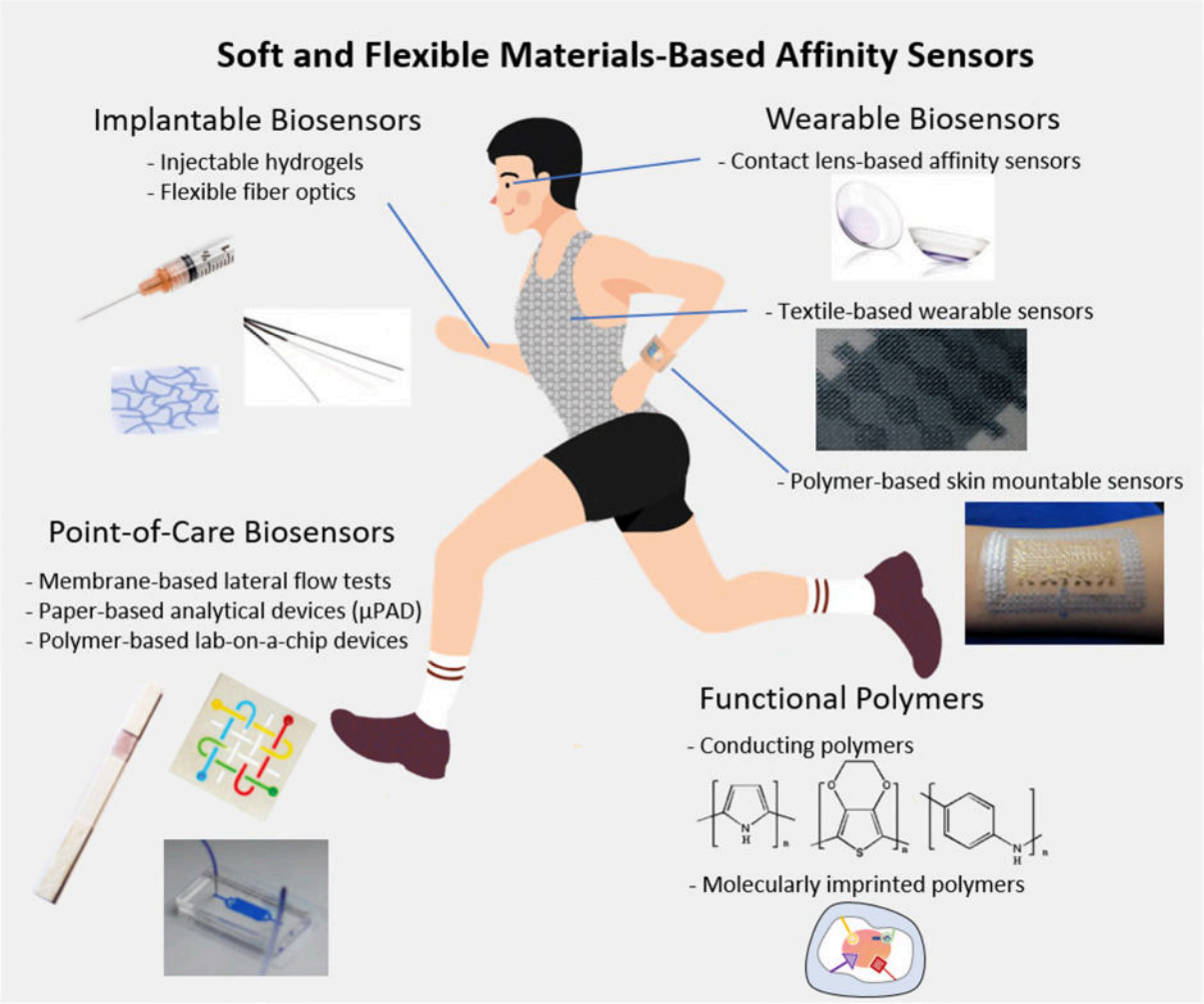


**Figure 1** Schematic illustration summarising applications of various soft and flexible materials used for the development of affinity biosensors ranging from point-of-care (PoC) tests, wearable biosensors and implantable affinity biosensors.

## 2 Conventional soft and flexible material-based affinity sensors for PoC tests

### 2.1 Membrane and paper-based affinity devices

The recent rise in popularity of flexible, stretchable biosensors and sensing devices, is driven by the emergence of multifarious wearable sensors for fitness and health monitoring. Previously, the principal market drivers for flexible-material based sensors were dominated by membrane and paper based analytical devices such as the lateral-flow membrane-based strip tests and microfluidic paper-based analytical devices (µPADs). The attractive features of using paper and membranes as soft and flexible materials for the construction of biosensors include their light-weight, low cost, portability, compatibility for immobilisation of biological

recognition molecules and inherent capillary forces, which facilitate operation without requiring an external pump. This makes them cost-effective and highly suitable for disposable point-of-care (PoC) diagnostic applications. However, the water adsorption properties and mechanically instability of membrane and paper make them less useful for wearable sensors. This review will look at recent advances in lateral-flow affinity tests and μPADs from a soft-material prospective and focus on additive manufacturing, paper and membrane engineering and their biosensing applications.

### 2.1.1 Lateral-flow membrane-based strip tests

Lateral-flow membrane-based strip tests, also known as lateral-flow immuno-chormatographic tests and lateral-flow immunoassays (LFIA), first appeared commercially in 1984, developed by Unilever and its subsidiary, Unipath, at Colworth in the UK. Lateral-flow strip tests subsequently became one of the most important platforms for Point-of-Care (PoC) diagnostics, with the market being worth around USD 5.14 billion in 2016 and potential for further rapid growth driven by the combination of LFIA with mobile-phone optical sensing technology (marketsandmarkets.com, 2017). The design of the lateral-flow test is based on integration of various membrane components in a serial order to enable different assay tasks for the realisation of single-step diagnostics. In general, a lateral-flow test comprises a sample membrane (cellulose), a conjugation membrane (glass fibre), an assay membrane (nitrocellulose) and an adsorption membrane (cellulose). The sample membrane allows the collection of sample fluid by adsorption. The collected sample is then driven to the conjugation membrane which contains the specific labelled secondary antibodies for the target analytes. The mixture then enters the nitrocellulose assay membrane with immobilised primary antibodies at the test zone, where an immunocomplex forms upon binding of the target analyte and the labelled secondary antibodies. Finally, the absorption membrane serves as a reservoir to collect the excess fluids. Various labelling strategies for optical and electrochemical transducers in lateral-flow tests can be found in our recent review article (Mak et al., 2016). From an engineering perspective, the high flexibility provided by the combination of various membrane components make lateral-flow tests a cost-effective analytical platform for applications in the areas of clinical diagnostics (Chan et al., 2013a), pathogen detection (Ngom et al., 2010), environmental monitoring (Cheng et al., 2017), food safety (Sajid et al., 2015), pharmaceutical analysis and drug testing (Taranova et al., 2013).

The analytical performance of lateral-flow tests has limitations due to the unidirectional fluidic flow and its optimisation is mainly restricted to the development of bioassay chemistry, membrane porosity and the biolabel system. These bottle necks have been around for many

years and have limited more advanced biosensor applications. Recently, a new research direction focusing on engineering the soft membrane materials via the fabrication of micropatterns within the lateral-flow test membrane could open up the micro-fluidic features of these strip tests and enable us to employ many of the classical fluidic concepts developed for lab-on-a-chip devices without the necessity of using micro-pumps. Two research groups, Spicar-Mihalic et al. (Spicar-Mihalic et al., 2013) and Nie et al. (Nie et al., 2013), reported almost simultaneously the use of a $CO_2$-laser to create channels on nitrocellulose membranes. The laser etching method is reagentless, simple and fast, and allows precise cutting of nitrocellulose membranes, used in lateral-flow tests. The effect of laser power on the nitrocellulose ablation processes was further studied by Hecht et al. (Hecht et al., 2016). They introduced a "cold ablation" method to reduce the heat exposure to the nitrocellulose membrane. The technique is based on focusing short laser pulses of femtosecond duration to etch the nitrocellulose membrane to reduce the time explore of laser onto the membrane. By reducing the heat exposure and optimising the procedure, local deformation of the cellulose material was improved.

The sensing principle of conventional lateral flow tests is mostly based on optical transduction coupled with external optical readers. Recently, the integration of electrochemical transducers onto the lateral-flow membrane has become popular in the research literature to realise the benefits associated with the integration of miniaturised electrochemical transducer and rapid signal response provide by an electrochemical readout. Akanda et al. (Akanda et al., 2014) first reported the integration of nitrocellulose membrane on the surface of a micropatterned ITO glass electrode to develop an integrated electrochemical lateral-flow test for detection of troponin I with a detection limit of 0.1 pg $mL^{-1}$. Sinawang et al. (Sinawang et al., 2016) later demonstrated the lamination of lateral-flow membrane on the surface of a commercial screen-printed gold electrode for the detection of dengue NS1 protein with a detection limit of 0.5 ng $mL^{-1}$. However, these configurations are based on the integration of hard-electrode materials with a soft nitrocellulose membrane, thus negating the flexible properties of the lateral-flow membranes. To overcome this limitation, Wicaksono et al. (Wicaksono and Putri, 2014) reported the integration of a soft carbon-based working electrode that was placed underneath the nitrocellulose membrane to construct electrochemical lateral-flow tests for melamine in milk sample. In addition, a platinised carbon paper electrode was integrated with a lateral-flow membrane for the construction of electrochemical fuel cells to create self-powered autonomous lateral flow tests (Esquivel et al., 2014). Other advanced soft-material electrodes, such as carbon nanotube (CNT) paper electrodes and micropatterned

polyaniline (PANI) graphene oxide (GO) composite electrodes have been used for the construction of electrochemical lateral-flow tests using a similar lamination process (Shi et al., 2015; Zhu et al., 2014). Nevertheless, all the above fabrication techniques are based on placing the electrodes on the surface or underneath the lateral-flow membrane. Ruiz-Vega et al. (Ruiz‐Vega et al., 2017) recently demonstrated the direct integration of micropatterned electrodes printed onto a lateral-flow membrane for the fabrication of a fully integrated electrochemical lateral-flow test for the detection of myeloperoxidase. A three-electrode system, composed of a silver reference electrode and graphite working/counter electrodes, was screen printed directly on the lateral-flow membrane. This approach provides an innovative solution for the seamless integration of the electrochemical transducer with the lateral-flow membrane, while preserving the advantageous soft-material properties of the membrane.

Much research effort has been focused on the development of advanced labelling technologies for lateral-flow tests in the search for improved sensitivity. Examples include quantum dots (Taranova et al., 2015), carbon nanaoparticles (Blažková et al., 2010), nanocrystals (Mak et al., 2011) and upconverting phosphors (Liang et al., 2017). Some of the latest attempts to improve analytical performance have returned to classical metal-based nanoparticles. Loynahan et al. (Loynachan et al., 2017) reported using platinum nanoparticles (Pt NPs) as an amplification catalyst in lateral-flow tests for the detection of the biomarker p24 for HIV. The PtNP catalyst-based HIV lateral-flow device delivered a broad linear dynamic range across 4 orders of magnitude from 1 to 10000 pg $mL^{-1}$ and detection limits of 0.8 pg $mL^{-1}$, which out-performed both commercial and published membrane and paper-based p24 tests for HIV. The strategy of the PtNP catalyst is similar to earlier work reported by Parolo et al. using a AuNP-loaded enzyme (horseradish peroxidase) as a biocatalyst to enhance the sensitivity of lateral-flow tests (Parolo et al., 2013). However, both reported techniques had a limitation that required an additional step of applying substrate molecules for the catalytic reaction to achieve improved sensitivities. Zhan et al. (Zhan et al., 2017) reported a rational and systematic AuNP strategy by combining diffusion, convection and binding affinity for the development of C-reactive protein (CPR) lateral-flow tests, with an improved analytical sensitivity of 256 fold. This demonstrated the possibility of optimising just the AuNPs size and diffusion kinetics to boost the analytical performance of lateral-flow tests.

### 2.1.2 Microfluidic paper-based analytical devices (µPADs)

Using micro channels patterned on paper to perform chemical assays has a long history , but micro paper analytical devices (µPADs) were popularised by Martinez et al., in 2007 and have since become a hot topic (Martinez et al., 2007). µPADs make use of microfluidics to

create micro-channels on paper and guide the flow of fluid to detection zones containing capture biomaterials by capillary force. The micropatterns and microchannels are created using hydrophilic and hydrophobic barriers to confine and guide the fluidic flow (Xia et al., 2016). Compared with lateral-flow tests, μPADs facilitate advanced multidirectional microfluidic features on paper to perform multiple and complex analytical tasks. There are several techniques reported for the fabrication of μPADs includes photolithography (Martinez et al., 2008), wax printing (Chandler, 2000), ink jet printing (Delaney et al., 2011), micro-plotting (Bruzewicz et al., 2008), screen printing (Dungchai et al., 2011) and laser etching (Chitnis et al., 2011). Among these techniques, wax printing and ink jet printing are the most common and benefit from the simplicity of the fabrication process and relatively low material cost. To fabricate high density microfluidic partners in paper, workers have demonstrated the creation of 3D μPADs by stacking 2D patterned paper (Morbioli et al., 2017). The 3D-μPAD allows fluid transport in the x-, y- and z-direction, thus accommodating multiple assays within a smaller sized 3D-μPAD. Martinez et al. (Martinez et al., 2008) demonstrated the simultaneous handling of four sample solution impregnated into different sample inlets and reaching the target outlets without mixing within a 3D-μPAD. This provides an easy way to distribute sample solution from a single inlet to multiple test zones to reduce tedious sample addition procedures. The 3D-μPAD could potentially be useful for multiplexed analysis and high through-put screening with reduced cost and simplified assay procedures. Vellla et al. (Vella et al., 2012) demonstrated using a 3D-μPAD with multiple test zones loaded with various enzymatic markers, alkaline phosphatase and aspartate aminotransferase, to analyse liver function in a blood sample. The applications of μPADs and 3D-μPADs for environmental monitoring (Kim and Yeo, 2016) and healthcare diagnostics (Fu and Wang, 2018) are also summarised in these recent review articles.

Fabrication of 3D-μPADs typically requires the tedious assembly of multiple layers of 2D-μPADs sheets that restricts mass production. To realise the mass production of 3D-μPADs in a compatible way with the flexible nature of the paper substrate, the concept of paper origami to create folded 3D-μPADs has been introduced (Liu and Crooks, 2011). The origami folded 3D-μPADs allow facile and large-scale paper device fabrication by printing microchannel patterns onto a 2D paper followed by simple paper folding. Scida et al. (Scida et al., 2013) reported an origami 3D-μPAD using wax-printed paper immobilised with quencher-labeled ssDNA probes for optical detection of DNA. The DNA 3D-μPADs were configured with four test zones that allow simultaneous independent detection with no crosstalk between the fluidic pathways and a limit of detection of 3.1 ± 0.4 nM. Ge et al. (Ge, L. et al., 2012) developed an

origami 3D-μPAD with immobilsed antibodies for multiplexed chemiluminescence immunoassay. The 3D-μPAD innunoassy allowed the simultaneous detection of four cancer markers, a-fetoprotein (AFP), cancer antigen 153 (CA153), cancer antigen 199 (CA199) and carcinoembryonic (CEA), with limit of detection of 1.0 ng $mL^{-1}$, 0.4 U $mL^{-1}$, 0.06 U $mL^{-1}$ and 0.02 ng $mL^{-1}$, respectively. As an alternative to optical intensity measurement, Tian et al. (Tian et al., 2017) demonstrated a distance-based origami 3D-μPAD for visual detection of invertase concentration based on affinity capturing of the coloured polymerised enzymatic product generated by the invertase. The amount of coloured product captured along the flow distance on the paper channel was proportional to the invertase concentration. The distance-based 3D-μPAD detected invertase over a concentration range of 22.4 nM to 1.12 μM. The same authors further demonstrated the detection of cocaine and adenosine using a similar distance-based principle.

Apart from optical detection, quantitative multiplexed analysis can also be performed with electrochemical detection. Ge et al. (Ge, S. et al., 2012) demonstrated using a 3D-μPAD consisting of 24 test zones loaded with different target specific antibodies for the simultaneous detection of cancer markers (a-fetoprotein, cancer antigen 125, cancer antigen 153 and carcinoembryonic) in serum sample. Liu et al. (Liu et al., 2012) reported the development of a self-powered electrochemical origami 3D-μPAD functionalised with aptamer for the affinity detection of adenosine. Specific aptamer was immobilised onto wax-printed paper via the streptavidin-biotin interaction. The "self-power" was generated by a glucose oxidase-based half-cells, for the conversion of $[Fe(CN)_6]^{3-}$ to $[Fe(CN)_6]^{4-}$. The concentration gradients between $[Fe(CN)_6]^{3-}$ and $[Fe(CN)_6]^{4-}$ in the sensing half-cell and control half-cell, generated a voltage different to power the 3D-μPADs. The electrochemical aptamer 3D-μPAD detected adenosine with a sensitivity of 0.48 μA $M^{-1}$ and limit of detection of 11.8 μM. Yang et al. (Yang et al., 2016) developed a simple, scalable, and cost-effective strategy for fabrication of a sensing electrode based on waste newspaper. Using parylene C-post-treated waste newspapers (P-paper), which have a porous structure, as a flexible and disposable substrate, a 200 nm thick gold and silver layer was coated on the P-paper to form a three-electrode system. Immobilised ssDNA on the working electrode surface acted as an affinity recognition element for highly sensitive and specific detection of pathogenic *Escherichia coli* through DNA hybridisation. The P-paper electrodes showed the potential to serve as disposable, flexible sensing platforms for point-of-care testing. Besides affinity sensing, the applications of electrochemical 3D-μPADs for catalytic detection of various healthcare biomarkers has been summarised in a recent review article (Mettakoonpitak et al., 2016).

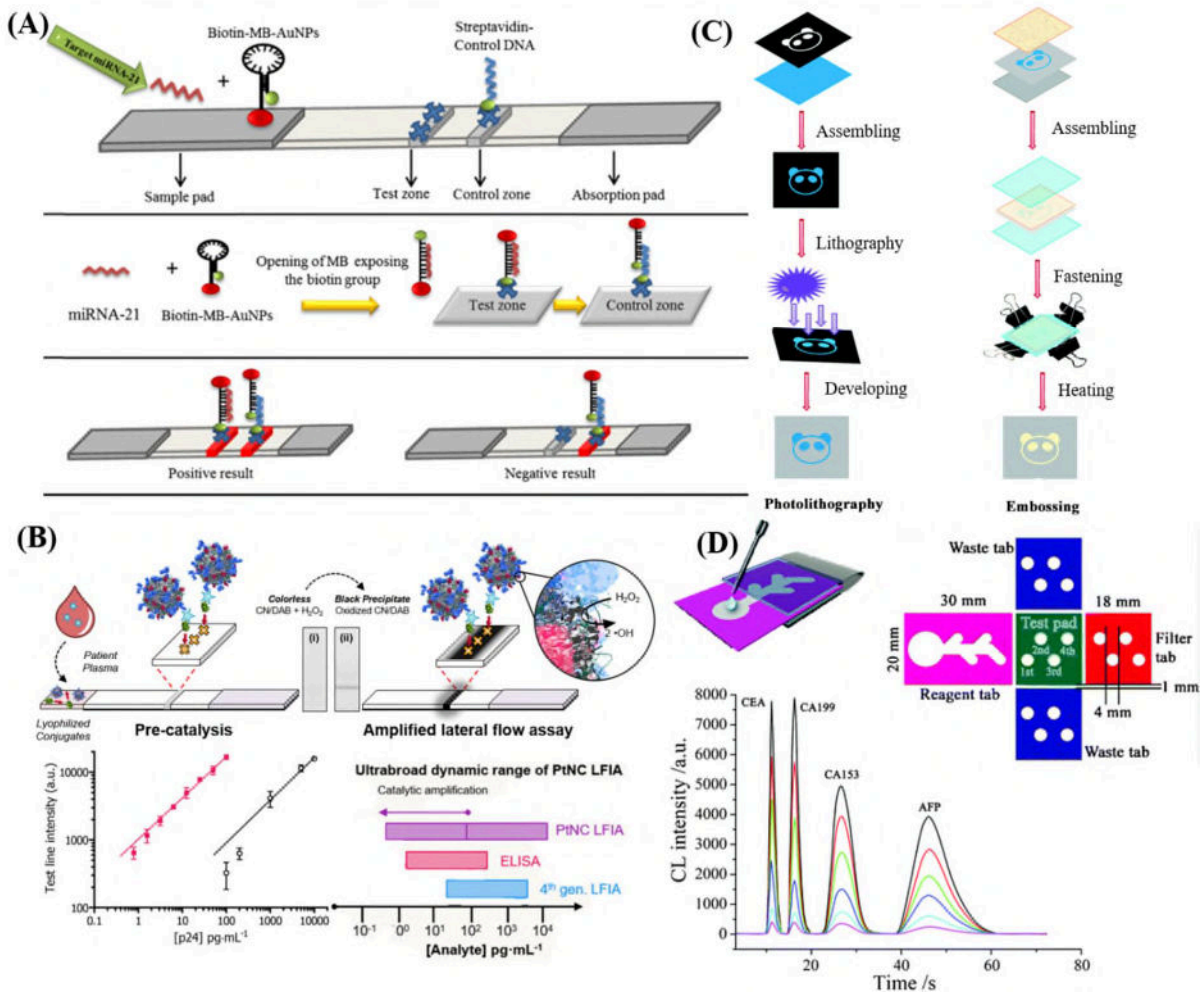


**Figure 2**. Conventional soft and flexible material-based affinity sensors for point-of care applications. (A) Basic design of a lateral-flow membrane-based strip tests for miRNA-21 detection. Adapted with permission from ref. (Kor et al., 2016). (B) Lateral-flow immunoassays (LFIAs) detection of HIV biomarker (p24) with enhanced ultrabroad dynamic range enabled by porous platinum core-shell nanocatalysts. Adapted with permission from ref. (Loynachan et al., 2017) (C) Fabrication of 2D and 3D μPADs by photolithography-patterning microchannels and embossing. Adapted with permission from ref. (Yu and Shi, 2015) (D) Low-cost and multiplexed 3D origami-based immunoassay-device and simultaneous detection of four tumour markers. Adapted with permission from ref. (Ge, L. et al., 2012)

### 2.2 Synthetic polymer-based affinity sensors

Synthetic polymers are man-made macromolecules with repeated subunits synthesised through polymerisation of monomers. Synthetic polymers have attracted extensive interest in variety of fields because of their low-cost, versatility and tailorable physicochemical properties.

In this section, we briefly summarise the application of some representative synthetic polymers for affinity sensors, ranging from the non-functional polymer polydimethylsiloxane (PDMS), to functional conducting polymers (CPs) and molecularly imprinted polymers (MIPs).

### 2.2.1 Polydimethylsiloxane (PDMS)-based affinity sensors

PDMS is a silicon-based hybrid organic/inorganic polymer consisting of an inorganic -Si-O- backbone and organic component side chain. The special organic/inorganic structure endows PDMS with excellent physicochemical properties, such as optical transparency, hydrophobicity, chemically inertness, permeability, non-toxicity and good biocompatibility. In addition, PDMS is chemically and mechanically robust with good flexibility and ease of prototyping as well as having a low cost. Based on these advantages, PDMS has been widely researched and used as matrix in variety of fields ranging from microfluidics (Whitesides, 2006) and sensors (pressure, strain and tactile sensor) (Chen et al., 2018), to protective coatings (Eduok et al., 2017), energy harvesting (Park et al., 2018) and optical ultrasound generation (Noimark et al., 2018).

Among the various applications, PDMS is one of the key materials employed for mold, fabrication and prototyping of microfluidic systems (channels and chambers) due to its good flexibility, ease of prototyping and other desirable properties (Whitesides, 2006). The application of microfluidic platforms in analysis have many advantages such as miniaturisation of instrumentation to reduce the quantity of samples and reagents, minimise time and cost, improve reproducibility, automate separations and detections, and provide the integration necessary for small wearable and implanted biosensors. Different microfluidic platforms based on PDMS have been proposed to provide microchannels or microchambers for affinity sensors in recent years. Separation and detection of different analytes with high resolution and sensitivity can be achieved by combing these microfluidic platforms and affinity receptors with different transducing elements, such as fluorescence and luminescence-based monitoring (Wu et al., 2016), cantilever vibration (Wang et al., 2013), micro-ring resonators (De Vos et al., 2009) and electrical assays based on impedance (Furniturewalla et al., 2018), conductimetry (Díaz-González et al., 2015) and amperometry (Jang et al., 2006). For instance, Wu et al. (Wu et al., 2016) introduced a closed bipolar electrode (BPE)-electrochemiluminescence (ECL) strategy for the detection of specific cancer cells (HL-60 cells), in which a two-channel polydimethylsiloxane (PDMS) chip (sensing channel and reporting channel) was connected through a U-shaped indium tin oxide BPE at a glass surface. A sandwich-type cancer cell detection model was developed at the cathode of the BPE with two recognition molecules (folic acid and an aptamer). The sensitive detection of HL-60 cells with a limit as low as 18 cells in 30 mL of cell suspension was achieved. Díaz-González et al. (Díaz-González et al., 2015)

proposed an automated electrical readout system consisting of interdigitated electrode transducers and a PDMS microfluidic structure. The PDMS microfluidic structure created microwells over the transducers, realising the simultaneous conductimetric detection of up to 36 biorecognition events. The performance of the automated electrical readout system was evaluated by measuring a microarray for atrazine based on a competitive enzymatic immunoassay. The impedimetric system showed similar sensitivity to that of a fluorescence scanner for the analysis of this pesticide.

In addition to the application of PDMS for microfluidic platforms in affinity sensors, PDMS or structured PDMS have also drawn attention as an integrated optical sensing element (Charrier et al., 2012; Fan et al., 2015). For instance, Boulart et al. (Boulart et al., 2013) reported a sensitive film formed from a PDMS layer incorporating cryptophane-A molecules for *in situ*, real time methane ($CH_4$) measurements in aqueous environments. The system was based on the refractive index (RI) modulation of the sensitive film using surface plasmon resonance (SPR). The sensor showed detection limits down to 3 nM, a sensitivity of 6 to 7 $\times 10^{-6}$ RIU $nM^{-1}$, and response times of 1 to 2 min.

As material science and microelectromechanical (MEMS) technology has developed, many methods have become available for fabricating PDMS substrates, such as lithography (photo-, soft- and X-ray-), printing technology (3D), mechanical microcutting, micromilling, direct laser plotting etc. (Faustino et al., 2016). However, the application of PDMS in affinity sensors is limited by some inherent properties including high hydrophobicity, chemically inertness and non-conductivity, which is not conducive to the attachment and immobilisation of molecules for affinity recognition and some transducing techniques. In order to overcome these limitations, many techniques have been developed to tailor the surface and electrical properties, which can be classified into PDMS surface modification and PDMS composite modification. For PDMS surface modification, plasma treatment is the most commonly used method (Wolf et al., 2018). In addition to plasma treatment, deposition of surfactants, functionalised reagents and electrically conductive layers have been widely used as modifiers to create functional PDMS (Wolf et al., 2018). For instance, Jang et al. (Jang et al., 2006) adopted plasma treatment for the internal surface of PDMS channels and then chemically modified them with vinyl group-terminated silane monolayer. After converting the tailored vinyl group into a carboxylic group, the surface-functionalised PDMS channel facilitated immobilisation of biotin molecules and was used in an electrochemical enzyme immunoassay for capturing target antibody via the avidin-biotin linkage. In addition, a variety of fillers have been doped into PDMS matrices to provide PDMS with corresponding functionalised properties

by physical blending, solution mixing, chemical crosslinking, *in-situ* polymerisation etc., including carbonaceous materials (graphene, graphite, carbon black and carbon nanotubes etc.), metallic materials (gold nanoparticles, silver nanowires, nickel etc.), magnetic materials (iron balls, carbonyl iron) and fluorescent probes (dye, quantum dots) (Khan and Lorenzelli, 2017; Noimark et al., 2018; Wolf et al., 2018).

Similarly to PDMS, a group of other organic polymers showed the potential to be applied in the field of affinity sensors as substrates independently or combined together with PDMS, such as poly(methyl methacrylate) (PMMA) (Díaz-González et al., 2015), polystyrene (PS) (Ungerböck et al., 2013), poly(perfluoroether) (PFPE) (Zhao et al., 2018a), polyethylene terephthalate (PET) (Yaqoob et al., 2015) and polyurethane (PU) (Hong et al., 2017). The application of PDMS and other organic polymers in flexible and stretchable affinity sensors are discussed in detail in Section 3.

### 2.2.2 Conducting polymers (CPs)

Conducting polymers, or intrinsically conducting polymers (ICPs), are organic polymers with π-conjugated double bonds, that are electrically conductive in a similar way to metals or semiconductors. Research in the area of organic CPs can be traced back to middle of 19th century, but only since Shirakawa et al. discovered the metallic conductivity of crystalline polyacetylene doped with halogen (p-type dopants) in 1977, has the field of CPs developed rapidly in both the academic and industrial communities(Yang et al., 2017). In the past four decades, over 25 kinds of conducting polymer systems have been established and applied in various fields. Desirable organic polymer properties such as flexibility and structural diversity were maintained, while optical, electrochemical and electrical/electronic properties were introduced to make them well suited for applications in energy, electrochromic devices, sensors and actuators, transistors, drug delivery and bioengineering.(Ibanez et al., 2018; Li et al., 2009) Here, we focus mainly on polypyrrole (PPy), polyaniline (PANI), and poly(3,4-ethylenedioxythiophene) (PEDOT) and their application in affinity sensors, because they are the most commonly studied CPs.

The synthesis of CPs is achieved mainly by chemical and electrochemical oxidative polymerisation, i.e. radical cations generated from aromatic monomer, coupling and eliminating protons reactions resulting in elongation of oligomers. A doping process is necessary to render them conductive by introducing positive (p-doping) or negative (n-doping) charge carriers and counter ions with opposite charges as dopant into the CPs matrix for charge compensation. In addition to rendering them conductive, the utilisation of different dopants can not only affect the structure, morphology, wettability and solution processability properties, but also endow the

CPs with new functionalities with increased affinity in biological applications when doped with specifically functionalised biomolecules. For instance, poly(styrene sulfonic acid) (PSS) is commonly used as a counterion for commercially available PEDOT:PSS with water processability, since PSS can balance the positive charges on the PEDOT backbone and keep the PEDOT segments dispersed in water, due to its high hydrophilicity (Kirchmeyer and Reuter, 2005).

On the other hand, the CPs can be further functionalised with specific properties to expand their application, especially for use in affinity sensors with enhanced sensitivity and selectivity. The first step is to synthesis CPs containing active groups covalently bonded to the π-conjugated backbones by monomer derivatives. This strategy for functionality can solve the limitations inherently suffered by the doping process i.e.: 1) lack of control in the amount of dopant, 2) doping of large biomolecular composites affecting the surface and bulk properties of CPs, 3) dopant leakage from and incorporation into bulk CPs during operation. In addition, researchers have the freedom to design monomer derivatives bearing target capturing elements for specific recognition during detection. In recent years, a lot of monomer derivatives bearing functionalised groups have been synthesised, such as hydroxymethyl (Daprà et al., 2013), carboxyl (Sheikhzadeh et al., 2016), ester (Miodek et al., 2014), etc., and these have been utilised in affinity sensors for detection of cells (Sekine et al., 2011), viruses (Hai et al., 2017), proteins (Xie et al., 2009) and DNA (Luo et al., 2009; Tansil et al., 2011). For instance, Hai et al. (Hai et al., 2017) synthesised a 3,4-ethylenedioxythiophene (EDOT) derivative containing an oxylamine moiety (EDOTOA). The EDOTOA was electrochemically copolymerised with EDOT and then 2,6-sialyllactose was covalently immobilised as a recognition element for hemagglutinin in the envelope of the human influenza A virus (H1N1). Specific interaction and detection of H1N1 were performed using a quartz crystal microbalance (QCM) and potentiometry which enhanced sensitivity by 2 orders of magnitude compared to commercially available assay kits. However, in this strategy the compact structure of CPs is somewhat difficult to achieve due to the steric hindrance of the side chains on the backbone during polymerisation process.

Another strategy to achieve desirable characteristics of CPs for practical applications in affinity sensors is the creation of conducting polymer composites (CPCs). Conducting polymer composites can be classified according to the choice of compositing components, such as surfactants, carbon nanomaterials, metal and metal complexes, and especially bioactive molecules. The effective immobilisation of bioactive molecules as recognition elements in CPs and CPCs plays a crucial role in achieving affinity sensors with high sensitivity and selectivity.

The immobilisation of bioactive molecules (such as nucleotides, aptamers, antigens and antibodies) can be achieved by physical adsorption, physical entrapment, covalent bonding and affinity bonding techniques. These immobilisation procedures, together with the advantages and disadvantages for each technique, have been extensively researched and reviewed in detail (Balint et al., 2014). It should be noted that immobilisation can be achieved simultaneously with the polymerisation and doping process or by post-treatment of the prepared CPs substrates, by pre-treatment of the monomers (monomer derivatives). For instance, Goda et al. (Goda et al., 2015) developed a new EDOT derivative bearing a zwitterionic phosphorylcholine group (EDOTPC) through pre-treatment via Michael-type addition thiol-ene "click" reaction. Then the EDOTPC was copolymerised with EDOT via electropolymerisation and used as affinity protein sensor for human C-reactive protein (CRP), with detection limit of 37 nM and a dynamic range of 10-160 nM, which covered the clinically relevant CRP levels. Wang et al. (Wang et al., 1999) described a label-free approach for *in situ* electrochemical detection of DNA hybridisation, relying on the doping of oligonucleotide probes as the sole counter anion within PPy films by entrapment during the electropolymerisation and doping process. The oligonucleotide probes maintained their hybridisation activity within the host polymer network and label-free monitoring of DNA hybridisation was realised. Bo et al. (Bo et al., 2011) modified novel and biocompatible polyaniline nanowires (PANIw) with oxidised graphene composite layers at an electrode (PANIw/graphene/GCE). The immobilisation of the DNA probe on the surface of electrode was performed through post-treatment of the electrode resulting in increased immobilisation efficiency due to the unique synergetic effect of graphene and PANIw. The resulting graphene/PANIw with immobilised DNA exhibited a good differential pulse voltammetry (DPV) current response for the complementary DNA sequences.

CPs have been extensively utilised in immunosensors because they can be readily functionalised for antibody immobilisation as described above. The specific antigen-antibody interactions then are transduced into corresponding electrochemical and optical signals through either a direct approach (label-free methods) or indirect approach (labeling of antibody or the antigen followed by sandwich, competition or capture immunoassay). Conducting polymer composite immunosensors mainly use electrochemical detection because their unique electrical properties provides a direct electrical readout with high sensitivity and selectivity, using techniques such as potentiometry (Zhang et al., 2015), amperometry (Shan and Ma, 2017), voltammetry (Wang et al., 2016b) and impedimetry (Wang et al., 2015). For instance, Liu et al. (Liu et al., 2018) constructed three-dimensional (3D) macroporous polyaniline (PANI) doped with poly(sodium4-styrene sulfonate) (PSS) by using a hard-template method. The 3D

macroporous PANI acted as a large surface area substrate for the immobilisation of alpha-fetoprotein (AFP) antibodies and it exhibited good affinity sensing performance toward its target AFP with differential pulse voltammetry (DPV). Another important example is conducting polymer composite-based impedimetric immunosensors, which are label-free and offer fast assay responses. Wang et al. (Wang et al., 2015) synthesised reduced graphene oxide (rGO), polypyrrole (PPy) and pyrrole propylic acid (PPa) nanocomposites for sensitive impedimetric immunosensors to measure Aflatoxin $B_1$ ($AFB_1$). The rGO improved the conductivity and stability, and PPa provided covalent linkers for probe immobilisation (anti-$AFB_1$ monoclonal antibody) through EDC/NHS chemistry, while PPy endowed the film with electroactivity from its inherent electrochemical doping/dedoping properties for impedance measurements. This protocol solved the limitation of low sensitivity, due to $AFB_1$ being a small molecule resulting in low impedance change during detection, with enhanced sensitivity by the synergistic effect of the three combined components. A detection limit of 10 fg $mL^{-1}$ and a wide dynamic range of 10 fg $mL^{-1}$ to 10 pg $mL^{-1}$ with excellent specificity were achieved.

CP-based DNA sensors play an ever-increasing role for a wide range of applications in the food industry, environmental monitoring, DNA diagnostics, drug discovery and forensics. CP-based DNA sensors rely on three key steps: immobilisation of DNA probes onto a CP-based sensing surface; complementary DNA target recognition by hybridisation; and signal transduction. Here, the signal transduction can be classified into direct assay and indirect detection approaches. In the direct assay, the specific recognition of target molecules by the probe without label can be detected by the changing electrical properties of the conducting polymer composites directly through amperometry (Ionescu et al., 2006), coulometry (Song and Jin, 2015), voltammetry (Galán et al., 2015) and impedimetry (Tran et al., 2014). For instance, Galán et al. (Galán et al., 2015) developed a label-free electrochemical DNA sensor for a specific “Hepatitis C” virus sequence based on azido-derivatised PEDOT modified electrode. By using “click” chemistry, the acetylene-terminated DNA probe was successfully immobilised onto the PEDOT electrode. DNA hybridisation caused changes in the electrochemical properties of the PEDOT and was detected by differential pulse voltammetry with a detection limit of 0.13 nM, showing the promise of the approach for label-free and reagentless DNA hybridisation sensor development. In contrast, indirect detection assay using a label usually involves end-point detection of a marker through fluorescence, colorimetry or electrochemistry. The commonly used labels are enzymes (Wang et al., 2014a), fluorophores (Zhang et al., 2012) and redox markers (Booth et al., 2012).

Besides the use of CPs in immunosensors and DNA sensors, work has focused on the application of CPs containing chemical receptors such as phenylboronic acid (PBA) for the affinity sensing of glucose. Compared with glucose oxidase and lectin concanavalin A, that are intolerant to long-term use and storage due to denaturation and their antigenic nature, PBA, as an artificial mimic of lectin, can strongly bind to 1,2-or 1,3-diols through reversible ester formation (Andreyev et al., 2014). Although it lacks specificity for glucose (also binding fructose, galactose, lactate etc.), PBA shows considerable promise for glucose-sensing, especially for continuous glucose monitoring (CGM) and for smart insulin-regulatory systems. Pringsheim et al. (Pringsheim et al., 1999) demonstrated a film co-polymerised from aniline and 3-aminophenylboronic, showing absorption spectra changes on addition of saccharides at pH 7.2, which is useful for sensing saccharides and considered to be advantageous over other sugar-sensitive materials. The same effect was also found by Huh et al. (Huh et al., 2007). More recently, Aytac et al. (Aytaç et al., 2011) synthesised 3-(1H-pyrrol-1-yl)phenylboronic acid monomer and used for electrochemical polymerisation to fabricate a layer of boronic acid containing CP sensing surface on a supporting platinum (Pt) electrode by cyclic voltammetry (CV). Different kinds of saccharides (*D*-glucose, *D* -fructose, *D* -galactose, *D* -lactose and *D* -sucrose) were examined by potentiometric detection and it was found that the binding interaction between polypyrrole-phenylboronic acid and saccharides followed the order of *D*-fructose > *D*-glucose > *D*-galactose > *D*-lactose > *D*-sucrose. Selected publications for CP-based affinity sensors are summarised in Table 1.

**Table 1** Summarisation of selected publications for CPs based affinity sensors.

| Sensing assay | CPs | Analyte | Technique | Linear range | LOD | Reference |
|---|---|---|---|---|---|---|
| Immunosensor | Poly(EDOT-EDOTPC) | C-reactive protein | DPV | 10-160 nM | 37 nM | (Goda et al., 2015) |
| | PEDOT | Ampicillin and kanamycin A | Impedance | 100 $pM^{-1}$ μM for ampicillin, 10 $nM^{-1}$ mM for kanamycin A | - | (Daprà et al., 2013) |
| | PPy-COOH | *S. Typhimurium* | Impedance | $10^2$-$10^8$ CFU $mL^{-1}$ | 3 CFU $mL^{-1}$ | (Sheikhzadeh et al., 2016) |
| | PEDOT | CEA antibodies | DPV | 1 pg $mL^{-1}$-0.1 mg $mL^{-1}$ | 0.3 pg $mL^{-1}$ | (Wang, W. et al., 2016) |
| | PPy | Cellular prions $PrP^C$ | DPV | 1 pM-1 μM | 0.8 pM | (Miodek et al., 2014) |
| | PANI | Cardiac troponin | Potentiometry | - | 56 fM | (Zhang et al., 2015) |
| DNA | PEDOT | DNA | SWV | - | 100 pM | (Tansil et al., 2011) |
| | PPy | DNA | Amperometry | 1-7 μg | - | (Wang et al., 1999) |
| | PPy | tDNA | Conductivity | 0.4-1.0 μM | - | (Song and Jin, 2015) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | PANI | DNA | DPV | $2.12\times10^{-6}$-$2.12\times10^{-12}$ mol $L^{-1}$ | $3.25\times10^{-13}$ mol $L^{-1}$ | (Bo et al., 2011) |
| | PANI | Fusion gene | DPV | 10 pM-1000 pM | 2.11 pM | (Wang, L. et al., 2014) |
| Glucose | PANI-3-aminophenylboronic acid | Glucose | Absorbance | -100 mM | 45 mM | (Pringsheim et al., 1999) |
| | Poly(3-aminophenylboronic acid) | Glucose | Conductivity | $-3.1\times10^{-2}$ mg $L^{-1}$ | 3.46 mM | (Badhulika et al., 2014) |
| | Poly(aniline-co-AB) | Glucose | Absorbance | -1 mM | - | (Huh et al., 2007) |
| | PPy-phenylboronic acid | Glucose | Potentiometry | 0.05-0.52 mM | 0.008 mM | (Aytaç et al., 2011) |

Note: EDOTPC - 3,4-ethylenedioxythiophene bearing phosphorylcholine group; DPV - differential pulse voltammetry; HAU - hemagglutinating units; QCM - quartz crystal microbalance; SWV - square wave voltammetry; PAA - 3-pyrrolylacrylic acid; AB - 3-aminobenzeneboronic acid.

### 2.2.3 Molecularly imprinted polymers (MIPs)

Molecularly imprinted polymers (MIPs) are synthetic polymeric materials designed with specific and selective recognition capabilities by virtue of cavities inside the polymer network. Molecularly imprinting involves the use of a suitable crosslinking reagent to polymerise functional monomers, which have self-assembled around a target template (imprinting) molecule via covalent or noncovalent bonding, followed by the subsequent removal of the template molecule to leave cavities that can be used for re-recognition of the target template by the shape, size and complementary bonding groups of the cavities (Uzun and Turner, 2016). Template imprinting results in "artificial receptors" with excellent chemical stability and robustness under harsh conditions, that are inexpensive and easy to produce to natural receptors, including for targets where no natural receptors are available. MIPs have been used for separation and adsorption science (Boysen et al., 2017), catalysis (Mirata and Resmini, 2015), drug delivery (Wackerlig and Schirhagl, 2015), sensing and biosensing (Uzun and Turner, 2016) etc. Among these applications, the use of MIPs in sensors is the one of the most interesting topics because of their high specificity, selectivity and stability. Hence, we discuss here MIP synthesis, sensitivity enhancement, sensing readout techniques and limitations.

Several basic elements are generally necessary for the synthesis of MIPs: 1) template; 2) functional monomers; 3) cross-linkers; 4) porogenic solvents; and 5) initiator. A diverse range of molecules have been used as templates to prepare MIPs for affinity sensing, in which small organic or biological molecules are widely used while large molecules such as macromolecules, proteins, cells and viruses still present challenges since they are less rigid and are difficult templates to remove. With any particular target template (analyte), corresponding functional monomers are selected to provide complementary binding sites by covalent or non-covalent interaction. Wulff et al. (Wulff et al., 1973) first established the molecular imprinting concept by covalently bonding the functional groups (polymerisable vinyl derivatives) to template molecules (D-glyceric acid and D-mannitol), polymerisation, splitting-off templates and finally D-glyceric acid and D-mannitol uptake. Mosbach (Arshady and Mosbach, 1981) subsequently established the alternative of non-covalent imprinting using as hydrogen bonding,

ionic interactions, π-π interactions and Van der Walls forces, and these are now the dominant interactions due to their simplicity, and the quick removal and rebinding of the template (Gupta et al., 2016). Cross-linkers and porogenic solvents are essential during the molecule imprinting process for morphology formation, mechanical stability, flexibility and porous structure, respectively. The polymerisation reaction is then triggered by initiators through free radical polymerisation, photopolymerisation or electropolymerisation. After completion of polymerisation, the template is removed by ether solvent extraction or chemical cleavage according to the binding approach, resulting in recognition sites within the polymer matrix possessing high specificity. Several kinds of functional materials can be introduced into MIP composites for signal transducing, increased sensitivity and signal amplification in affinity sensing, such as quantum dots (Zhou et al., 2014), metal and metallic oxides (Zamora-Gálvez et al., 2016), conducting polymers(Tan et al., 2016) and carbon materials (Zhu et al., 2018). For example, Zhou et al. (Zhou et al., 2014) developed a fluorescent sensor based on a graphene quantum dot (GQD)/MIP composite by anchoring the MIP layer outside the silica coated GQDs using 3-aminopropyltriethoxysilane (APTS) as the functional monomer and tetraethoxysilane (TEOS) as a crosslinker in the presence of paranitrophenol (4-NP). The combination of GQDs and MIP endows the composite with stable fluorescent properties and template selectivity. Due to resonance energy transfer from GQDs (donor) to 4-NP (acceptor), the fluorescence of the MIP-coated GQDs composite can be efficiently quenched when 4-NP molecules rebind to the binding sites. The sensor exhibited a good linear range from 0.02 to 3.00 μg $mL^{-1}$, with a detection limit of 9.00 ng $mL^{-1}$ (S/N=3).

Due to their superior characteristics of stability, specificity and signal amplification, MIP-based composites have been extensively used in affinity sensors by in combination with a variety of transducing techniques, such as electrochemical (Zhong et al., 2018), optical (Yan et al., 2018), thermal (Athikomrattanakul et al., 2011), and gravimetric methods (Fang et al., 2016). Table 2 summaries selected publications of MIP-based affinity sensors utilising different transducing techniques.

Electrochemical MIP sensors were first reported in 2002 and combine the advantages of MIPs and electrochemical transducers (Piletsky and Turner, 2002). Electrochemical transducers can transform the specific bonding between MIPs and analytes into an electrochemical readable signal by voltammetry (Tan et al., 2015), impedance (Bakas et al., 2014), and amperometry (Zhang et al., 2014). However, molecularly imprinted electrochemical sensors exhibit several limitations, such as low electro-conductivity, diffusion kinetics and integration with electrochemical transducers. To solve these problems, several strategies have been developed to improve the structure and properties of MIP composites. Incorporating conducting nanomaterials provides advantages of excellent mass transport, highly effective surface area, superior catalysis, improved conductivity and electron transfer, and thus contributes to the improvement of sensitivity, detection limit and binding capacity. Several examples of nanomaterials incorporating MIPs for affinity sensors are summarised in Table 2. Creation of structured MIPs, such as ultrathin MIP films, core-shell structures, nanoparticles and meso/micro/macro-porous structures improve sensitivity, detection limits and kinetics. For instance, Yang et al. (Yang et al., 2015b) presented a three-dimensional (3D) molecularly imprinted electrochemical sensor by using ordered mesoporous carbon material (CMK-3). The 3D structure delivered a highly porous surface structure, speedy responses and ultra-high sensitivity due to facilitated mass and electron transport.

MIPs also show much promise as recognition elements in optical affinity sensors. The commonly researched molecularly imprinted optical sensors can be classified into fluorimetry, surface plasmon resonance (SPR) and colorimetry according to the introduced additional functional features. In the case of optical MIP affinity sensors, fluorescent MIP sensors have been widely developed by incorporating fluorescent organic dyes, inorganic quantum dots, up-converters and fluorescent functional monomers. For instance, Xu and Lu (Xu and Lu, 2016) synthesised mesoporous structured molecularly imprinted polymers capped carbon dots (M-MIPs@CDs) by using amino-CDs as “functional monomers” for imprinting with a simplified imprinting process. The fluorescence sensor showed more rapid response and higher sensitivity for determination of TNT with more accessible recognition sites compared to non-mesoporous

structured fluorescence MIPs (MIPs@CDs). MIP-based SPR techniques have also attracted extensive attention for sensing of various targets based on the variation of refractive index with label free sensing, fast response and high sensitivity (Verma and Gupta, 2013). Moreover, colorimetric MIP-based sensors are capable of portable and rapid analysis especially for point-of-care testing, because of the megascopic signal and lack of need for expensive or sophisticated instruments. For instance, Li et al. (Li et al., 2011) deposited molecularly imprinted photonic hydrogel (MIPH) film with a highly ordered three-dimensional macroporous structure by a non-covalent approach using cholesterol as a template molecule. After binding cholesterol, the MIPH film showed a significantly readable optical signal directly self-reporting within less than 2 min. The colorimetric measurement of cholesterol concentration is based on the cholesterol enlarged blue shift effect of the Bragg diffraction peak of the MIPH film. The easy to operate colorimetric sensor possessed high selectivity, high sensitivity, high stability and was label-free.

In addition to electrochemical and optical transducing platforms for MIP sensors, some other readout techniques are also available to combine with the specific recognition properties of MIPs, such as mass-sensitive devices (e.g. quartz crystal microbalance) (Fang et al., 2016), thermal readouts (isothermal titration calorimetry (Zhao et al., 2011), thermistor (Athikomrattanakul et al., 2011) and heat transfer (Peeters et al., 2016) ), and Raman (Hu et al., 2015). For instance, Fang et al. (Fang et al., 2016) developed a three-dimensional (3D) molecularly imprinted QCM sensor by modification of a gold electrode with gold nanoparticles/mesoporous carbon CMK-3 composites and subsequent electropolymerisation of o-aminothiophenol on the modified electrode surface. The AuNPs@CMK-3 acted as signal amplifier because the 3D structure produced a large surface area that could increase the amount of effective imprinted sites. The QCM sensor exhibited a linear frequency shift to target CIT in the dynamic range from $6.0 \times 10^{-9}$ to $2.0 \times 10^{-7}$ mol $L^{-1}$ with a low detection limit of $1.8 \times 10^{-9}$ mol $L^{-1}$ (S/N = 3). Some selected thermal readout and Raman MIP sensors are summarised in Table 2.

Although MIP sensors have already shown several potential applications with good performance, some important factors or limitations should be taken into consideration for

improvements when designing MIP affinity sensors: 1) MIPs have been successfully applied for small molecules, while large molecules and biological molecules and compounds remain challenging, such as proteins, cells; 2) sensitivity and the detection limit need further improvement by incorporation with other functional materials; 3) there is a need to avoid high levels of non-specific binding due to the rich complementary functionalities inside the cavities.

**Table** 2 Selected publications of MIP-based affinity sensors with different transducing techniques

| Transducer | Techniques | Probe-Receptor | Analyte | LOD | Reference |
|---|---|---|---|---|---|
| Electrochemical | CV | Ferrocene-labeled MIPs | Vancomycin | 83 μM | (Mazzotta et al., 2016) |
| | DPV | rGO@Au-MIPs | Carbofuran | $2.0 \times 10^{-8}$ mg $L^{-1}$ | (Tan et al., 2015) |
| | LSV | MIP/PB-CMK-3 | Metolcarb | $9.3 \times 10^{-11}$ M | (Yang et al., 2015b) |
| | EIS | MIP/sol–gel | MOI | 5.14 μg $L^{-1}$ | (Bakas et al., 2014) |
| | CA | Au-MIPs | p-Aminothiophenol | $1.28 \times 10^{-12}$ mg $mL^{-1}$ | (Zhang et al., 2014) |
| Optical | Fluorescence | Carbon dots/Mesoporous MIPs | Trinitrotoluene | 17 nM | (Xu and Lu, 2016) |
| | Ratiometric fluorescence | Core-shell structured MIPs@QDs | Trinitrotoluene | 15 nM | (Xu and Lu, 2015) |
| | Up-conversion | NaYF4: Er, Yb/MIPs | Enrofloxacin | 8 ng $L^{-1}$ | |
| | SPR | Molecularly imprinted hydrogel | Vitamin $B_3$ | - | (Verma and Gupta, 2013) |
| | Colorimetry | $ZnFe_2O_4$ @MIP membrane | Bisphenol A | 6.18 nM | (Kong et al., 2017) |
| Mass | QCM | MIPs | Lovastatin | 0.03 nM | (Eren et al., 2015) |
| Thermal | Isothermal titration calorimetry | MIPs | Patulin | - | (Zhao et al., 2011) |

| | | | | | |
|---|---|---|---|---|---|
| | Thermistors | MIPs | Nitrofurantoin | 2.99 μM | (Athikomrattanakul et al., 2011) |
| | Heat - transfer | MIPs-SPEs | Dopamine | $4 \times 10^{-6}$ M | (Peeters et al., 2016) |
| Raman | Surface-enhanced Raman | MIPs | Melamine | 0.015 mM | (Hu et al., 2015) |

Note: MWCNTs - multi-walled carbon nanotubes; rGO - reduced graphene oxide; CV - cyclic voltammetry; DPV - differential pulse voltammetry; LSV - linear sweep voltammetry; EIS - electrochemical impedance spectroscopy; MOI - Methidathion organophosphorous insecticide; SWV – square wave voltammetry; CA – chronoamperometry; QDs – quantum dots; SPR - surface plasmon resonance; QCM - quartz crystal microbalance; SPEs - screen-printed electrodes.

## 3. Wearable soft and flexible material-based affinity sensors

Daily health monitoring for significant physiological signals is of particular importance for disease prediction and treatment. Over the past several decades, the development of material science and engineering has promoted the advent of house-hold miniaturised devices and paper-based sensing tools based on electronic, piezoelectric, optical and electrochemical transducers for detecting a large range of physiological signals, ranging from heart rate and temperature, to pH, metabolites, ions and pathogens. For example, the most commonly used sensor for point-of-care in our daily life is portable glucometers with disposable electrode strips. However, continuous analyte monitoring to provide real-time information has been more difficult to achieve, especially for affinity sensors. In recent years, flexible and wearable sensors have received tremendous attention for personalised monitoring and management, due to their low-cost, lightweight, high flexibility and stretchability, and potential for non-invasive continuous monitoring (Zhao et al., 2017). Various configurations of wearable sensors have been developed and demonstrated for daily health monitoring based on the development of flexible and stretchable electronics and optoelectronics (Bauer, 2013; Ruh et al., 2014). In this section, flexible and wearable affinity sensors based on soft and flexible materials are summarised, including skin-mountable, textile material-based and contact lens-based affinity sensors. The application of membrane, paper, polymer described above are also discussed here as substrates or functional components for flexible and stretchable affinity sensors.

### 3.1 Flexible, stretchable and skin-mountable affinity sensors

Conventional chemical and biological sensors are miniaturised or integrated on non-transparent and rigid substrates, such as metal, glass or silicon, thus limiting their utility for wearable devices. Skin-mountable sensors built on flexible and stretchable substrates allow the possibility of wearable sensing devices that can be laminated softly and non-invasively onto the skin. Sometimes, skin-mountable sensors refer to electronic skins (E-skins) (Hammock et al., 2013a). In recent years, tremendous effort has been devoted to skin-mountable sensors based on electronics and optoelectronics that offer flexibility, stretchability, transparency, multimodularity and compatibility with the skin, by pioneers such as Rogers and Bao's groups

(Xu et al., 2014; Yeo et al., 2013). Although a variety of physiological parameters can be detected by various skin-mountable sensors, most of them focus on physical phenomena, including temperature, strain and pressure sensing for body movement, touch, heart beat and humidity and their combining multi-sensing (Kim et al., 2014; Lee et al., 2016; Xu et al., 2014). The application of wearable sensors in chemical and biochemical sensing is much more challenging with a more complex mode of operation compared to physical sensing due to the requirement for specific molecular recognition and by implication, often a need for molecular contact. Even so, metabolic parameter detection has been realised by skin-mountable sensors in sweat, saliva or tears, with intended applications such as diabetes monitoring and therapy (Lee et al., 2017), hormones (Parlak et al., 2018), pH (Lee et al., 2016), lactate (Gao et al., 2016) and alcohol measurement (Kim et al., 2016a).

For the key metabolites such as glucose, lactate and uric acid etc., catalytic reactions driven by corresponding enzymes and catalytic materials have been applied in the skin-mountable sensors. Lee et al. (Lee et al., 2016) developed a stretchable device composed of a serpentine bilayer of gold mesh and gold-doped graphene that forms an efficient electrochemical interface for the stable transfer of electrical signals. The heater, temperature, humidity, glucose and pH sensors and polymeric microneedles that can be thermally activated to deliver drugs were integrated into skin-mounted device for diabetes monitoring and therapy. In this device, the glucose was measured through electrochemical signal by reduction of $H_2O_2$ generated from the glucose oxidase in conjunction with the solid-state Ag/AgCl counter electrode. The same group presented another wearable/disposable sweat-based glucose monitoring device integrated with a feedback transdermal drug delivery module. The glucose monitoring is based on a Prussian blue catalyst and glucose oxidase deposited porous gold electrode (Lee et al., 2017). Gao et al. (Gao et al., 2016) presented a mechanically flexible and fully integrated wearable sensor array for multiplexed *in situ* perspiration analysis, which simultaneously and selectively measured sweat metabolites (such as glucose and lactate) and electrolytes (such as sodium and potassium ions), as well as the skin temperature (to calibrate the response of the sensors). The glucose and lactate sensors were based on the catalytic effect of glucose oxidase and lactate oxidase

immobilised with Prussian blue on Au electrode. Wang's group developed several kinds of wearable Tattoo-based biosensing system, in which catalytic systems such as alcohol-oxidase/Prussian blue, lactate oxidase/Prussian blue, and uricase/Prussian blue, were applied for non-invasive alcohol, lactate and uric acid monitoring in sweat or saliva, respectively (Kim et al., 2015b; Kim et al., 2016a). In these applications, pH sensors and temperature sensors are commonly incorporated to eliminate the influence of pH and temperature variation on the readings due to variation in the catalytic activity of the enzyme. The longevity and storage conditions of such sensors should also be carefully considered. Wearable and implantable affinity sensors offering high sensitivity, selectivity and stability are less well developed. In the light of these recent advances, we summarise below some flexible affinity sensors that can be potentially used for wearable and implantable sensing applications.

Flexible thin-film transistors (TFTs) are a category of field effect transistors (FETs) and consist of an active semiconductor thin film layer, metallic contacts (typically Au for source and drain electrode) and dielectric layer over a flexible supporting substrate, replacing the conventional solid substrate while maintaining good electrical performance. Flexible TFTs have attracted extensive attention for chemical and biological sensors with many advantages, such as low-cost, flexibility, high sensitivity and feasibility. The commonly used substrates for TFTs in sensors are polyimide (PI), polyethylene terephthalate (PET), polyethylene naphthalate (PEN), polydimethoxysilane (PDMS) and polyethersulfone (PES) to provide the flexibility. The active semiconductor thin-film layers are the critical element for sensing performance. The active semiconductor used in flexible sensors can be classified into single-wall carbon nanotube (SWCNT) (Lee and Cui, 2010), graphene (Kwon et al., 2012), small molecules (Hammock et al., 2013b), metal oxide (Rim et al., 2015), organic polymers (Kim et al., 2012) and conducting polymers (Zhao et al, 2018b). In addition to chemical sensors (humidity , ions and pH ) and catalytic biosensors (glucose and lactate ) realised with flexible TFTs, DNA (Jung et al., 2014; Lin et al., 2011), proteins (Hammock et al., 2013b; Lu et al., 2009) and some other biomarkers (Kwon et al., 2012; Spanu et al., 2015) have also been measured with flexible TFT-based affinity sensors . Kim et al. (Kim et al., 2012) fabricated a flexible and disposable DNA

hybridisation sensor using pentacene thin-film transistors (TFTs) on an indium tin oxide (ITO) coated PES substrate. The ss-DAN (poly A) was immobilised on the pentacene surface and the complementary ss-DNA (poly A+T) hybridisation with different lengths and concentrations could influence the field-effect mobility because the phosphate group imparted a negative charge on the DNA backbone and attracts holes from the channel region thus decreasing the $I_{DS}$ and field-effect mobility. Most recently, Parlak et al. (Parlak et al., 2018) developed a molecularly selective nanoporous membrane-based, wearable organic electrochemical device for non-invasive cortisol sensing. The biorecognition of cortisol was based on an artificial MIP nanoporous membrane (MS) with a laser-patterned microcapillary channel array for sample acquisition. PEDOT:PSS-based organic electrochemical transistors (OECTs) including a planar Ag/AgCl gate, act as the transducer and the device delivered a dynamic range of 0.01 to 10.0 μM. The MS-OECTs were fabricated on a styrene-ethylene-butylene-styrene (SEBS) elastomer substrate to allow the flexibility and stretchability of the wearable sensor. Finally, the integrated devices were successfully used with both *ex situ* methods using skin-like microfluidics, and on human subjects with on-body real-sample analysis using the wearable sweat diagnostics platform.

Flexible electrochemical electrodes using soft electroactive materials play a very important role for the construction of wearable architectures and devices due to the increasing demand for portable, flexible, and wearable electronic devices. The application of flexible electrochemical electrodes in several fields, such as lithium ion batteries (LIBs) (Gwon et al., 2014), electrochemical capacitors (Kim et al., 2015) and sensing/biosensing platforms (Windmiller and Wang, 2013) enables the miniaturisation of monitoring systems into wearable devices. Among the flexible sensing/biosensing platforms, physical sensors (temperature, body motion etc.) and catalytic chemical/biological sensors (glucose etc.) have been extensively researched (Foster et al., 2013; Manjakkal et al., 2018). Apart from these, several kinds of flexible affinity sensing platforms have been developed for immunosensors and DNA sensors, such as cancer biomarkers (Kamakoti et al., 2016), cardiac biomarkers (Kumar et al., 2016), cytokines (Garcia-Cruz et al., 2015), hormones (Munje et al., 2017) and DNA hybridisation

(Kokkinos et al., 2014; Li and Lee, 2015). Different electroactive materials with structured morphology including metals (films, nanorods, nanoparticles) (Kamakoti et al., 2016), metallic compounds (nanosheets, nanoparticles, quantum dots) (Kinnamon et al., 2017; Shanmugam et al., 2016), conducting polymers (nanowires, films) (Garcia-Cruz et al., 2015), carbonaceous materials (CNTs, graphene,) have been deposited on flexible substrate (such as PI, PET and paper) and combined with specific immobilised recognition elements for affinity sensing. The specific recognition can be transduced with techniques such as voltammetry, impedance and amperometry. For instance, Liu et al. (Liu et al., 2014) reported a electrochemical multiplexed immunosensor on a flexible polydimethylsiloxane (PDMS) slice deposited with 8 × 8 nano-Au film electrodes. The PDMS slice was combined with predesigned hollowed-out PMMA plate to create spatial separation between every electrode for multiplexed microchips. Three kinds of primary antibodies linked with magnetic beads ($Ab_1$-MBs) were coupled onto the electrodes via magnet force and then horse radish peroxidase (HRP) labelled antibody-conjugated gold nanorods (HRP-$Ab_2$-gold NRs) were immobilised on the surface of the electrodes using the corresponding antigen. The detection of three cancer biomarkers in prostate cancer patients, prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), and interleukin-6 (IL-6) were realised using the flexible microchip array with electrochemical detection of $H_2O_2$. The development of flexible electrochemical electrodes underpins the foundation and potential application in wearable affinity sensing devices. However, several limitations yet to be solved and developed for the realisation of routinely used wearable sensors, such as the integration of sensing platforms with wireless transmitters, analyte collection and transportation.

In addition to the electronic-based flexible thin-film transistors and electrochemical electrodes, optoelectronics using optical, fluorometric and colorimetric assays from conventional benchtop biofluid analyses also show potential to be integrated and miniaturised into wearable devices. Wearable optical assays are based on the light scattering/absorption on special targets, in which light sources (ranging from UV to deep infrared) and detectors are needed. The most widely used wearable optical sensors focused on the determination the key physiological parameters of temperature, blood pressure, heart/beat rate and oximetry by

haemoglobin (Kim et al., 2017; Kim et al., 2016b). The integration and miniaturisation of chip-level optoelectronics assembled onto flexible and stretchable substrates including light sources, detectors and optoelectronic circuits are suitable for continuous measurement (Kim et al., 2016b; Ruh et al., 2014). The optical detection of glucose in interstitial fluid based on thermal emission, light absorption spectroscopy and photo acoustic spectroscopy have been explored for non-invasive continuous glucose detection.(Newman and Turner, 2005) By combing a specific recognition element into the system, these optical assays could be used for affinity sensing (Bajgrowicz-Cieslak et al., 2017; Daikuzono et al., 2017; Jiang et al., 2018). For instance, Bajgrowicz-Cieslak et al. (Bajgrowicz-Cieslak et al., 2017) developed an optical glucose sensor based on a hexagonal diffraction grating imprinted on a flexible hydrogel. The covalently incorporated boronic acids in the 2.5D-copolymer matrix could bind to glucose, resulting the polymer network swelling and altering its physical and optical properties. Illumination of the 2.5D structure with a monochromatic light source in transmission mode allowed reversible and quantitative measurements of variation in the glucose (1-200 mM) concentration by first order lattice interspace tracking.

Fluorometric and colorimetric assays have already shown utility in wearable chemical and biological sensing without affinity, such as a wearable glove sensor for pesticide (Xu et al., 2018b), wearable platform for sweat $Cl^-$ (Xu and Yan, 2018), ions (Anzenbacher Jr et al., 2012), pH (Yao et al., 2018) and glucose sensing (Yao et al., 2018) and so on. The most representative colorimetric assay for wearable sensors is the soft, wearable microfluidic device for the capture, storage, and colorimetric sensing of sweat developed by Rogers's group (Koh et al., 2016). His team reported a soft epidermal microfluidic device that can directly and reliably harvest sweat from skin to different channels and reservoirs. Four different paper-based colorimetric chemical assays resided in the central reservoirs for multiparametric sensing of markers, including chloride and hydronium ions, glucose and lactate, through either enzymatic or chromogenic reactions. Fluorometric and colorimetric affinity sensors can be realised by combing affinity recognition with such flexible platforms for DNA, protein and cancer markers sensing (Basu et al., 2017; He et al., 2018). He et al. (He et al., 2018) reported a flexible and wearable biosensor

for affinity diagnosis of neurodegenerative disease by detecting the biomarker IgG and ADc-NTP based on nanostructure of *Morpho menelaus* butterfly wings. The butterfly wings were peeled off into the bright blue up layer with a hierarchical scaly micro/nanostructure with aligned microgroove and brown under layer with an ordered structure. The upper layer was used to fabricate microfluidic chips with immobilised antibody (goat anti-human IgG and rabbit anti-AD7c-NTP) onto the detection zone for fluorescent affinity sensing of IgG and AD7c-NTP biomarker, simultaneously. The under layer was utilised to produce the flexible electronic sensor with blade-coated conductive ink to obtain an electrical signal through measuring the frequency of static tremors of neurodegenerative patients. The integrated wearable sensors comprising the microfluidic chip and electronic sensor demonstrated good sensing performance by combing the smartphone-based device and could be effective for the tentative diagnosis of neurodegenerative disease.

Despite the popularity of the area, the application of flexible affinity sensors still faces several limitations. The majority of biomarkers are not measurable without direct chemical detection, since affinity sensors are based on the specific recognition between affinity binding receptor and analyte. Affinity sensors have been extensively researched for routine samples such as blood and urine, but they have not yet found wide-spread use in non-invasive wearable sensors. Non-invasively extracting biomarker analytes from the body exudates such as sweat, saliva and tears, is difficult and there are uncertainties about the correlation of their concentration with biofluids.

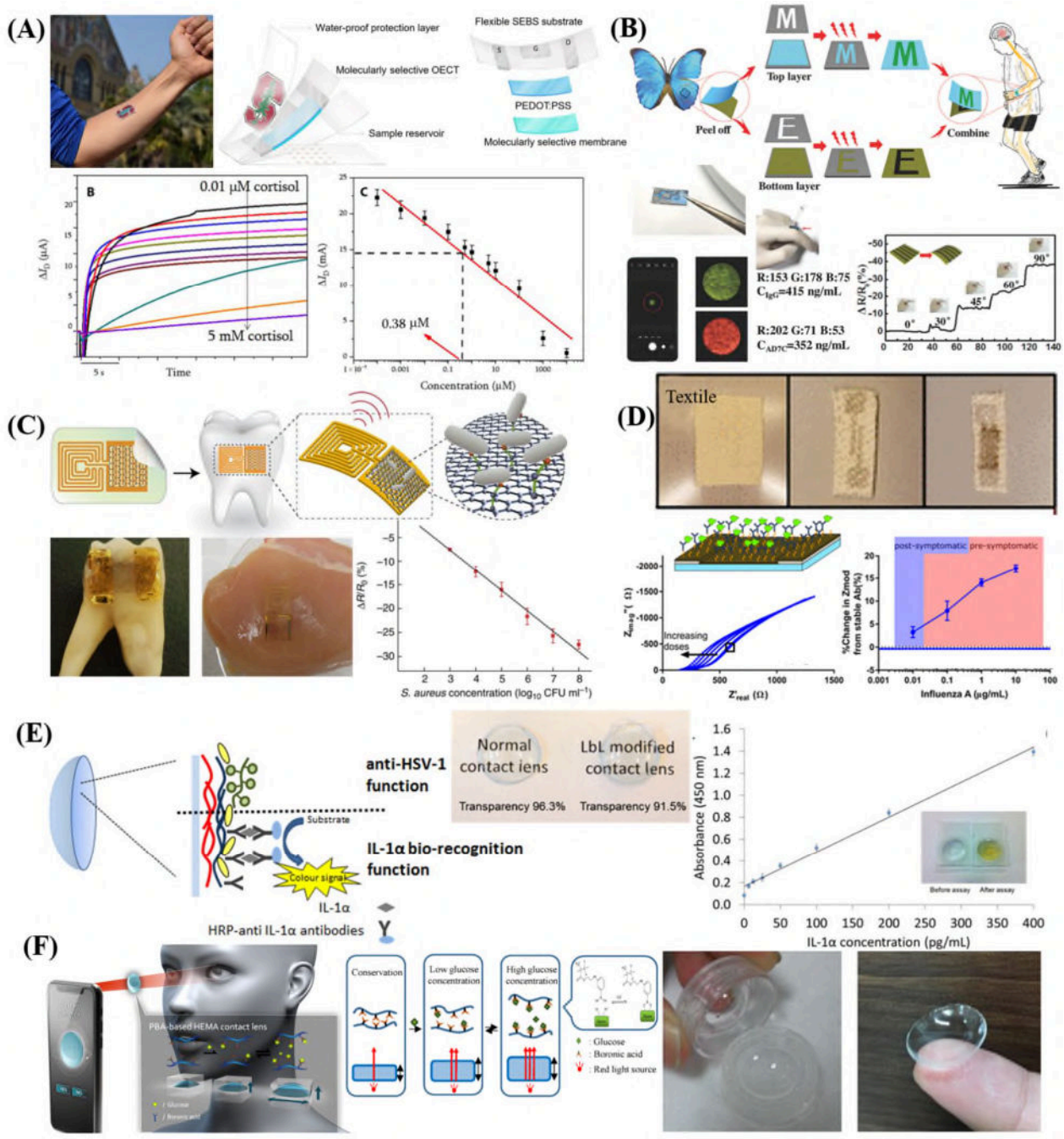


**Figure 3.** Wearable soft and flexible material-based affinity sensor. (A) Patch-type wearable cortisol sensor consisting of microcapillary channel arrays, sample reservoir and OECT sensor layers. Adapted with permission from ref.(Parlak et al., 2018) (B) *Morpho menelaus* butterfly wings based wearable sensor integrating fluorescent immunoassay and electronic sensing for neurodegenerative disease. Adapted with permission from ref.(He et al., 2018) (C) Graphene-silk based wireless nanosensors with antimicrobial peptides sensing elements for bio-selective detection of bacteria at single-cell levels. Adapted with permission from ref.(Mannoor et al., 2012) (D) Flexible screen-printed electrodes on textile for inexpensive and wearable detection

of influenza. Adapted with permission from ref.(Kinnamon et al., 2018) (E) Contact lens (theranostic lens) with a dual-functional hybrid surface to modulate and detect a pathogenic attack (HSV serotype-1). Adapted with permission from ref.(Mak et al., 2015) (F) Portable noninvasive contact lens with smartphone imaging program for an ideal tear fluid glucose detection for diabetes patients based on phenylboronic acid-HEMA hydrogel. Adapted with permission from ref.(Lin et al., 2018)

### 3.2 Textile-based affinity sensors

Fabrics and textiles are ideal materials as functional base substrates for flexible and wearable devices, because of their daily routine utilisation, safety, low-cost, light-weight, flexibility, large surface area and good mechanical stability. Fabrics and textiles represent an excellent class of substrates and examples used include cotton (Guinovart et al., 2013), silk (Zhu et al., 2016), polyester/Lycra (Morris et al., 2009), nylon (Kokkinos et al., 2016), wounding dressing bandages (Kassal et al., 2015) etc. In general, suitable fabrics and textiles as a platform for integrating sensing elements are chemically inert. Active materials should be integrated into the textile structure through printing and coating , ranging from carbon materials (carbon ink (Choudhary et al., 2015), CNTs (Guinovart et al., 2013) and graphene (Mannoor et al., 2012)) and metallic materials (Ag ink (Nomura et al., 2018), copper (Stefan-van Staden et al., 2015)) to conducting polymers (PEDOT:PSS) (Pal et al., 2016), to endow electrical conductivity, transducing and transmission capabilities (Diamond et al., 2008). Besides the post-treatment of fabric with active materials, intrinsic conducting fabric and thread (Liu and Lillehoj, 2016), conducting polymer fibre and nanotubes (Eom et al., 2017) and metallic fibres (Cho et al., 2011) can also be used to form textiles with woven, non-woven or knitted structures. The combination of flexible and wearable textiles with electronics added either intrinsically or extrinsically provide sensor platforms for diagnostic and monitoring applications.

In common with the flexible stretchable and skin-mountable sensors described in section 3.1, textile-based sensors are currently mainly used for physical monitoring, such as strain and pressure (Wang et al., 2014b), electrocardiogram heart rate (Yang et al., 2015a), temperature

and humidity (Mattana et al., 2013) and body motion (Li et al., 2017). Some efforts have been devoted to chemical sensing, including pH (Morris et al., 2009), ions (Guinovart et al., 2013) and catalytic detection of lactate (Malon et al., 2014), glucose (Liu and Lillehoj, 2016) and other biomarkers (Kassal et al., 2015) in body fluids such as tears, sweat, urine and blood. Recent progress in the application of smart fabrics or electronic textile-based materials for these physical and chemical sensors have been reviewed in detail recently (Castano and Flatau, 2014; Heo et al., 2018). Despite the successful realisation of physical and chemical sensors based on flexible and wearable textile materials, relatively few textile-based affinity sensing platforms have been described to date for the routine monitoring of important analytes.

Mannoor et al. (Mannoor et al., 2012) described a graphene-based wireless bacteria detector on tooth enamel using water-soluble silk fibroin. A monolayer graphene-based sensing element with wireless readout coil was printed on silk fibroin. Then the ultra-thin nanosensors were transferred to tooth enamel via the dissolution of supporting silk film. Specific biological recognition of pathogenic bacteria was achieved by self-assembling of bifunctional antimicrobial peptides onto the graphene. The graphene was contacted by interdigitated electrodes patterned with an inductive coil antenna, achieving remote powering and readout. The fabricated device showed bio-selective detection of pathogenic bacteria with detection limit down to single-cell levels. The silk films here act as an efficient transient medium for transferring materials onto tissues via intimate contact and dissolution due to the elasticity and biodegradability imparted by the unique molecular structure of silk.

Some textile-based flexible, disposable and portable affinity sensors have been developed for environmental determinations. Kinnamon et al. (Kinnamon et al., 2018) demonstrated a textile screen-printed biosensor coupled with affinity assay for the detection of environmentally exposed influenza A virus. A consumer utility textile was printed with conductive silver ink as base electrode array for electrochemical impedance spectroscopy (EIS), and graphene oxide transduction layer was printed on as framework for assembling the biorecognition elements (influenza A-specific antibody) on the sensor. The textile sensor was utilised for influenza A detection in biofluid analog buffer with the dynamic range from 10 ng $mL^{-1}$ to 10 μg $mL^{-1}$ and

a detection limit of 10 ng $mL^{-1}$. The sensor shows the potential to be integrated into common textiles and worn by at-risk populations to detect exposure to the virus before symptoms manifest. Similarly, Kokkinos et al. (Kokkinos et al., 2016) described a new type of integrated lab-on-a-membrane foldable device for duplex determination of biomolecules (Bovine CN and Bovine IgG) in milk samples with quantum dot labels on a nylon membrane. Two assay zones were located symmetrically on either side of a three-electrode system. In the assay zones, labeled quantum dots (Pb and Cd) could be released by competitive immunoassay and were determined simultaneously by anodic stripping voltammetry after folding the assay zones over a voltammetric cell. These new membrane devices enable duplex biosensing with low-cost and portability. Although these platforms showed the flexibility and portability required, application in wearable sensor technologies as diagnostic and external environment monitoring tools still needs further development.

Shim et al. (Shim et al., 2008) demonstrated the transformation of general commodity cotton threads into electronic textiles using a polyelectrolyte-based coating with carbon nanotubes (CNTs). The resulting CNT-cotton yarns possessed high electrical conductivity and some functionality due to biological modification of inter-nanotube tunneling junctions. The incorporated anti-albumin antibody acted as specific recognition element for albumin detection. Stefan-van Staden et al. (Stefan-van Staden et al., 2015) designed several stochastic sensors using Cu thin film, Ni thin film and Au nanostructured microspheres deposited on a textile material (veil). A panel of biomarkers could be detected simultaneously including epidermal growth factor receptor, neuron specific enolase, and carcinoembryonic antigen. Despite the successful affinity detection of biomarkers from whole blood samples using the textile materials, these proof-of-concepts are still some distance away from practical wearable monitoring.

### 3.3 Contact lens-based affinity sensors

Ocular fluid is an extracellular fluid excreted from the tear gland. A dense network of blood capillaries infiltrates the tear gland, facilitating the transport and exchange of molecules from serum to the tear gland. Thus, a bridge can be built between ocular fluid research and

systemic disease diagnostics. With the recent advance of proteomic technology, several important biomarkers in ocular fluid have been identified as having significant clinical diagnostic value for various diseases (Azkargorta et al., 2017). The contact lens is disposable, relatively cheap and serves as a platform to obtain direct intimate contact with ocular fluid and is therefore an attractive and a promising platform for point-of-care diagnostic tests.

Non-invasive tear glucose monitoring for diabetes with contact lenses has been of significant interest for scientists and industry. Most of the early work on contact lens-based glucose monitoring was based on electrochemical catalytic enzyme electrodes printed onto contact lenses (Chu et al., 2011; Yao et al., 2011). However, there are challenges in electrochemical contact lens-based glucose biosensors such as power supply, transmission of readout signal and user acceptance with respect to appearance. Therefore, alternative approaches based on optical affinity sensing techniques such as excited state charge transfer (Badugu et al., 2004), Förster resonance energy transfer (FRET) (March et al., 2006) and holographic materials (Domschke et al., 2006) have been developed for contact lens-based glucose monitoring (Farandos et al., 2015). In these configurations, the optical signal responses from the contact lens could be detected with an external optical reader, or even the naked eye, in a much simpler way (Badugu et al., 2005). User acceptability may again, however, be a problem with clearly visible devices. Badugu et al. (Badugu et al., 2004) described the incorporation of a boronic acid containing fluorophores (BAFs) into contact lenses for glucose sensing. The boronic acid acts as an electron withdrawing group, but upon binding with glucose it converts to an anionic form which no longer acts as an electron withdrawing group, and this causes a spectral change due to the interruption of the charge transfer properties of excited state. The BAF contact lens was employed for continuous detection of tear glucose level in the range of 50 to 500 μM. March et al. (March et al., 2006; March et al., 2004) demonstrated a FRET-based contact lens for glucose detection with immobilised tetramethylrhodamine isothiocyanate concanavalin A (TRITC-ConA) and fluorescein isothiocyanate dextran (FITC-dextran). The fluorescence signal of the TRITC-ConA/FITC-dextran complex is suppressed by a quenching effect due FRET. The presence of tear glucose completes with the ConA binding site and

releases the FITC-dextran causing an increase in fluorescence signal. The FRET-based glucose contact lenses were applied for clinical measurements in diabetic patients, however, there is a delay between the measured tear glucose level and the systematic blood glucose in this and the other devices that limits their utility. Domschke et al. (Domschke et al., 2006) reported a holographic contact lenses glucose sensor fabricated with 3-acrylamidophenylboronate (3-APB) as a reversible binding ligand for tear glucose monitoring in a clinical study. Upon binding with glucose, the interference fringes created by the 3-APB swelled that caused changes in the reflected light and resulted in a colour charge of the contact lens. A major advantage of the holographic glucose contact lens is that it does not require any fluorescence dyes and avoids the photobleaching associated with long-term use. Recently, Elsherif et al. (Elsherif et al., 2018a) reported the integration of phenylboronic acid functionalised hydrogel-based optical diffuser onto contact lens placed over an artificial eye for glucose measurement. The contact lens glucose sensor enabled detection with a continuous application of different glucose solution (0-50 mM) on the sensor surface. In another similar study, Elsherif et al. (Elsherif et al., 2018b) reported the combination of a holographic glucose contact lens with a smartphone for continuous glucose monitoring. An interference fringe structure was printed onto a glucose sensitive hydrogel containing phenylboronic acid as the binding ligand. The holographic glucose contact lens detected glucose concentration over the range 0-50 mM with a sensitivity of 12 nm $mM^{-1}$ and a short response time of 3 seconds for continuous monitoring. Nevertheless, the above mentioned boronic acid and ConA affinity glucose sensing mechanism has a common limitation of non-selectively binding of other sugar molecules and glycoproteins. However, the tear glucose concentration is significantly higher compared with other sugar molecules, and there it is still promise for reasonably accurate measurement of tear glucose levels.

Most of the previous work on ocular fluid diagnostics are focused on glucose rather than protein biomarker detection. Mak et. al. recently reported the development of a wearable theranostic contact lens with a dual functional hybrid surface for the detection of interleukin 1α (IL-1α) as biomarker for HSV-1 infection, as well as incorporating an anti-viral coating for HSV-1 (Mak et al., 2015). The theranostic lenses were fabricated using a Layer-by-Layer (LbL)

surface engineering technique for the immobilisation anti-IL-1α antibodies as the affinity molecules. The theranostic contact lenses showed effective anti-HSV-1 activity, good analytical performance for the detection of IL-1α (limit of detection of 1.43 pg $mL^{-1}$) and a wide linear range (0.625 to 400 pg $mL^{-1}$) covering the clinically relevant region. Subsequently, Veli et al. (Veli and Ozcan, 2018) applied a similar LbL approach for the construction of contact lens with immobilised capture antibodies for the detection of *Staphylococcus aureus* combined with a 3D imaging technique. The 3D imaging allowed high resolution full imaging of the curved contact surface and detection of *Staphylococcus aureus* by direct counting of the bound bacteria labelled with a latex microparticle and achieved a detection limit of ~16 bacteria $\mu L^{-1}$.

## 4. Implantable soft and flexible material-based affinity sensors

The recent popularity of wearable biosensors is driven by the demand for personalised continuous monitoring and health management. Despite the fact that various formats of wearable biosensors based on skin patches, textile materials and contact lenses have been developed for non-invasive continuous monitoring, there is a common problem concerning the accuracy of the measured non-invasive healthcare indicators in excreted body fluids (e.g. sweat and tears) using wearable biosensors and concerns about whether these correlate with the physiological biomarkers in the systematic blood circulation system within the body. Therefore, soft-material based implanted biosensors remain an important field for accurate continuous monitoring for clinical applications. For implanted biosensors, soft-materials are highly desirable due to their softness, conformity, flexibility and stretchability, which increase comfort and minimise damage to tissue around the implanted biosensor and biocompatibility. There is intensive research on injectable hydrogel sensors which has already been summarised in recent review articles (Jung et al., 2017; Le Goff et al., 2015). Here, we will focus on discussing the latest developments in implanted hydrogel affinity sensors, implanted microencapsulated sensors and on implanted fibre-based affinity biosensors that have been used for *in vivo* studies.

Hydrogels are versatile soft polymer networks and ideal substrates for implantable biosensing applications with their three-dimensional cross-linked structure, hydrophilicity,

tunable nature and good biocompatibility. Blood glucose detection and continuous monitoring remains one of the most important applications of biosensors and comprises about 85% of the world market. (Turner, 2013) Despite the existence of several successful *in-vivo* glucose monitoring systems based on invasive detection via catalytic elements (glucose oxidase or similar enzymes) and non-invasive wearable detection via spectroscopy, implantable glucose monitoring systems combining hydrogels with affinity sensing element (boronic acid) have attracted intense research interest. Shibata et al. (Shibata et al., 2010) reported the development of injectable fluorescence polyacrylamide hydrogel beads implanted in the skin of mice for *in vivo* glucose measurement. The polyacrylamide hydrogel beads were synthesised with a fluorescent diboronic acid monomer that enables reversible binding to glucose molecules. The *in vivo* analytical performance of the implanted glucose responsive hydrogel beads within mice were verified with blood glucose measurement using commercial sensors. The implanted hydrogel beads showed good correlation with the measured blood glucose concentration over a study period of 180 minutes. Moreover, the treated mice remained alive and the implanted hydrogel beads at the injection site did not show any abnormalities for over 30 days.

Mortellaro and DeHennis (Mortellaro and DeHennis, 2014) demonstrated a subcutaneously implantable wireless optical glucose sensor developed by Senseonics Inc., USA (www.senseonics.com ) - Eversense™ (made available in Europe by Roche) for an *in vivo* clinical study in 12 type-1 diabetic patients over a period of 28 days. The implantable sensor was composed of a fluorescently conjugated boronic acid-based polymer immobilised onto a miniaturised optical detector coupled with a water-resistant transmitter. The sensor antenna receives radio frequency energy from a transmitter and the boronic acid-based glucose indicating hydrogel and miniaturised optical detection system deliver glucose readings every 5 minutes. The accuracy of 19 implanted sensors were evaluated during 6 in-clinic sessions by comparing with blood glucose measured using commercial glucose sensor. The absolute relative difference for all implanted sensors was 11.67 ± 0.7% and Clarke error grid analysis showed that 99% of paired data points were in the combined zones. Further clinical studies are going on in Sweden that appear to support the clinical utility of these long-lived implantable

affinity sensors for monitoring diabetes, although the exactly how the required specificity is achieved in these devices is not entirely clear to us given the potential for cross reactivity with other sugars. If the reliability of these devices is substantiated, they are a game changer both in terms of the technology (optical affinity sensors as opposed to catalytic electrochemical devices) and their potential stability for long-term implantation. Tokuda et al. (Tokuda et al., 2014) reported the development of CMOS-based implantable glucose sensor composed of glucose responsive fluorescent hydrogel for *in vivo* glucose measurement in rats. The sensors were built by integration of a glucose responsive fluorescent phenylboronic acid-based hydrogel and a light emitting diodes (LEDs) as the excitation light sources with a CMOS image sensor packaged into a miniaturised implantable device. An intraperitoneal injection of glucose followed by an injection of insulin 40 minutes after the glucose injection were performed during the *in vivo* study and results were compared with blood glucose measured with commercial glucose sensors. The CMOS-based implantable glucose sensor showed a delayed response of 60 minutes for the measured glucose concentration compared with the standard blood glucose measurement. The author suspected that the delay may be caused by the diffusion of the blood glucose into the glucose-responsive fluorescence hydrogel and the limited surface area of the polyimide-based outer case packaging.

In addition to the intensive research on implanted hydrogel-based glucose sensors, some hydrogel encapsulated sensing systems have been developed for the detection of physical and physiologic parameters such as pH (Chan et al., 2013b), ions (Ozaydin-Ince et al., 2011), oxygen (Gamsey et al., 2016) and hydrogen peroxide (Kim et al., 2005). In order to extend the application of hydrogels to affinity detection of biomarkers, a wide range of biorecognition elements (antibody, nucleic acid and cells) and functional compositions (nanomaterials) have been explored. Choi et al.(Choi et al., 2013) reported the development of light-guiding hydrogels for real-time *in vivo* cell-based nanotoxicity sensing and light controlled optogenetic production of an antidiabetic glucagon-like peptide-1 (GLP-1) in live mice. They demonstrated the *in vivo* detection of cytotoxic effect of cadmium-based quantum dot with the implanted light-guiding hydrogels coupled with the heatshock-protein 70 (hsp70) which is activated when

cells are under cytotoxic stress and measures the green fluorescent protein (GFP) signal under the control of the hsp70 promoter. The light-guiding hydrogels showed a significant increase in green fluorescence in the CdTe-treated mice group compared with control at days 1 and 2 after treatment. These results demonstrated the first real-time *in vivo* measurement of systemic cellular nanotoxicity by cadmium-based quantum dots in mice animal model. Wang et al. (Wang et al., 2018) developed an *in vivo* nucleic acid qualitative detection system based on surface-enhanced Raman scattering (SERS) nanosensor implanted in the skin of a large animal model. The nanosensor embedded in agar gel matrix is composed of a stem-loop DNA probe labeled with plasmonic active nanosat for generation of Raman signal and complementary DNA probe for capturing the target nucleic acid analyte. *Ex vivo* and *in vivo* SERS detection for nucleic acid target provides a foundation for the future development of implanted hydrogen-based SERS affinity biosensors. Recently, magnetic hydrogels consisting of mirco and/or nanomagnetic particles in hydrogel matrices (ferrogels) have been widely researched for biomedical applications, such as tissue engineering, drug delivery, regenerative medicine and biosensing (Kurlyandskaya et al., 2017; Li et al., 2013). Among them, ferrogels hold great potential as implantable magnetic biosensors, combing biocompatible hydrogels, biological sensing elements and magnetic nanoparticle labels that respond to an external magnetic field. Despite limited research on these materials, some researchers used ferrogels as a model material to mimic natural biological tissues, laying the foundation for potentially implantable magnetic biosensors. Buznikov et al. (Buznikov et al., 2018) developed a magnetoimpedance (MI) biosensor prototype with a multilayered FeNi/Ni as sensitive element and ferrogels as mimic tissue. Giant magnetoimpedance sensor prototype responses were measured through effective stray field of magnetic nanoparticles and the corresponding model for MI was proposed. *In vivo* monitoring using the hydrogel encapsulated systems has not been realized to a substantial extent yet. A number of challenges still need to be solved such as insufficient stability of the bioreceptors (protein, nucleic acid, antibody), biocompatibility and biofouling of the implanted devices, and the development of wireless technology and power sources.

Optical fibres have been widely used for implanted biomedical and sensing (Nazempour et al., 2018). There are several advantages of using optical fibres for implanted biosensors compared with injectable hydrogels and microparticle sensing systems. An implanted fibre can be retained at the implanted site for a longer period of time compared with an injectable dispersion such as hydrogel or microparticles, which could diffuse from the implanted site. Also, the implanted fibre can be easily removed, which reduces the risk of harmful effects from the hydrogel inside the body. Miniaturised hollow fibre-based ConA biosensors have been available for some time as implanted biosensors for continuous glucose monitoring (Heo and Takeuchi, 2013). Typically, a hollow fibre is loaded with a dye conjugated ConA that is bound with quencher conjugated dextran molecules resulting in Förster resonance energy transfer (FRET) suppressing the fluorescence signal. The diffusion of glucose molecules into the implanted hollow fibre sensor will cause the dissociation of the dextran from the ConA complex and generate a fluorescence signal. Ballerstadt et al. (Ballerstadt et al., 2006) demonstrated the subcutaneous implantation of the hollow fibre-based ConA biosensors in rats. Cellulose hollow fibres were loaded with Cy7-ConA and Alexa 647-dextran. The fluorescence signal was read through the skin with an optical fibre used for both excitation and fluorescence detection. The implanted glucose biosensor used for *in vivo* glucose monitoring in rats was stable for up to 16 days and followed the blood glucose concentrations with a delay of less than 5 min. However, there was a time lag for glucose responses after 2 weeks implantation due to fouling around the implanted biosensor. In a subsequent study, Ballerstadt et al. (Ballerstadt et al., 2007) demonstrated using the hollow-fibre ConA biosensors for *in vivo* glucose concentration in pigs for up to 3 days. Despite some success with ConA-based implanted glucose sensors, the instability and leakage of immoblised ConA remain a hurdle towards long-term *in vivo* glucose monitoring. Moreover, the broad selectivity of ConA towards other saccharides and polysaccharides limited the specificity of the ConA-based affinity sensors. Cheung et al. (Cheung et al., 2008) demonstrated the incorporation of polyelectrolyte multi-layers onto a ConA-based hydrogel with permeability control to eliminate the high molecular weight polysaccharides diffused into the ConA-based hydrogel and improve the selectivity of ConA

detection system. Heo et al. (Heo et al., 2011) reported the development of a fluorescent hydrogel fibre for *in vivo* glucose monitoring in mice. Glucose-responsive monomers were co-polymerised with polyethylene glycol (PEG) and polyacrylamide (PAM) forming the glucose sensitive hydrogel fibres. This approach avoids the leakage of glucose sensing elements from the hydrogel fibre. The PEG-PAM hydrogel fibres also reduced inflammation responses compared with the PAM hydrogel fibres. The fluorescent hydrogel fibre was stable for *in vivo* glucose measurement up to 140 days and the responses were well correlated with the blood glucose concentration, demonstrating their potential application for long-term *in vivo* continuous glucose monitoring. Siegrist et al. (Siegrist et al., 2010) reported the use of a fluorescently labeled glucose recognition polypeptide immobilised in a polyacrylamide hydrogel matrix and placed on the tip of an optical fibre used for continuous glucose measurements. This demonstrated the possibility of coupling rationally engineered glucose binding proteins as biorecognition elements with optical fibres for real-time fluorescence-based glucose detection.

However, fluorescence detection may suffer from photobleaching and requires illumination. In another study, Yetisen et al. (Yetisen et al., 2017) demonstrated the development of phenylboronic acid-functionalised glucose sensitive hydrogel optical fibres for glucose monitoring. Hydrogel optical fibers were fabricated with poly(acrylamide-co-poly(ethylene glycol) diacrylate) p(AMco-PEGDA) core and a calcium alginate cladding that covalently coupled to 3-(acrylamido) phenylboronic acid (3-APBA) for sensing glucose. The boronic acid-based hydrogel glucose sensing mechanism is based on the binding of the glucose molecule to the boronic acid hydrogel causing a volume change or swelling of the hydrogel. Different forms of boronic acid-based hydrogels are summarised in a recent review article (Guan and Zhang, 2013). As glucose molecules diffuse into the hydrogel fibre and interact with the phenylboronic acid functional group, the Donnan osmotic pressure of the system increases due to swelling of the hydrogel. Changes in the osmotic pressure and the hydrogel density causes the change in the refractive index that affects light propagation through the hydrogel fibre and changes the intensity of output light. Thus, the glucose concentration is measured as a function of time

against the output light intensity. This hydrogel optical fibre allows measurement of glucose concentrations in real time within the diagnostic concentration range covering both diabetes and other health subjects.

Beside glucose monitoring, implanted optical fibres have also been used for biomarker detection *in vivo*. Zhang et al.(Zhang et al., 2018) developed an optical fibre device for serial monitoring of local cytokine release in discrete brain regions. The optical fibre was modified and labelled with capture antibody specific for the pro-inflammatory cytokine interleukin-1 beta (IL-1β). Based on the sandwich immunoassay, the optical fibre allowed IL-1β detection in the range of 3.8 – 500 pg $mL^{-1}$ in an *in-vitro* study. Measurement *in-vivo* was realised by introducing the immunocapture device into a perforated guide cannula in rat. Localised detection of IL-1β in the rat spinal cord was also realised using a stable immunocapture surface based on a biotin-streptavidin coupling strategy and fluorescent carboxylated supermagnetic iron oxide (SPIO) coupledIL-1β antibody conjugates as the biolabel (Zhang et al., 2019).

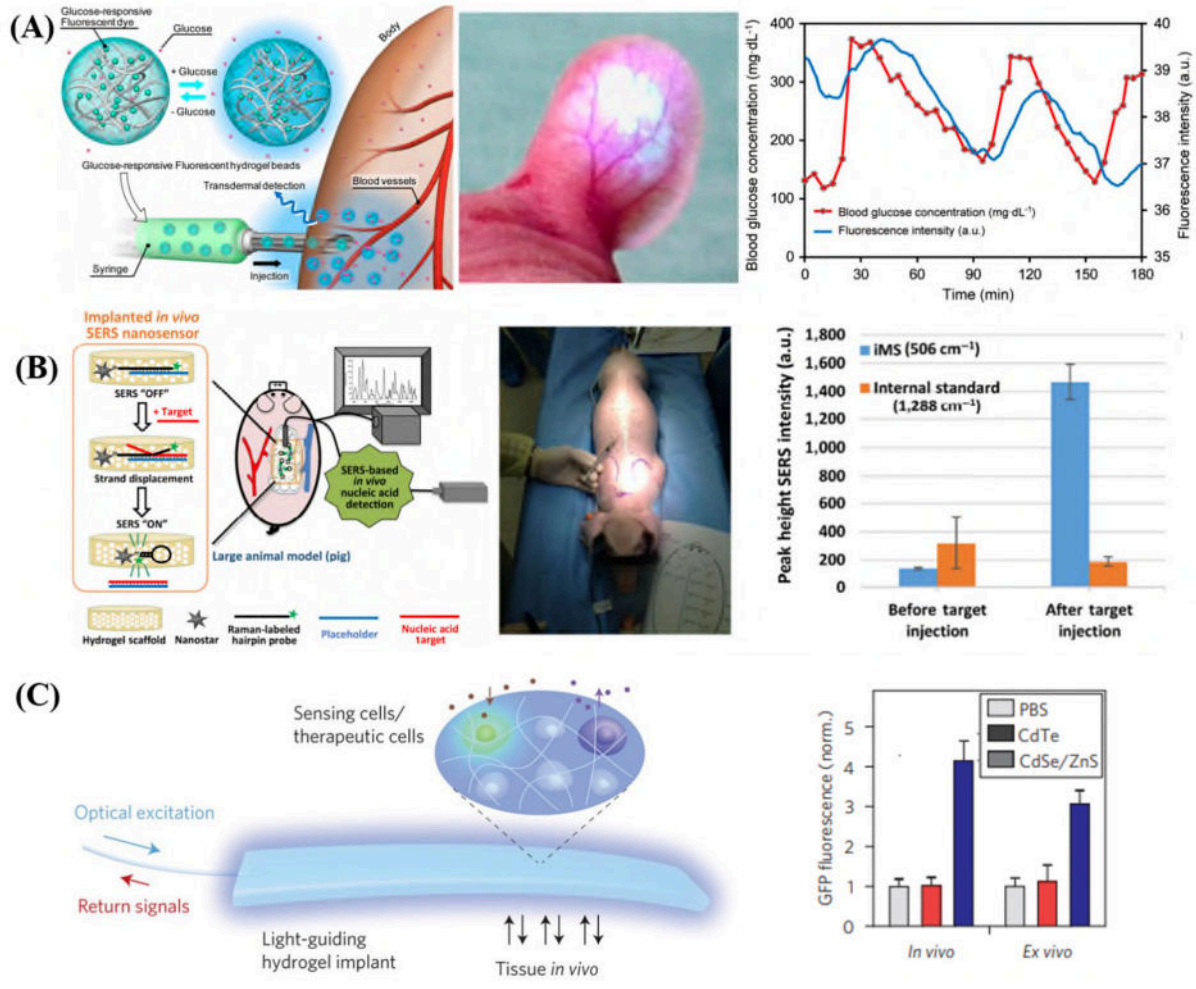

**Figure 4**. Implantable and injectable soft and flexible material-based affinity sensors. (A) Injectable hydrogel microbeads for fluorescence based *in vivo* continuous glucose monitoring. Adapted with permission from ref.(Shibata et al., 2010) (B) Surface-enhanced Raman scattering nanosensors for *in vivo* detection of nucleic acid targets in a large animal model. Adapted with permission from ref.(Wang et al., 2018) (C) Cell-integrated polyethylene glycol-based hydrogels for *in vivo* optical-sensing Adapted with permission from ref (Choi et al., 2013).

## 5. Challenges and Future perspectives

Historically, biomedical diagnostics have been performed by collecting blood, urine, wound or genetic samples followed by pretreatments and subsequent analysis using instruments in a central laboratory. The challenge now is to provide improved PoC tests, especially via wearable and implantable devices, to fulfill the increasingly recognised need for real-time, continuous, and even remote monitoring for individuals. The current trend to move away from conventional PoC tests towards wearable and implantable affinity biosensing devices, underlines the critical demand to improve the long-term reliability and response times of both continuous and discrete monitors, to enhance device integration and incorporate real-time data acquisition and analysis.

The primary concern for the PoC, wearable and implantable sensors, is accuracy and stability. Affinity biosensors employ bio-recognition molecules, such as antibodies, nucleic acid sequences and biological or biomimetic receptors, for affinity detection of analyte molecules, which result in the formation and subsequent dissociation of complexes. Understanding the functions of bio-recognition molecules and the binding mechanisms between targeted analytes and receptors underpins the development of affinity biosensors. The emerging field of MIPs offers interesting possibilities for new stable receptors while the incorporation of bio-recognition molecules into affinity sensing platforms during fabrication, device integration or practical operation also brings interesting opportunities. Operation in physiological environments, however, brings challenges such as fluctuations of pH, ionic strength and temperature. The majority of conventional PoC tests (e.g. lateral-flow membrane-based strips

and microfluidic paper-based analytical devices) are used for discrete measurements of analyte extracted as biological samples where conditions can be relatively well controlled. However, wearable and implantable devices have to deliver continuous detection of analyte in real time where conditions may be fluctuating and affecting binding kinetics. Hence, regular manual correction or systematic correction by integrated on-board calibrators are currently indispensable.

The response time and utility for continuous monitoring are key parameters to evaluate the feasibility of new affinity sensors. Response times can be in the order of several seconds to tens of minutes depending on diffusion of the analyte, transport and affinity interaction characteristics of the affinity sensor. The response time for PoC affinity sensors is typically within tens of minutes which is acceptable for discrete measurements of biomarkers for cancer, gene, infection and disease diagnostics. However, the response time for wearable and implantable affinity sensors intended for continuous monitoring of biomarkers must be much faster and is a challenge given the kinetics of affinity interactions between analyte and recognition molecules. Moreover, the implementation of continuous monitoring of many analytes remains a significant hurdle, due to irreversible affinity interactions between biorecognition elements and analytes resulting in non-reusable platform. Until now, the most successful implementation of wearable/implantable affinity sensors has been boronic acid-based glucose sensing. Building on this comparative success with the exploration of new affinity binding systems for biomarkers to expand the range of wearable/implantable sensors is a clear future direction for research. Moreover, to avoid adverse reactions to implanted devices, complimentary material science and engineering are needed to ensure biocompatibility for the extended lifetime of new devices.

Although conventional lateral-flow strip tests remain dominant in the market for affinity sensors, wearable/implantable sensors addressing the integration of complex components with multifunction will be the ultimate future goal. Sensors designed to measure different key parameters simultaneously for health monitoring, profiling a wide range of biomarkers, and detection of disease are required. Intensive research has been devoted to wearable physical

sensors based on flexible electronics (temperature, heart rate, body motion and strain), chemical sensors (pH, ions and humidity) and catalytic biosensors (glucose via catalyst, lactate and dopamine etc.). Attention now needs to focus more on affinity biosensors (such as glucose via boronic acid, pathogens, nucleic acid etc.) to establish a solid foundation for the integration of multiparameter wearable/implantable devices in the foreseeable future. These systems will need to be further integrated with power supplies, wireless data transmission and online back-end cloud servers for data analysis, storage and sharing.

The recent convergence of thinking around the escalating cost of delivering healthcare, the opportunities offered by mobile heath and the demand for more personalised medicine has stimulated enthusiasm for solutions based on biosensors. In addition, new areas have evolved where biosensors are recognised to have a pivotal role, such as in robotic surgery, tissue engineering and the production of biologics. These drivers have spurred on innovations in the area with exploration of conformable skin patches for non-invasive monitoring of sweat, contact lenses modified to monitor biomarkers in tears, sensors incorporated in textiles for both clothing and wound dressings and injectable hydrogel-based sensors for in-body sensing. The ultimate wide application of wearable/implantable biosensors needs significant improvements in size, durability and cost to meet the demand for worldwide distribution of decentralised and personalised sensing. Integration and miniaturisation of biosensor devices are an ongoing research trend. Advances in microscale engineering are addressing the challenges in the integration and miniaturisation of compact analytical devices by scaling down systems. Such devices provide distinct benefits compared with traditional approaches, such as simultaneous multiple measurements, ease of use and low manufacturing cost, especially where expensive biological materials are concerned. Soft and flexible materials will play a key role, but development needs to keep pace and materials have to evolve from simple mono-functional components to composites and hybrid materials that integrate several of the required recognition, transduction and transmission functions to deliver more manufacturable and efficient affinity sensor systems.

## Conclusions

With the demand for new sensing technology so clearly identified, the challenge is to harness the thousands of research reports on advanced materials to hone products that can meet these needs. Such new, inexpensive approaches will underpin new digital diagnostics, personalised medicine and fundamental biochemical research. Emerging soft and flexible materials are providing tools to fabricate systems with improved performance, while areas such as flexible electronics can show us the way to mass produce integrated systems at the right cost and with form factors that meet the rapidly evolving requirements for sensing interfaced with telecommunications and intelligent systems. The future importance of soft and flexible materials in affinity sensors for health management, therapy, food quality, environmental monitoring and research in the life sciences is clear and we need to bring chemists, engineers, users and entrepreneurs together to implement effective ways forward.

## References

Akanda, M.R., Joung, H.-A., Tamilavan, V., Park, S., Kim, S., Hyun, M.H., Kim, M.-G., Yang, H., 2014. An interference-free and rapid electrochemical lateral-flow immunoassay for one-step ultrasensitive detection with serum. Analyst 139(6), 1420-1425.

Andreyev, E.A., Komkova, M.A., Nikitina, V.N., Zaryanov, N.V., Voronin, O.G., Karyakina, E.E., Yatsimirsky, A.K., Karyakin, A.A., 2014. Reagentless polyol detection by conductivity increase in the course of self-doping of boronate-substituted polyaniline. Analytical chemistry 86(23), 11690-11695.

Anzenbacher Jr, P., Li, F., Palacios, M.A., 2012. Toward wearable sensors: fluorescent attoreactor mats as optically encoded cross‐reactive sensor arrays. Angewandte Chemie 124(10), 2395-2398.

Arshady, R., Mosbach, K., 1981. Synthesis of substrate‐selective polymers by host‐guest polymerization. Die Makromolekulare Chemie: Macromolecular Chemistry and Physics 182(2), 687-692.

Athikomrattanakul, U., Gajovic-Eichelmann, N., Scheller, F.W., 2011. Thermometric sensing of nitrofurantoin by noncovalently imprinted polymers containing two complementary functional monomers. Analytical chemistry 83(20), 7704-7711.

Aytaç, S., Kuralay, F., Boyacı, İ.H., Unaleroglu, C., 2011. A novel polypyrrole–phenylboronic acid based electrochemical saccharide sensor. Sensors and Actuators B: Chemical 160(1), 405-411.

Azkargorta, M., Soria, J., Acera, A., Iloro, I., Elortza, F., 2017. Human tear proteomics and peptidomics in ophthalmology: Toward the translation of proteomic biomarkers into clinical practice. Journal of proteomics 150359-367.
Badhulika, S., Tlili, C., Mulchandani, A., 2014. Poly (3-aminophenylboronic acid)-functionalized carbon nanotubes-based chemiresistive sensors for detection of sugars. Analyst 139(12), 3077-3082.
Badugu, R., Lakowicz, J.R., Geddes, C.D., 2004. Noninvasive continuous monitoring of physiological glucose using a monosaccharide-sensing contact lens. Analytical chemistry 76(3), 610-618.
Badugu, R., Lakowicz, J.R., Geddes, C.D., 2005. A glucose-sensing contact lens: from bench top to patient. Current Opinion in Biotechnology 16(1), 100-107.
Bajgrowicz-Cieslak, M., Alqurashi, Y., Elshereif, M.I., Yetisen, A.K., Hassan, M.U., Butt, H., 2017. Optical glucose sensors based on hexagonally-packed 2.5-dimensional photonic concavities imprinted in phenylboronic acid functionalized hydrogel films. RSC advances 7(85), 53916-53924.
Bakas, I., Hayat, A., Piletsky, S., Piletska, E., Chehimi, M.M., Noguer, T., Rouillon, R., 2014. Electrochemical impedimetric sensor based on molecularly imprinted polymers/sol–gel chemistry for methidathion organophosphorous insecticide recognition. Talanta 130294-298.
Balint, R., Cassidy, N.J., Cartmell, S.H., 2014. Conductive polymers: towards a smart biomaterial for tissue engineering. Acta biomaterialia 10(6), 2341-2353.
Ballerstadt, R., Evans, C., Gowda, A., McNichols, R., 2006. In vivo performance evaluation of a transdermal near-infrared fluorescence resonance energy transfer affinity sensor for continuous glucose monitoring. Diabetes technology & therapeutics 8(3), 296-311.
Ballerstadt, R., Evans, C., Gowda, A., McNichols, R., 2007. Fiber-coupled fluorescence affinity sensor for 3-day in vivo glucose sensing. Journal of diabetes science and technology 1(3), 384-393.
Basu, N., Konduri, A.K., Basu, P.K., Keshavan, S., Varma, M.M., Bhat, N., 2017. Flexible, Label-Free DNA Sensor using Platinum oxide as the sensing element. IEEE Sensors Journal 17(19), 6140-6147.
Bauer, S., 2013. Flexible electronics: sophisticated skin. Nature materials 12(10), 871.
Blažková, M., Rauch, P., Fukal, L., 2010. Strip-based immunoassay for rapid detection of thiabendazole. Biosensors and Bioelectronics 25(9), 2122-2128.
Bo, Y., Yang, H., Hu, Y., Yao, T., Huang, S., 2011. A novel electrochemical DNA biosensor based on graphene and polyaniline nanowires. Electrochimica Acta 56(6), 2676-2681.
Booth, M.A., Harbison, S., Travas‐Sejdic, J., 2012. Effects of Redox Couple on the Response of Polypyrrole‐Based Electrochemical DNA Sensors. Electroanalysis 24(6), 1311-1317.
Boulart, C., Prien, R., Chavagnac, V.r., Dutasta, J.-P., 2013. Sensing dissolved methane in aquatic environments: an experiment in the central Baltic Sea using surface plasmon resonance. Environmental science & technology 47(15), 8582-8590.
Boysen, R.I., Schwarz, L.J., Nicolau, D.V., Hearn, M.T., 2017. Molecularly imprinted polymer membranes and thin films for the separation and sensing of biomacromolecules. Journal of separation science 40(1), 314-335.

Bruzewicz, D.A., Reches, M., Whitesides, G.M., 2008. Low-cost printing of poly (dimethylsiloxane) barriers to define microchannels in paper. Analytical chemistry 80(9), 3387-3392.
Buznikov, N., Safronov, A., Orue, I., Golubeva, E., Lepalovskij, V., Svalov, A., Chlenova, A., Kurlyandskaya, G., 2018. Modelling of magnetoimpedance response of thin film sensitive element in the presence of ferrogel: Next step toward development of biosensor for in-tissue embedded magnetic nanoparticles detection. Biosensors and Bioelectronics 117366-372.
Castano, L.M., Flatau, A.B., 2014. Smart fabric sensors and e-textile technologies: a review. Smart Materials and Structures 23(5), 053001.
Chan, C.P.Y., Mak, W.C., Cheung, K.Y., Sin, K.K., Yu, C.M., Rainer, T.H., Renneberg, R., 2013a. Evidence-based point-of-care diagnostics: current status and emerging technologies. Annual Review of Analytical Chemistry 6191-211.
Chan, K.W., Liu, G., Song, X., Kim, H., Yu, T., Arifin, D.R., Gilad, A.A., Hanes, J., Walczak, P., Van Zijl, P.C., 2013b. MRI-detectable pH nanosensors incorporated into hydrogels for in vivo sensing of transplanted-cell viability. Nature materials 12(3), 268.
Chandler, J.A., 2000. Assay device for detecting the presence of an analyte involving sequential delivery of reagents through a liquid circuit. Google Patents.
Charrier, J., Brandily, M.-L., Lhermite, H., Michel, K., Bureau, B., Verger, F., Nazabal, V., 2012. Evanescent wave optical micro-sensor based on chalcogenide glass. Sensors and Actuators B: Chemical 173468-476.
Chen, J., Zheng, J., Gao, Q., Zhang, J., Zhang, J., Omisore, O.M., Wang, L., Li, H., 2018. Polydimethylsiloxane (PDMS)-Based Flexible Resistive Strain Sensors for Wearable Applications. Applied Sciences 8(3), 345.
Cheng, N., Xu, Y., Huang, K., Chen, Y., Yang, Z., Luo, Y., Xu, W., 2017. One-step competitive lateral flow biosensor running on an independent quantification system for smart phones based in-situ detection of trace Hg(II) in tap water. Food Chemistry 214169-175.
Cheung, K.Y., Mak, W.C., Trau, D., 2008. Reusable optical bioassay platform with permeability-controlled hydrogel pads for selective saccharide detection. Analytica Chimica Acta 607(2), 204-210.
Chitnis, G., Ding, Z., Chang, C.-L., Savran, C.A., Ziaie, B., 2011. Laser-treated hydrophobic paper: an inexpensive microfluidic platform. Lab on a Chip 11(6), 1161-1165.
Cho, G., Jeong, K., Paik, M.J., Kwun, Y., Sung, M., 2011. Performance evaluation of textile-based electrodes and motion sensors for smart clothing. IEEE Sensors Journal 11(12), 3183-3193.
Choi, M., Choi, J.W., Kim, S., Nizamoglu, S., Hahn, S.K., Yun, S.H., 2013. Light-guiding hydrogels for cell-based sensing and optogenetic synthesis in vivo. Nature photonics 7(12), 987.
Choudhary, T., Rajamanickam, G., Dendukuri, D., 2015. Woven electrochemical fabric-based test sensors (WEFTS): a new class of multiplexed electrochemical sensors. Lab on a Chip 15(9), 2064-2072.
Chu, M.X., Miyajima, K., Takahashi, D., Arakawa, T., Sano, K., Sawada, S.-i., Kudo, H., Iwasaki, Y., Akiyoshi, K., Mochizuki, M., 2011. Soft contact lens biosensor for in situ monitoring of tear glucose as non-invasive blood sugar assessment. Talanta 83(3), 960-965.

Daikuzono, C., Delaney, C., Tesfay, H., Florea, L., Oliveira, O., Morrin, A., Diamond, D., 2017. Impedance spectroscopy for monosaccharides detection using responsive hydrogel modified paper-based electrodes. Analyst 142(7), 1133-1139.
Daprà, J., Lauridsen, L.H., Nielsen, A.T., Rozlosnik, N., 2013. Comparative study on aptamers as recognition elements for antibiotics in a label-free all-polymer biosensor. Biosensors and Bioelectronics 43315-320.
De Vos, K., Girones, J., Claes, T., De Koninck, Y., Popelka, S., Schacht, E., Baets, R., Bienstman, P., 2009. Multiplexed antibody detection with an array of silicon-on-insulator microring resonators. IEEE Photonics Journal 1(4), 225-235.
Delaney, J.L., Hogan, C.F., Tian, J., Shen, W., 2011. Electrogenerated chemiluminescence detection in paper-based microfluidic sensors. Analytical chemistry 83(4), 1300-1306.
Diamond, D., Coyle, S., Scarmagnani, S., Hayes, J., 2008. Wireless sensor networks and chemo-/biosensing. Chemical reviews 108(2), 652-679.
Díaz-González, M., Pablo Salvador, J., Bonilla, D., Pilar Marco, M., Fernández-Sánchez, C., Baldi, A., 2015. A microfluidic device for the automated electrical readout of low-density glass-slide microarrays. Biosensors and Bioelectronics 74698-704.
Domschke, A., March, W.F., Kabilan, S., Lowe, C., 2006. Initial clinical testing of a holographic non-invasive contact lens glucose sensor. Diabetes technology & therapeutics 8(1), 89-93.
Dungchai, W., Chailapakul, O., Henry, C.S., 2011. A low-cost, simple, and rapid fabrication method for paper-based microfluidics using wax screen-printing. Analyst 136(1), 77-82.
Eduok, U., Faye, O., Szpunar, J., 2017. Recent developments and applications of protective silicone coatings: A review of PDMS functional materials. Progress in Organic Coatings 111124-163.
Elsherif, M., Hassan, M.U., Yetisen, A.K., Butt, H., 2018a. Glucose Sensing with Phenylboronic Acid Functionalized Hydrogel-Based Optical Diffusers. ACS nano 12(3), 2283-2291.
Elsherif, M., HASSAN, M.U., Yetisen, A.K., Butt, H., 2018b. Wearable Contact Lens Biosensors for Continuous Glucose Monitoring using Smartphones. ACS nano.
Eom, J., Jaisutti, R., Lee, H., Lee, W., Heo, J.-S., Lee, J.-Y., Park, S.K., Kim, Y.-H., 2017. Highly sensitive textile strain sensors and wireless user-interface devices using all-polymeric conducting fibers. ACS applied materials & interfaces 9(11), 10190-10197.
Eren, T., Atar, N., Yola, M.L., Karimi-Maleh, H., 2015. A sensitive molecularly imprinted polymer based quartz crystal microbalance nanosensor for selective determination of lovastatin in red yeast rice. Food chemistry 185430-436.
Esquivel, J., Del Campo, F., de la Fuente, J.G., Rojas, S., Sabate, N., 2014. Microfluidic fuel cells on paper: meeting the power needs of next generation lateral flow devices. Energy & Environmental Science 7(5), 1744-1749.
Fan, X., Jia, C., Yang, J., Li, G., Mao, H., Jin, Q., Zhao, J., 2015. A microfluidic chip integrated with a high-density PDMS-based microfiltration membrane for rapid isolation and detection of circulating tumor cells. Biosensors and Bioelectronics 71380-386.
Fang, G., Liu, G., Yang, Y., Wang, S., 2016. Quartz crystal microbalance sensor based on molecularly imprinted polymer membrane and three-dimensional Au nanoparticles@

mesoporous carbon CMK-3 functional composite for ultrasensitive and specific determination of citrinin. Sensors and Actuators B: Chemical 230272-280.
Farandos, N.M., Yetisen, A.K., Monteiro, M.J., Lowe, C.R., Yun, S.H., 2015. Contact lens sensors in ocular diagnostics. Advanced healthcare materials 4(6), 792-810.
Faustino, V., Catarino, S.O., Lima, R., Minas, G., 2016. Biomedical microfluidic devices by using low-cost fabrication techniques: A review. Journal of Biomechanics 49(11), 2280-2292.
Foster, C.W., Metters, J.P., Banks, C.E., 2013. Ultra flexible paper based electrochemical sensors: effect of mechanical contortion upon electrochemical performance. Electroanalysis 25(10), 2275-2282.
Fu, L.-M., Wang, Y.-N., 2018. Detection Methods and Applications of Microfluidic Paper-Based Analytical Devices. TrAC Trends in Analytical Chemistry.
Furniturewalla, A., Chan, M., Sui, J., Ahuja, K., Javanmard, M., 2018. Fully integrated wearable impedance cytometry platform on flexible circuit board with online smartphone readout. Microsystems & Nanoengineering 4(1), 20.
Galán, T., Prieto-Simón, B., Alvira, M., Eritja, R., Götz, G., Bäuerle, P., Samitier, J., 2015. Label-free electrochemical DNA sensor using “click”-functionalized PEDOT electrodes. Biosensors and Bioelectronics 74751-756.
Gamsey, S., Wisniewski, N., Helton, K., McMillan, W., 2016. Oxygen sensors. Google Patents.
Gao, W., Emaminejad, S., Nyein, H.Y.Y., Challa, S., Chen, K., Peck, A., Fahad, H.M., Ota, H., Shiraki, H., Kiriya, D., 2016. Fully integrated wearable sensor arrays for multiplexed in situ perspiration analysis. Nature 529(7587), 509.
Garcia-Cruz, A., Lee, M., Zine, N., Sigaud, M., Bausells, J., Errachid, A., 2015. Poly (pyrrole) microwires fabrication process on flexible thermoplastics polymers: application as a biosensing material. Sensors and Actuators B: Chemical 221940-950.
Ge, L., Wang, S., Song, X., Ge, S., Yu, J., 2012. 3D Origami-based multifunction-integrated immunodevice: low-cost and multiplexed sandwich chemiluminescence immunoassay on microfluidic paper-based analytical device. Lab on a Chip 12(17), 3150-3158.
Ge, S., Ge, L., Yan, M., Song, X., Yu, J., Huang, J., 2012. A disposable paper-based electrochemical sensor with an addressable electrode array for cancer screening. Chemical Communications 48(75), 9397-9399.
Goda, T., Toya, M., Matsumoto, A., Miyahara, Y., 2015. Poly (3, 4-ethylenedioxythiophene) bearing phosphorylcholine groups for metal-free, antibody-free, and low-impedance biosensors specific for C-reactive protein. ACS applied materials & interfaces 7(49), 27440-27448.
Guan, Y., Zhang, Y., 2013. Boronic acid-containing hydrogels: synthesis and their applications. Chemical Society Reviews 42(20), 8106-8121.
Guinovart, T., Parrilla, M., Crespo, G.A., Rius, F.X., Andrade, F.J., 2013. Potentiometric sensors using cotton yarns, carbon nanotubes and polymeric membranes. Analyst 138(18), 5208-5215.
Gupta, B.D., Shrivastav, A.M., Usha, S.P., 2016. Surface plasmon resonance-based fiber optic sensors utilizing molecular imprinting. Sensors 16(9), 1381.
Gwon, H., Hong, J., Kim, H., Seo, D.-H., Jeon, S., Kang, K., 2014. Recent progress on flexible lithium rechargeable batteries. Energy & Environmental Science 7(2), 538-551.

Hai, W., Goda, T., Takeuchi, H., Yamaoka, S., Horiguchi, Y., Matsumoto, A., Miyahara, Y., 2017. Specific recognition of human influenza virus with PEDOT bearing sialic acid-terminated trisaccharides. ACS applied materials & interfaces 9(16), 14162-14170.
Hammock, M.L., Chortos, A., Tee, B.C.K., Tok, J.B.H., Bao, Z., 2013a. 25th anniversary article: the evolution of electronic skin (e ‐ skin): a brief history, design considerations, and recent progress. Advanced materials 25(42), 5997-6038.
Hammock, M.L., Knopfmacher, O., Naab, B.D., Tok, J.B.-H., Bao, Z., 2013b. Investigation of protein detection parameters using nanofunctionalized organic field-effect transistors. ACS nano 7(5), 3970-3980.
He, Z., Elbaz, A., Gao, B., Zhang, J., Su, E., Gu, Z., 2018. Disposable Morpho menelaus Based Flexible Microfluidic and Electronic Sensor for the Diagnosis of Neurodegenerative Disease. Advanced healthcare materials 7(5), 1701306.
Hecht, L., van Rossum, D., Dietzel, A., 2016. Femtosecond-laser-structured nitrocellulose membranes for multi-parameter Point-of-Care tests. Microelectronic Engineering 15852-58.
Heo, J.S., Eom, J., Kim, Y.H., Park, S.K., 2018. Recent Progress of Textile ‐ Based Wearable Electronics: A Comprehensive Review of Materials, Devices, and Applications. Small 14(3), 1703034.
Heo, Y.J., Shibata, H., Okitsu, T., Kawanishi, T., Takeuchi, S., 2011. Long-term in vivo glucose monitoring using fluorescent hydrogel fibers. Proceedings of the National Academy of Sciences 108(33), 13399-13403.
Heo, Y.J., Takeuchi, S., 2013. Towards smart tattoos: implantable biosensors for continuous glucose monitoring. Advanced healthcare materials 2(1), 43-56.
Hong, S.Y., Oh, J.H., Park, H., Yun, J.Y., Jin, S.W., Sun, L., Zi, G., Ha, J.S., 2017. Polyurethane foam coated with a multi-walled carbon nanotube/polyaniline nanocomposite for a skin-like stretchable array of multi-functional sensors. NPG Asia Materials 9(11), e448.
Hu, Y., Feng, S., Gao, F., Li-Chan, E.C., Grant, E., Lu, X., 2015. Detection of melamine in milk using molecularly imprinted polymers–surface enhanced Raman spectroscopy. Food chemistry 176123-129.
Huang, X., Liu, Y., Cheng, H., Shin, W.J., Fan, J.A., Liu, Z., Lu, C.J., Kong, G.W., Chen, K., Patnaik, D., 2014. Materials and designs for wireless epidermal sensors of hydration and strain. Advanced Functional Materials 24(25), 3846-3854.
Huh, P., Kim, S.-C., Kim, Y., Wang, Y., Singh, J., Kumar, J., Samuelson, L.A., Kim, B.-S., Jo, N.-J., Lee, J.-O., 2007. Optical and electrochemical detection of saccharides with poly (aniline-co-3-aminobenzeneboronic acid) prepared from enzymatic polymerization. Biomacromolecules 8(11), 3602-3607.
Ibanez, J.G., Rincon, M.E., Gutierrez-Granados, S., Chahma, M.h., Jaramillo-Quintero, O.A., Frontana-Uribe, B.A., 2018. Conducting polymers in the fields of energy, environmental remediation, and chemical–chiral sensors. Chemical reviews 118(9), 4731-4816.
Ionescu, R.E., Herrmann, S., Cosnier, S., Marks, R.S., 2006. A polypyrrole cDNA electrode for the amperometric detection of the West Nile Virus. Electrochemistry Communications 8(11), 1741-1748.

Jang, Y., Oh, S.Y., Park, J.-K., 2006. In situ electrochemical enzyme immunoassay on a microchip with surface-functionalized poly (dimethylsiloxane) channel. Enzyme and microbial technology 39(5), 1122-1127.
Jiang, N., Butt, H., Montelongo, Y., Liu, F., Afewerki, S., Ying, G.L., Dai, Q., Yun, S.H., Yetisen, A.K., 2018. Laser Interference Lithography for the Nanofabrication of Stimuli‐Responsive Bragg Stacks. Advanced Functional Materials 28(24), 1702715.
Jung, I.Y., Kim, J.S., Choi, B.R., Lee, K., Lee, H., 2017. Hydrogel based biosensors for in vitro diagnostics of biochemicals, proteins, and genes. Advanced healthcare materials 6(12), 1601475.
Jung, J., Kim, S.J., Lee, K.W., Yoon, D.H., Kim, Y.-g., Kwak, H.Y., Dugasani, S.R., Park, S.H., Kim, H.J., 2014. Approaches to label-free flexible DNA biosensors using low-temperature solution-processed InZnO thin-film transistors. Biosensors and Bioelectronics 5599-105.
Kamakoti, V., Panneer Selvam, A., Radha Shanmugam, N., Muthukumar, S., Prasad, S., 2016. Flexible molybdenum electrodes towards designing affinity based protein biosensors. Biosensors 6(3), 36.
Kassal, P., Kim, J., Kumar, R., de Araujo, W.R., Steinberg, I.M., Steinberg, M.D., Wang, J., 2015. Smart bandage with wireless connectivity for uric acid biosensing as an indicator of wound status. Electrochemistry Communications 566-10.
Khan, S., Lorenzelli, L., 2017. Recent advances of conductive nanocomposites in printed and flexible electronics. Smart Materials and Structures 26(8), 083001.
Kim, B.C., Hong, J.Y., Wallace, G.G., Park, H.S., 2015a. Recent progress in flexible electrochemical capacitors: electrode materials, device configuration, and functions. Advanced Energy Materials 5(22), 1500959.
Kim, J.-M., Jha, S.K., Lee, D.-H., Chand, R., Jeun, J.-H., Kim, Y.-S., 2012. A flexible pentacene thin film transistors as disposable DNA hybridization sensor. Journal of Industrial and Engineering Chemistry 18(5), 1642-1646.
Kim, J., Jeerapan, I., Imani, S., Cho, T.N., Bandodkar, A., Cinti, S., Mercier, P.P., Wang, J., 2016a. Noninvasive alcohol monitoring using a wearable tattoo-based iontophoretic-biosensing system. Acs Sensors 1(8), 1011-1019.
Kim, J.-Y., Yeo, M.-K., 2016. A fabricated microfluidic paper-based analytical device (μPAD) for in situ rapid colorimetric detection of microorganisms in environmental water samples. Molecular & Cellular Toxicology 12(1), 101-109.
Kim, J., Gutruf, P., Chiarelli, A.M., Heo, S.Y., Cho, K., Xie, Z., Banks, A., Han, S., Jang, K.I., Lee, J.W., 2017. Miniaturized battery‐free wireless systems for wearable pulse oximetry. Advanced functional materials 27(1), 1604373.
Kim, J., Imani, S., de Araujo, W.R., Warchall, J., Valdés-Ramírez, G., Paixão, T.R.L.C., Mercier, P.P., Wang, J., 2015b. Wearable salivary uric acid mouthguard biosensor with integrated wireless electronics. Biosensors and Bioelectronics 741061-1068.
Kim, J., Lee, M., Shim, H.J., Ghaffari, R., Cho, H.R., Son, D., Jung, Y.H., Soh, M., Choi, C., Jung, S., 2014. Stretchable silicon nanoribbon electronics for skin prosthesis. Nature communications 55747.
Kim, J., Salvatore, G.A., Araki, H., Chiarelli, A.M., Xie, Z., Banks, A., Sheng, X., Liu, Y., Lee, J.W., Jang, K.-I., Heo, S.Y., Cho, K., Luo, H., Zimmerman, B., Kim, J., Yan, L., Feng, X., Xu,

S., Fabiani, M., Gratton, G., Huang, Y., Paik, U., Rogers, J.A., 2016b. Battery-free, stretchable optoelectronic systems for wireless optical characterization of the skin. Science Advances 2(8).
Kim, S.-H., Kim, B., Yadavalli, V.K., Pishko, M.V., 2005. Encapsulation of enzymes within polymer spheres to create optical nanosensors for oxidative stress. Analytical chemistry 77(21), 6828-6833.
Kinnamon, D., Ghanta, R., Lin, K.-C., Muthukumar, S., Prasad, S., 2017. Portable biosensor for monitoring cortisol in low-volume perspired human sweat. Scientific reports 7(1), 13312.
Kinnamon, D.S., Krishnan, S., Brosler, S., Sun, E., Prasad, S., 2018. Screen Printed Graphene Oxide Textile Biosensor for Applications in Inexpensive and Wearable Point-of-Exposure Detection of Influenza for At-Risk Populations. Journal of The Electrochemical Society 165(8), B3084-B3090.
Kirchmeyer, S., Reuter, K., 2005. Scientific importance, properties and growing applications of poly (3, 4-ethylenedioxythiophene). Journal of Materials Chemistry 15(21), 2077-2088.
Koh, A., Kang, D., Xue, Y., Lee, S., Pielak, R.M., Kim, J., Hwang, T., Min, S., Banks, A., Bastien, P., 2016. A soft, wearable microfluidic device for the capture, storage, and colorimetric sensing of sweat. Science Translational Medicine 8(366), 366ra165-366ra165.
Kokkinos, C., Angelopoulou, M., Economou, A., Prodromidis, M., Florou, A., Haasnoot, W., Petrou, P., Kakabakos, S., 2016. Lab-on-a-membrane foldable devices for duplex drop-volume electrochemical biosensing using quantum dot tags. Analytical chemistry 88(13), 6897-6904.
Kokkinos, C., Economou, A., Speliotis, T., Petrou, P., Kakabakos, S., 2014. Flexible microfabricated film sensors for the in situ quantum dot-based voltammetric detection of DNA hybridization in microwells. Analytical chemistry 87(2), 853-857.
Kong, Q., Wang, Y., Zhang, L., Ge, S., Yu, J., 2017. A novel microfluidic paper-based colorimetric sensor based on molecularly imprinted polymer membranes for highly selective and sensitive detection of bisphenol A. Sensors and Actuators B: Chemical 243130-136.
Kor, K., Turner, A.P., Zarei, K., Atabati, M., Beni, V., Mak, W.C., 2016. Structurally responsive oligonucleotide-based single-probe lateral-flow test for detection of miRNA-21 mimics. Analytical and bioanalytical chemistry 408(5), 1475-1485.
Kumar, S., Sen, A., Kumar, S., Augustine, S., Yadav, B.K., Mishra, S., Malhotra, B.D., 2016. Polyaniline modified flexible conducting paper for cancer detection. Applied Physics Letters 108(20), 203702.
Kurlyandskaya, G., Novoselova, I.P., Schupletsova, V., Andrade, R., Dunec, N., Litvinova, L., Safronov, A., Yurova, K., Kulesh, N., Dzyuman, A., 2017. Nanoparticles for magnetic biosensing systems. Journal of Magnetism and Magnetic Materials 431249-254.
Kwon, O.S., Park, S.J., Hong, J.-Y., Han, A.-R., Lee, J.S., Lee, J.S., Oh, J.H., Jang, J., 2012. Flexible FET-type VEGF aptasensor based on nitrogen-doped graphene converted from conducting polymer. ACS nano 6(2), 1486-1493.
Le Goff, G.C., Srinivas, R.L., Hill, W.A., Doyle, P.S., 2015. Hydrogel microparticles for biosensing. European polymer journal 72386-412.
Lee, D., Cui, T., 2010. Low-cost, transparent, and flexible single-walled carbon nanotube nanocomposite based ion-sensitive field-effect transistors for pH/glucose sensing. Biosensors and Bioelectronics 25(10), 2259-2264.

Lee, H., Choi, T.K., Lee, Y.B., Cho, H.R., Ghaffari, R., Wang, L., Choi, H.J., Chung, T.D., Lu, N., Hyeon, T., 2016. A graphene-based electrochemical device with thermoresponsive microneedles for diabetes monitoring and therapy. Nature nanotechnology 11(6), 566.
Lee, H., Song, C., Hong, Y.S., Kim, M.S., Cho, H.R., Kang, T., Shin, K., Choi, S.H., Hyeon, T., Kim, D.-H., 2017. Wearable/disposable sweat-based glucose monitoring device with multistage transdermal drug delivery module. Science advances 3(3), e1601314.
Li, C., Bai, H., Shi, G., 2009. Conducting polymer nanomaterials: electrosynthesis and applications. Chemical Society Reviews 38(8), 2397-2409.
Li, J., Lee, E.-C., 2015. Carbon nanotube/polymer composite electrodes for flexible, attachable electrochemical DNA sensors. Biosensors and Bioelectronics 71414-419.
Li, J., Zhang, Z., Xu, S., Chen, L., Zhou, N., Xiong, H., Peng, H., 2011. Label-free colorimetric detection of trace cholesterol based on molecularly imprinted photonic hydrogels. Journal of Materials Chemistry 21(48), 19267-19274.
Li, J., Zhao, J., Rogers, J.A., 2018. Materials and Designs for Power Supply Systems in Skin-Interfaced Electronics. Accounts of chemical research 52(1), 53-62.
Li, Y., Huang, G., Zhang, X., Li, B., Chen, Y., Lu, T., Lu, T.J., Xu, F., 2013. Magnetic hydrogels and their potential biomedical applications. Advanced Functional Materials 23(6), 660-672.
Li, Y., Li, Y., Su, M., Li, W., Li, Y., Li, H., Qian, X., Zhang, X., Li, F., Song, Y., 2017. Electronic Textile by Dyeing Method for Multiresolution Physical Kineses Monitoring. Advanced Electronic Materials 3(10), 1700253.
Liang, Z., Wang, X., Zhu, W., Zhang, P., Yang, Y., Sun, C., Zhang, J., Wang, X., Xu, Z., Zhao, Y., 2017. Upconversion nanocrystals mediated lateral-flow nanoplatform for in vitro detection. ACS applied materials & interfaces 9(4), 3497-3504.
Lin, P., Luo, X., Hsing, I.M., Yan, F., 2011. Organic electrochemical transistors integrated in flexible microfluidic systems and used for label‐free DNA sensing. Advanced Materials 23(35), 4035-4040.
Lin, Y.-R., Hung, C.-C., Chiu, H.-Y., Chang, P.-H., Li, B.-R., Cheng, S.-J., Yang, J.-W., Lin, S.-F., Chen, G.-Y., 2018. Noninvasive Glucose Monitoring with a Contact Lens and Smartphone. Sensors 18(10), 3208.
Liu, H., Crooks, R.M., 2011. Three-dimensional paper microfluidic devices assembled using the principles of origami. Journal of the American Chemical Society 133(44), 17564-17566.
Liu, H., Xiang, Y., Lu, Y., Crooks, R.M., 2012. Aptamer‐based origami paper analytical device for electrochemical detection of adenosine. Angewandte Chemie 124(28), 7031-7034.
Liu, J., Lu, C.-Y., Zhou, H., Xu, J.-J., Chen, H.-Y., 2014. Flexible gold electrode array for multiplexed immunoelectrochemical measurement of three protein biomarkers for prostate cancer. ACS applied materials & interfaces 6(22), 20137-20143.
Liu, S., Ma, Y., Cui, M., Luo, X., 2018. Enhanced electrochemical biosensing of alpha-fetoprotein based on three-dimensional macroporous conducting polymer polyaniline. Sensors and Actuators B: Chemical 2552568-2574.
Liu, X., Lillehoj, P.B., 2016. Embroidered electrochemical sensors for biomolecular detection. Lab on a Chip 16(11), 2093-2098.
Liu, Y., He, K., Chen, G., Leow, W.R., Chen, X., 2017. Nature-inspired structural materials for flexible electronic devices. Chemical reviews 117(20), 12893-12941.

Loynachan, C.N., Thomas, M.R., Gray, E.R., Richards, D.A., Kim, J., Miller, B.S., Brookes, J.C., Agarwal, S., Chudasama, V., McKendry, R.A., 2017. Platinum Nanocatalyst Amplification: Redefining the Gold Standard for Lateral Flow Immunoassays with Ultrabroad Dynamic Range. ACS nano 12(1), 279-288.
Lu, M., Lee, D., Xue, W., Cui, T., 2009. Flexible and disposable immunosensors based on layer-by-layer self-assembled carbon nanotubes and biomolecules. Sensors and Actuators A: Physical 150(2), 280-285.
Luo, S.-C., Xie, H., Chen, N., Yu, H.-h., 2009. Trinity DNA detection platform by ultrasmooth and functionalized PEDOT biointerfaces. ACS applied materials & interfaces 1(7), 1414-1419.
Mak, W.C., Beni, V., Turner, A.P., 2016. Lateral-flow technology: From visual to instrumental. TrAC Trends in Analytical Chemistry 79297-305.
Mak, W.C., Cheung, K.Y., Orban, J., Lee, C.-J., Turner, A.P., Griffith, M., 2015. Surface-engineered contact lens as an advanced theranostic platform for modulation and detection of viral infection. ACS applied materials & interfaces 7(45), 25487-25494.
Mak, W.C., Sin, K., Chan, C.P.Y., Wong, L.W., Renneberg, R., 2011. Biofunctionalized indigo-nanoparticles as biolabels for the generation of precipitated visible signal in immunodipsticks. Biosensors and Bioelectronics 26(7), 3148-3153.
Malon, R.S., Chua, K., Wicaksono, D.H., Córcoles, E.P., 2014. Cotton fabric-based electrochemical device for lactate measurement in saliva. Analyst 139(12), 3009-3016.
Manjakkal, L., Sakthivel, B., Gopalakrishnan, N., Dahiya, R., 2018. Printed flexible electrochemical pH sensors based on CuO nanorods. Sensors and Actuators B: Chemical 26350-58.
Mannoor, M.S., Tao, H., Clayton, J.D., Sengupta, A., Kaplan, D.L., Naik, R.R., Verma, N., Omenetto, F.G., McAlpine, M.C., 2012. Graphene-based wireless bacteria detection on tooth enamel. Nature communications 3763.
March, W., Lazzaro, D., Rastogi, S., 2006. Fluorescent measurement in the non-invasive contact lens glucose sensor. Diabetes technology & therapeutics 8(3), 312-317.
March, W.F., Mueller, A., Herbrechtsmeier, P., 2004. Clinical trial of a noninvasive contact lens glucose sensor. Diabetes technology & therapeutics 6(6), 782-789.
marketsandmarkets.com, 2017. Lateral Flow Assay Market by Product (Reader, Kit), Application (Clinical (Pregnancy, Infectious Disease, Lipid, Cardiac Marker), Veterinary, Drug Development, Food Safety), Technique (Competitive, Multiplex, Sandwich), End User - Global Forecast to 2022. www.marketsandmarkets.com Report Code: MD 4158.
Martinez, A.W., Phillips, S.T., Butte, M.J., Whitesides, G.M., 2007. Patterned paper as a platform for inexpensive, low‐volume, portable bioassays. Angewandte Chemie International Edition 46(8), 1318-1320.
Martinez, A.W., Phillips, S.T., Whitesides, G.M., 2008. Three-dimensional microfluidic devices fabricated in layered paper and tape. Proceedings of the National Academy of Sciences 105(50), 19606-19611.
Mattana, G., Kinkeldei, T., Leuenberger, D., Ataman, C., Ruan, J.J., Molina-Lopez, F., Quintero, A.V., Nisato, G., Tröster, G., Briand, D., 2013. Woven temperature and humidity sensors on flexible plastic substrates for e-textile applications. IEEE Sens. J 13(10), 3901-3909.

Mazzotta, E., Turco, A., Chianella, I., Guerreiro, A., Piletsky, S.A., Malitesta, C., 2016. Solid-phase synthesis of electroactive nanoparticles of molecularly imprinted polymers. A novel platform for indirect electrochemical sensing applications. Sensors and Actuators B: Chemical 229174-180.
Mettakoonpitak, J., Boehle, K., Nantaphol, S., Teengam, P., Adkins, J.A., Srisa‐Art, M., Henry, C.S., 2016. Electrochemistry on Paper‐based Analytical Devices: A Review. Electroanalysis 28(7), 1420-1436.
Miodek, A., Castillo, G., Hianik, T., Korri-Youssoufi, H., 2014. Electrochemical aptasensor of cellular prion protein based on modified polypyrrole with redox dendrimers. Biosensors and Bioelectronics 56104-111.
Mirata, F., Resmini, M., 2015. Molecularly imprinted polymers for catalysis and synthesis. Molecularly Imprinted Polymers in Biotechnology, pp. 107-129. Springer.
Morbioli, G.G., Mazzu-Nascimento, T., Milan, L.A., Stockton, A.M., Carrilho, E., 2017. Improving sample distribution homogeneity in three-dimensional microfluidic paper-based analytical devices by rational device design. Analytical chemistry 89(9), 4786-4792.
Morris, D., Coyle, S., Wu, Y., Lau, K.T., Wallace, G., Diamond, D., 2009. Bio-sensing textile based patch with integrated optical detection system for sweat monitoring. Sensors and Actuators B: Chemical 139(1), 231-236.
Mortellaro, M., DeHennis, A., 2014. Performance characterization of an abiotic and fluorescent-based continuous glucose monitoring system in patients with type 1 diabetes. Biosensors and Bioelectronics 61227-231.
Munje, R.D., Muthukumar, S., Prasad, S., 2017. Lancet-free and label-free diagnostics of glucose in sweat using Zinc Oxide based flexible bioelectronics. Sensors and Actuators B: Chemical 238482-490.
Nazempour, R., Zhang, Q., Fu, R., Sheng, X., 2018. Biocompatible and Implantable Optical Fibers and Waveguides for Biomedicine. Materials 11(8), 1283.
Newman, J.D., Turner, A.P.F., 2005. Home blood glucose biosensors: a commercial perspective. Biosensors and Bioelectronics 20(12), 2435-2453.
Ngom, B., Guo, Y., Wang, X., Bi, D., 2010. Development and application of lateral flow test strip technology for detection of infectious agents and chemical contaminants: a review. Analytical and bioanalytical chemistry 397(3), 1113-1135.
Nie, J., Liang, Y., Zhang, Y., Le, S., Li, D., Zhang, S., 2013. One-step patterning of hollow microstructures in paper by laser cutting to create microfluidic analytical devices. Analyst 138(2), 671-676.
Noimark, S., Colchester, R.J., Poduval, R.K., Maneas, E., Alles, E.J., Zhao, T., Zhang, E.Z., Ashworth, M., Tsolaki, E., Chester, A.H., 2018. Polydimethylsiloxane composites for optical ultrasound generation and multimodality imaging. Advanced Functional Materials 28(9), 1704919.
Nomura, K.-i., Horii, Y., Kanazawa, S., Kusaka, Y., Ushijima, H., 2018. Fabrication of a Textile-Based Wearable Blood Leakage Sensor Using Screen-Offset Printing. Sensors 18(1), 240.
Ozaydin-Ince, G., Dubach, J.M., Gleason, K.K., Clark, H.A., 2011. Microworm optode sensors limit particle diffusion to enable in vivo measurements. Proceedings of the National Academy of Sciences 108(7), 2656-2661.

Pal, R.K., Farghaly, A.A., Wang, C., Collinson, M.M., Kundu, S.C., Yadavalli, V.K., 2016. Conducting polymer-silk biocomposites for flexible and biodegradable electrochemical sensors. Biosensors and Bioelectronics 81294-302.
Park, H.-W., Huynh, N.D., Kim, W., Lee, C., Nam, Y., Lee, S., Chung, K.-B., Choi, D., 2018. Electron blocking layer-based interfacial design for highly-enhanced triboelectric nanogenerators. Nano Energy 509-15.
Parlak, O., Keene, S.T., Marais, A., Curto, V.F., Salleo, A., 2018. Molecularly selective nanoporous membrane-based wearable organic electrochemical device for noninvasive cortisol sensing. Science advances 4(7), eaar2904.
Parolo, C., de la Escosura-Muñiz, A., Merkoçi, A., 2013. Enhanced lateral flow immunoassay using gold nanoparticles loaded with enzymes. Biosensors and Bioelectronics 40(1), 412-416.
Peeters, M.M., van Grinsven, B., Foster, C.W., Cleij, T.J., Banks, C.E., 2016. Introducing thermal wave transport analysis (TWTA): a thermal technique for dopamine detection by screen-printed electrodes functionalized with molecularly imprinted polymer (MIP) particles. Molecules 21(5), 552.
Piletsky, S.A., Turner, A.P., 2002. Electrochemical sensors based on molecularly imprinted polymers. Electroanalysis: An International Journal Devoted to Fundamental and Practical Aspects of Electroanalysis 14(5), 317-323.
Pringsheim, E., Terpetschnig, E., Piletsky, S.A., Wolfbeis, O.S., 1999. A Polyaniline with Near‐Infrared Optical Response to Saccharides. Advanced Materials 11(10), 865-868.
Ray, T.R., Choi, J., Bandodkar, A.J., Krishnan, S., Gutruf, P., Tian, L., Ghaffari, R., Rogers, J.A., 2019. Bio-integrated wearable systems: a comprehensive review. Chemical reviews.
Rim, Y.S., Bae, S.-H., Chen, H., Yang, J.L., Kim, J., Andrews, A.M., Weiss, P.S., Yang, Y., Tseng, H.-R., 2015. Printable ultrathin metal oxide semiconductor-based conformal biosensors. ACS nano 9(12), 12174-12181.
Ruh, D., Reith, P., Sherman, S., Theodor, M., Ruhhammer, J., Seifert, A., Zappe, H., 2014. Stretchable optoelectronic circuits embedded in a polymer network. Advanced Materials 26(11), 1706-1710.
Ruiz‐Vega, G., Kitsara, M., Pellitero, M.A., Baldrich, E., del Campo, F.J., 2017. Electrochemical Lateral Flow Devices: Towards Rapid Immunomagnetic Assays. ChemElectroChem 4(4), 880-889.
Sajid, M., Kawde, A.-N., Daud, M., 2015. Designs, formats and applications of lateral flow assay: A literature review. Journal of Saudi Chemical Society 19(6), 689-705.
Scida, K., Li, B., Ellington, A.D., Crooks, R.M., 2013. DNA detection using origami paper analytical devices. Analytical chemistry 85(20), 9713-9720.
Sekine, J., Luo, S.C., Wang, S., Zhu, B., Tseng, H.R., Yu, H.h., 2011. Functionalized conducting polymer nanodots for enhanced cell capturing: the synergistic effect of capture agents and nanostructures. Advanced Materials 23(41), 4788-4792.
Shan, J., Ma, Z., 2017. A review on amperometric immunoassays for tumor markers based on the use of hybrid materials consisting of conducting polymers and noble metal nanomaterials. Microchimica Acta 184(4), 969-979.

Shanmugam, N.R., Muthukumar, S., Prasad, S., 2016. Ultrasensitive and low-volume point-of-care diagnostics on flexible strips–a study with cardiac troponin biomarkers. Scientific reports 633423.
Sheikhzadeh, E., Chamsaz, M., Turner, A.P.F., Jager, E.W.H., Beni, V., 2016. Label-free impedimetric biosensor for Salmonella Typhimurium detection based on poly [pyrrole-co-3-carboxyl-pyrrole] copolymer supported aptamer. Biosensors and Bioelectronics 80194-200.
Shi, Z., Tian, Y., Wu, X., Li, C., Yu, L., 2015. A one-piece lateral flow impedimetric test strip for label-free clenbuterol detection. Analytical Methods 7(12), 4957-4964.
Shibata, H., Heo, Y.J., Okitsu, T., Matsunaga, Y., Kawanishi, T., Takeuchi, S., 2010. Injectable hydrogel microbeads for fluorescence-based in vivo continuous glucose monitoring. Proceedings of the National Academy of Sciences.
Shim, B.S., Chen, W., Doty, C., Xu, C., Kotov, N.A., 2008. Smart electronic yarns and wearable fabrics for human biomonitoring made by carbon nanotube coating with polyelectrolytes. Nano letters 8(12), 4151-4157.
Siegrist, J., Kazarian, T., Ensor, C., Joel, S., Madou, M., Wang, P., Daunert, S., 2010. Continuous glucose sensor using novel genetically engineered binding polypeptides towards in vivo applications. Sensors and Actuators B: Chemical 149(1), 51-58.
Sinawang, P.D., Rai, V., Ionescu, R.E., Marks, R.S., 2016. Electrochemical lateral flow immunosensor for detection and quantification of dengue NS1 protein. Biosensors and Bioelectronics 77400-408.
Song, M.-J., Jin, J.-H., 2015. Label-free Electrochemical Detection of the Human Adenovirus 40/41 Fiber Gene. Analytical Sciences 31(3), 159-163.
Spanu, A., Lai, S., Cosseddu, P., Tedesco, M., Martinoia, S., Bonfiglio, A., 2015. An organic transistor-based system for reference-less electrophysiological monitoring of excitable cells. Scientific reports 58807.
Spicar-Mihalic, P., Toley, B., Houghtaling, J., Liang, T., Yager, P., Fu, E., 2013. CO2 laser cutting and ablative etching for the fabrication of paper-based devices. Journal of Micromechanics and Microengineering 23(6), 067003.
Stefan-van Staden, R.-I., Comnea-Stancu, I.R., Surdu-Bob, C.C., Badulescu, M., 2015. Nanostructured materials detect epidermal growth factor receptor, neuron specific enolase and carcinoembryonic antigen. Nanoscale 7(38), 15689-15694.
Tan, F., Cong, L., Li, X., Zhao, Q., Zhao, H., Quan, X., Chen, J., 2016. An electrochemical sensor based on molecularly imprinted polypyrrole/graphene quantum dots composite for detection of bisphenol A in water samples. Sensors and Actuators B: Chemical 233599-606.
Tan, X., Hu, Q., Wu, J., Li, X., Li, P., Yu, H., Li, X., Lei, F., 2015. Electrochemical sensor based on molecularly imprinted polymer reduced graphene oxide and gold nanoparticles modified electrode for detection of carbofuran. Sensors and Actuators B: Chemical 220216-221.
Tansil, N.C., Kantchev, E.A.B., Gao, Z., Yu, H.-h., 2011. Electropolymerization of intercalator-grafted conducting polymer for direct and amplified DNA detection. Chemical Communications 47(5), 1533-1535.
Taranova, N., Berlina, A., Zherdev, A., Dzantiev, B., 2015. 'Traffic light'immunochromatographic test based on multicolor quantum dots for the simultaneous detection of several antibiotics in milk. Biosensors and Bioelectronics 63255-261.

Taranova, N.A., Byzova, N.A., Zaiko, V.V., Starovoitova, T.A., Vengerov, Y.Y., Zherdev, A.V., Dzantiev, B.B., 2013. Integration of lateral flow and microarray technologies for multiplex immunoassay: application to the determination of drugs of abuse. Microchimica Acta 180(11-12), 1165-1172.
Tian, T., An, Y., Wu, Y., Song, Y., Zhu, Z., Yang, C., 2017. Integrated distance-based origami paper analytical device for one-step visualized analysis. ACS applied materials & interfaces 9(36), 30480-30487.
Tokuda, T., Takahashi, M., Uejima, K., Masuda, K., Kawamura, T., Ohta, Y., Motoyama, M., Noda, T., Sasagawa, K., Okitsu, T., 2014. CMOS image sensor-based implantable glucose sensor using glucose-responsive fluorescent hydrogel. Biomedical optics express 5(11), 3859-3870.
Tran, T.L., Chu, T.X., Huynh, D.C., Pham, D.T., Luu, T.H.T., Mai, A.T., 2014. Effective immobilization of DNA for development of polypyrrole nanowires based biosensor. Applied Surface Science 314260-265.
Trung, T.Q., Lee, N.E., 2016. Flexible and Stretchable Physical Sensor Integrated Platforms for Wearable Human‐Activity Monitoringand Personal Healthcare. Advanced materials 28(22), 4338-4372.
Turner, A.P., 2013. Biosensors: sense and sensibility. Chemical Society Reviews 42(8), 3184-3196.
Ungerböck, B., Charwat, V., Ertl, P., Mayr, T., 2013. Microfluidic oxygen imaging using integrated optical sensor layers and a color camera. Lab on a Chip 13(8), 1593-1601.
Uzun, L., Turner, A.P.F., 2016. Molecularly-imprinted polymer sensors: realising their potential. Biosensors and Bioelectronics 76131-144.
Veli, M., Ozcan, A., 2018. Computational Sensing of Staphylococcus aureus on Contact Lenses Using 3D Imaging of Curved Surfaces and Machine Learning. ACS nano 12(3), 2554-2559.
Vella, S.J., Beattie, P., Cademartiri, R., Laromaine, A., Martinez, A.W., Phillips, S.T., Mirica, K.A., Whitesides, G.M., 2012. Measuring markers of liver function using a micropatterned paper device designed for blood from a fingerstick. Analytical chemistry 84(6), 2883-2891.
Verma, R., Gupta, B.D., 2013. Fiber optic SPR sensor for the detection of 3-pyridinecarboxamide (vitamin B3) using molecularly imprinted hydrogel. Sensors and Actuators B: Chemical 177279-285.
Wackerlig, J., Schirhagl, R., 2015. Applications of molecularly imprinted polymer nanoparticles and their advances toward industrial use: a review. Analytical chemistry 88(1), 250-261.
Walker, M., 2016. Healthcare in 2030: Goodbye hospital, hello home-spital.
Wang, B., Huang, F., Nguyen, T., Xu, Y., Lin, Q., 2013. Microcantilever-based label-free characterization of temperature-dependent biomolecular affinity binding. Sensors and Actuators B: Chemical 176653-659.
Wang, D., Hu, W., Xiong, Y., Xu, Y., Li, C.M., 2015. Multifunctionalized reduced graphene oxide-doped polypyrrole/pyrrolepropylic acid nanocomposite impedimetric immunosensor to ultra-sensitively detect small molecular aflatoxin B1. Biosensors and Bioelectronics 63185-189.

Wang, H.-N., Register, J.K., Fales, A.M., Gandra, N., Cho, E.H., Boico, A., Palmer, G.M., Klitzman, B., Vo-Dinh, T., 2018. Surface-enhanced Raman scattering nanosensors for in vivo detection of nucleic acid targets in a large animal model. Nano Research1-12.
Wang, J., Jiang, M., Fortes, A., Mukherjee, B., 1999. New label-free DNA recognition based on doping nucleic-acid probes within conducting polymer films. Analytica Chimica Acta 402(1), 7-12.
Wang, L., Hua, E., Liang, M., Ma, C., Liu, Z., Sheng, S., Liu, M., Xie, G., Feng, W., 2014a. Graphene sheets, polyaniline and AuNPs based DNA sensor for electrochemical determination of BCR/ABL fusion gene with functional hairpin probe. Biosensors and Bioelectronics 51201-207.
Wang, S., Chinnasamy, T., Lifson, M.A., Inci, F., Demirci, U., 2016a. Flexible substrate-based devices for point-of-care diagnostics. Trends in biotechnology 34(11), 909-921.
Wang, W., Cui, M., Song, Z., Luo, X., 2016b. An antifouling electrochemical immunosensor for carcinoembryonic antigen based on hyaluronic acid doped conducting polymer PEDOT. RSC Advances 6(91), 88411-88416.
Wang, X., Gu, Y., Xiong, Z., Cui, Z., Zhang, T., 2014b. Silk‐molded flexible, ultrasensitive, and highly stable electronic skin for monitoring human physiological signals. Advanced materials 26(9), 1336-1342.
Whitesides, G.M., 2006. The origins and the future of microfluidics. Nature 442(7101), 368.
Wicaksono, W.P., Putri, A.P., 2014. Electrochemical Immunochromatographic Strip Test for Melamine Biosensor in Milk Products Using Silver Nanoparticles as Probe. Applied Mechanics and Materials, pp. 1624-1628. Trans Tech Publ.
Windmiller, J.R., Wang, J., 2013. Wearable electrochemical sensors and biosensors: a review. Electroanalysis 25(1), 29-46.
Wolf, M.P., Salieb-Beugelaar, G.B., Hunziker, P., 2018. PDMS with designer functionalities–properties, modifications strategies, and applications. Progress in Polymer Science.
Wu, M.S., Liu, Z., Xu, J.J., Chen, H.Y., 2016. Highly specific electrochemiluminescence detection of cancer cells with a closed bipolar electrode. ChemElectroChem 3(3), 429-435.
Wulff, G., Sarhan, A., Zabrocki, K., 1973. Enzyme-analogue built polymers and their use for the resolution of racemates. Tetrahedron Letters 14(44), 4329-4332.
Xia, Y., Si, J., Li, Z., 2016. Fabrication techniques for microfluidic paper-based analytical devices and their applications for biological testing: A review. Biosensors and Bioelectronics 77774-789.
Xie, H., Luo, S.C., Yu, H.h., 2009. Electric‐Field‐Assisted Growth of Functionalized Poly (3, 4‐ethylenedioxythiophene) Nanowires for Label‐Free Protein Detection. Small 5(22), 2611-2617.
Xu, M., Obodo, D., Yadavalli, V.K., 2018a. The design, fabrication, and applications of flexible biosensing devices–a review. Biosensors and Bioelectronics.
Xu, S., Lu, H., 2015. Ratiometric fluorescence and mesoporous structure dual signal amplification for sensitive and selective detection of TNT based on MIP@ QD fluorescence sensors. Chemical Communications 51(15), 3200-3203.
Xu, S., Lu, H., 2016. Mesoporous structured MIPs@CDs fluorescence sensor for highly sensitive detection of TNT. Biosensors and Bioelectronics 85950-956.

Xu, S., Zhang, Y., Jia, L., Mathewson, K.E., Jang, K.-I., Kim, J., Fu, H., Huang, X., Chava, P., Wang, R., 2014. Soft microfluidic assemblies of sensors, circuits, and radios for the skin. Science 344(6179), 70-74.
Xu, X.-Y., Yan, B., 2018. A fluorescent wearable platform for sweat Cl− analysis and logic smart-device fabrication based on color adjustable lanthanide MOFs. Journal of Materials Chemistry C 6(7), 1863-1869.
Xu, X.-Y., Yan, B., Lian, X., 2018b. Wearable glove sensor for non-invasive organophosphorus pesticide detection based on a double-signal fluorescence strategy. Nanoscale 10(28), 13722-13729.
Yan, X., Li, H., Su, X., 2018. Review of optical sensors for pesticides. TrAC Trends in Analytical Chemistry 1031-20.
Yang, J., Liu, Y., Liu, S., Li, L., Zhang, C., Liu, T., 2017. Conducting polymer composites: material synthesis and applications in electrochemical capacitive energy storage. Materials Chemistry Frontiers 1(2), 251-268.
Yang, M., Jeong, S.W., Chang, S.J., Kim, K.H., Jang, M., Kim, C.H., Bae, N.H., Sim, G.S., Kang, T., Lee, S.J., 2016. Flexible and disposable sensing platforms based on newspaper. ACS applied materials & interfaces 8(51), 34978-34984.
Yang, X., Chen, Z., Elvin, C.S.M., Janice, L.H.Y., Ng, S.H., Teo, J.T., Wu, R., 2015a. Textile fiber optic microbend sensor used for heartbeat and respiration monitoring. IEEE Sens. J 15(2), 757-761.
Yang, Y., Cao, Y., Wang, X., Fang, G., Wang, S., 2015b. Prussian blue mediated amplification combined with signal enhancement of ordered mesoporous carbon for ultrasensitive and specific quantification of metolcarb by a three-dimensional molecularly imprinted electrochemical sensor. Biosensors and Bioelectronics 64247-254.
Yao, H., Shum, A.J., Cowan, M., Lähdesmäki, I., Parviz, B.A., 2011. A contact lens with embedded sensor for monitoring tear glucose level. Biosensors and Bioelectronics 26(7), 3290-3296.
Yao, J., Ji, P., Wang, B., Wang, H., Chen, S., 2018. Color-tunable luminescent macrofibers based on CdTe QDs-loaded bacterial cellulose nanofibers for pH and glucose sensing. Sensors and Actuators B: Chemical 254110-119.
Yaqoob, U., Phan, D.-T., Uddin, A.S.M.I., Chung, G.-S., 2015. Highly flexible room temperature NO2 sensor based on MWCNTs-WO3 nanoparticles hybrid on a PET substrate. Sensors and Actuators B: Chemical 221760-768.
Yeo, W.H., Kim, Y.S., Lee, J., Ameen, A., Shi, L., Li, M., Wang, S., Ma, R., Jin, S.H., Kang, Z., 2013. Multifunctional epidermal electronics printed directly onto the skin. Advanced Materials 25(20), 2773-2778.
Yetisen, A.K., Jiang, N., Fallahi, A., Montelongo, Y., Ruiz‐Esparza, G.U., Tamayol, A., Zhang, Y.S., Mahmood, I., Yang, S.A., Kim, K.S., 2017. Glucose‐Sensitive Hydrogel Optical Fibers Functionalized with Phenylboronic Acid. Advanced Materials 29(15), 1606380.
Yu, L., Shi, Z.Z., 2015. Microfluidic paper-based analytical devices fabricated by low-cost photolithography and embossing of Parafilm®. Lab on a Chip 15(7), 1642-1645.

Zamora-Gálvez, A., Ait-Lahcen, A., Mercante, L.A., Morales-Narváez, E., Amine, A., Merkoçi, A., 2016. Molecularly imprinted polymer-decorated magnetite nanoparticles for selective sulfonamide detection. Analytical chemistry 88(7), 3578-3584.
Zhan, L., Guo, S.-z., Song, F., Gong, Y., Xu, F., Boulware, D.R., McAlpine, M.C., Chan, W.C., Bischof, J.C., 2017. The role of nanoparticle design in determining analytical performance of lateral flow immunoassays. Nano letters 17(12), 7207-7212.
Zhang, K., Arman, A., Anwer, A.G., Hutchinson, M.R., Goldys, E.M., 2019. An optical fiber based immunosensor for localized detection of IL-1β in rat spinal cord. Sensors and Actuators B: Chemical 282122-129.
Zhang, K., Baratta, M.V., Liu, G., Frank, M.G., Leslie, N.R., Watkins, L.R., Maier, S.F., Hutchinson, M.R., Goldys, E.M., 2018. A novel platform for in vivo detection of cytokine release within discrete brain regions. Brain, Behavior, and Immunity 7118-22.
Zhang, Q., Prabhu, A., San, A., Al-Sharab, J.F., Levon, K., 2015. A polyaniline based ultrasensitive potentiometric immunosensor for cardiac troponin complex detection. Biosensors and Bioelectronics 72100-106.
Zhang, X., Peng, Y., Bai, J., Ning, B., Sun, S., Hong, X., Liu, Y., Liu, Y., Gao, Z., 2014. A novel electrochemical sensor based on electropolymerized molecularly imprinted polymer and gold nanomaterials amplification for estradiol detection. Sensors and Actuators B: Chemical 20069-75.
Zhang, Y., Liu, S., Wang, L., Luo, Y., Tian, J., Asiri, A.M., Al-Youbi, A.O., Sun, X., 2012. Novel use of poly (3, 4-ethylenedioxythiophene) nanoparticles for fluorescent nucleic acid detection. ACS combinatorial science 14(3), 191-196.
Zhao, D., Jia, J., Yu, X., Sun, X., 2011. Preparation and characterization of a molecularly imprinted polymer by grafting on silica supports: a selective sorbent for patulin toxin. Analytical and bioanalytical chemistry 401(7), 2259.
Zhao, S., Li, J., Cao, D., Zhang, G., Li, J., Li, K., Yang, Y., Wang, W., Jin, Y., Sun, R., 2017. Recent advancements in flexible and stretchable electrodes for electromechanical sensors: strategies, materials, and features. ACS applied materials & interfaces 9(14), 12147-12164.
Zhao, Y., Dai, S., Chu, Y., Wu, X., Huang, J., 2018a. A flexible ionic synaptic device and diode-based aqueous ion sensor utilizing asymmetric polyelectrolyte distribution. Chemical Communications 54(59), 8186-8189.
Zhao, Y., Liu, L., Luo, T., Hong, L., Peng, X., Austin, R.H., Qu, J., 2018b. A platinum-porphine/poly(perfluoroether) film oxygen tension sensor for noninvasive local monitoring of cellular oxygen metabolism using phosphorescence lifetime imaging. Sensors and Actuators B: Chemical 26988-95.
Zhong, C., Yang, B., Jiang, X., Li, J., 2018. Current Progress of Nanomaterials in Molecularly Imprinted Electrochemical Sensing. Critical reviews in analytical chemistry 48(1), 15-32.
Zhou, Y., Qu, Z.-b., Zeng, Y., Zhou, T., Shi, G., 2014. A novel composite of graphene quantum dots and molecularly imprinted polymer for fluorescent detection of paranitrophenol. Biosensors and Bioelectronics 52317-323.
Zhu, B., Wang, H., Leow, W.R., Cai, Y., Loh, X.J., Han, M.Y., Chen, X., 2016. Silk fibroin for flexible electronic devices. Advanced Materials 28(22), 4250-4265.

Zhu, X., Shah, P., Stoff, S., Liu, H., Li, C.-z., 2014. A paper electrode integrated lateral flow immunosensor for quantitative analysis of oxidative stress induced DNA damage. Analyst 139(11), 2850-2857.
Zhu, X., Zeng, Y., Zhang, Z., Yang, Y., Zhai, Y., Wang, H., Liu, L., Hu, J., Li, L., 2018. A new composite of graphene and molecularly imprinted polymer based on ionic liquids as functional monomer and cross-linker for electrochemical sensing 6-benzylaminopurine. Biosensors and Bioelectronics 10838-45.

**Cranfield University**

**CERES https://dspace.lib.cranfield.ac.uk**

School of Aerospace, Transport and Manufacturing (SATM) Staff publications (SATM)

2019-05-06

# Soft and flexible material-based affinity sensors

Meng, Lingyin

Elsevier

Meng L, Turner APF, Mak WC. (2019) Soft and flexible material-based affinity sensors.
Biotechnology Advances, Volume 39, March-April 2019, Article number 107398
https://doi.org/10.1016/j.biotechadv.2019.05.004
*Downloaded from Cranfield Library Services E-Repository*