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## Pen-on-paper strategies for point-of-care testing of human health

Zedong Li <sup>a, b</sup>, Hao Liu <sup>a, b</sup>, Xiacong He <sup>a, b</sup>, Feng Xu <sup>a, b</sup>, Fei Li <sup>a, b, \*</sup><sup>a</sup> The Key Laboratory of Biomedical Information Engineering of Ministry of Education, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an, 710049, PR China<sup>b</sup> Bioinspired Engineering and Biomechanics Center (BEBEC), Xi'an Jiaotong University, Xi'an, 710049, PR China

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## ABSTRACT

Nowadays, point-of-care testing (POCT) techniques have achieved flourishing development in human health monitoring, where paper-based POCT platforms have exhibited superior properties of low cost, easy accessibility and eco-friendliness. For fabrication of paper-based POCT platforms, the pen-on-paper (PoP) strategies through directly writing desired functional materials on paper have been creatively developed in recent years. The PoP strategies are characterized by simplicity, rapid prototyping and do-it-yourself capability, and are also likely to realize scalable manufacturing through integration with software-controlled plotter. In this review, we firstly introduce various kinds of papers and pens employed in the PoP strategies, and then summarize the state-of-art advances of PoP strategies for making paper-based POCT platforms. Subsequently, we discuss the representative applications of PoP strategies for human health monitoring. Conclusions, current challenges and future perspectives of the PoP strategies for human health related POCT uses are finally given.

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## 1. Introduction

Point-of-care testing (POCT) techniques, characterized by advantageous features including low cost, practicability and miniaturization, have been undergoing rapid development in recent years [1–3]. One of the most extensively investigated applications of POCT lies in human health monitoring, including evaluation of indexes associated with human health from human ambient environment (e.g., volatile organic compounds [4–6] and food contaminations [7–9]) and human body (e.g., human motion [10–12] and human diseases [13–17]). For these applications, the POCT platforms are preferable to meet the requirement of being ASSURED (i.e., affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free and deliverable to end-users) proposed by the World Health Organization (WHO) [18]. In addition, the design of POCT platforms is also dependent on surrounding environment, where rapid prototyping techniques are required for fabricating such on-demand platforms for in-situ use [19]. Recently, significant efforts have been devoted to developing various POCT platforms, among which paper-based platforms have been

demonstrated to be well suitable candidates owing to their evident advantages of ubiquity, flexibility, disposability and eco-friendliness [20–24]. More importantly, paper holds the capability of wicking fluids by capillary force, avoiding the need of external pumping which is often compulsorily required for other chip-based POCT paradigms. Hence, the paper-based platforms show superior application perspective in the POCT field.

In general, three key steps are involved in fabricating paper-based POCT platforms, i.e., (1) fabrication of paper testing substrates, (2) construction of sensing components on the substrate, and (3) deposition of reagents. The paper testing substrates mainly refer to the pretreated papers for functional modification (e.g., hydrophobic treatment). The sensing components, converting target information to more easily detectable signals, are subsequently patterned on the paper substrates. To achieve identification and analysis of specific targets during assays, the deposition of reagents is carried out. Till now, various methods have been developed to realize these three steps. For instance, photolithography [25] and computer-controlled knife cutting techniques [26] have been used for fabricating paper testing substrates. Laser etching [27] and screen printing [28,29] have been employed to deposit sensing components on paper. And inkjet printing technique [30–33] has found applications for the deposition of reagents. Even though these techniques have been well developed in lab, they are either time- or energy-consuming, which can't meet

\* Corresponding author. The Key Laboratory of Biomedical Information Engineering of Ministry of Education, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an, 710049, PR China.

E-mail address: [feili@mail.xjtu.edu.cn](mailto:feili@mail.xjtu.edu.cn) (F. Li).

the demand of being ASSURED and rapid prototyping for practical POCT applications. Thus, they are not ideal for fabricating paper-based POCT platforms.

Recently, pen-on-paper (PoP) strategies, which are based on directly writing functional materials on paper with various pens, have been introduced for fabricating paper-based POCT platforms [34]. For example, a commercial marker pen has been adopted to construct barrier-defined microfluidic channels on paper through directly writing hydrophobic ink [35]. Commercial pencils have been employed to write graphite-based conductive materials as electrodes of electrochemical sensing components on paper [36–38]. “Biopen” has also been designed and applied to the deposition of biomaterials (e.g., gold nanoparticles, cells) on paper to achieve detection of biomarkers (e.g., nucleic acid) [39]. Compared to the traditional methods for fabricating paper-based POCT platforms, the PoP strategies have remarkable advantages of simplicity, inexpensiveness, do-it-yourself (DIY) and rapid prototyping capabilities, thus holding a great application potential for practical uses, especially those in resource-limited areas.

In this review, we summarize the state-of-art development of PoP strategies in fabrication of POCT platforms (Fig. 1). Firstly, different kinds of papers with varying properties and pens (including regular pens and self-made pens) employed in the PoP strategies are introduced. Subsequently, the most recent advances of the PoP strategies employed to realize the three key steps of constructing POCT platforms are illustrated. After that, the representative POCT applications through using the PoP strategies in human health monitoring are introduced and discussed, including monitoring of human ambient environment and human body. Finally, conclusions, current challenges and future perspectives of the PoP strategies in the POCT of human health field are given.

## 2. PoP strategies for writing materials on paper

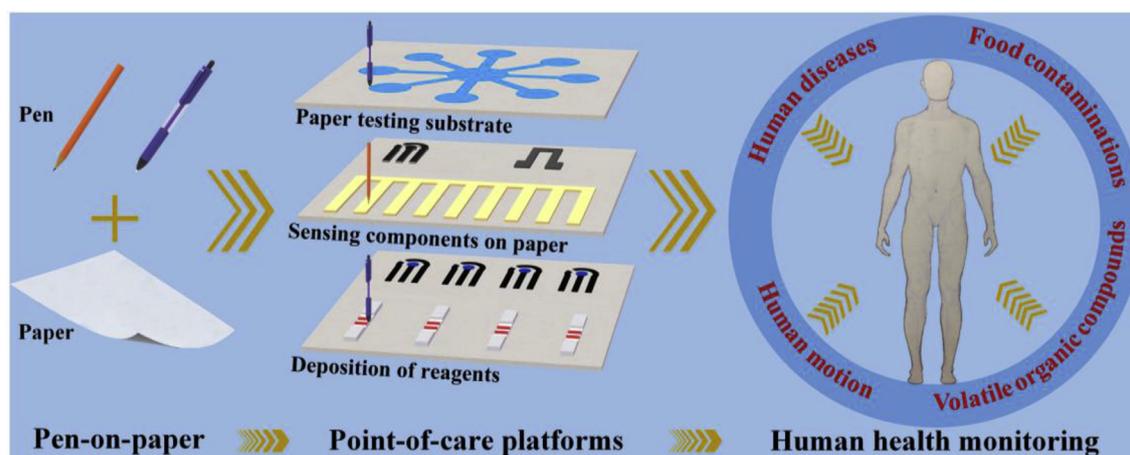
Papers and pens are the two key constituents in the PoP strategies. To meet the requirements of different application scenarios (e.g., for making paper electronics and paper microfluidics), papers with different properties are firstly selected. Pens, mainly classified by solvent-free pens (e.g., pencil) and solvent-based pens (e.g., ball pen), show different capabilities for engineering different functional components on papers. In this section, the types and properties of papers and pens used in the PoP strategies are introduced.

### 2.1. Papers

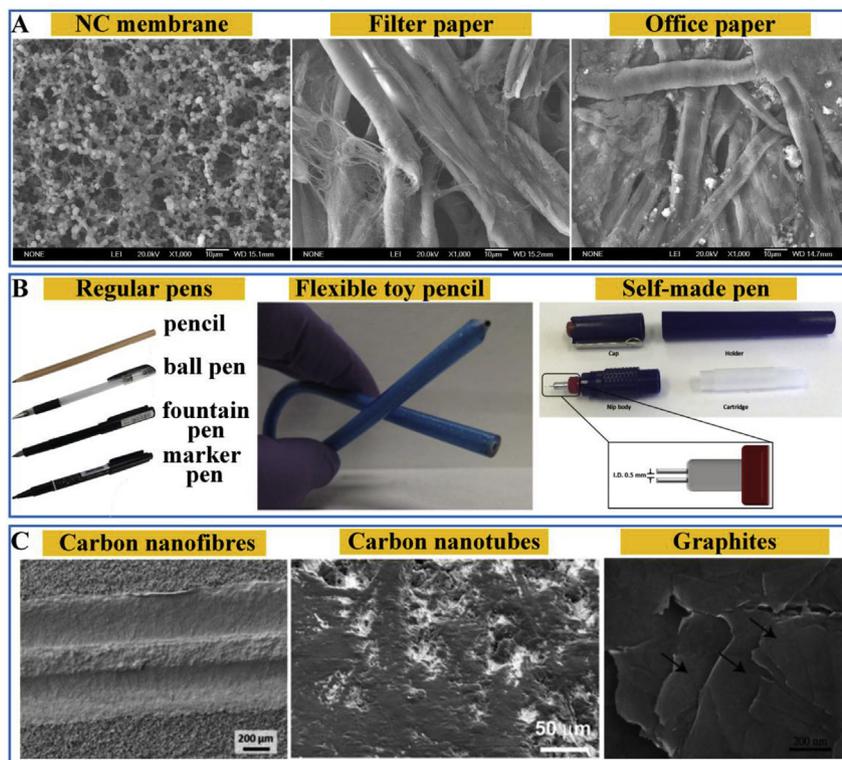
Due to the characteristics of ubiquity, accessibility, eco-friendliness, mechanical flexibility, hydrophilicity and dielectric property, papers have gained increasing interests as substrates of POCT platforms, which can be classified into paper microfluidics [40] and paper electronics [41]. At present, various types of papers have been used for fabricating POCT platforms, such as chromatography paper [42,43], filter paper [44], copy paper [45] and weighing paper [46,47]. And due to the variance in raw materials and production processes, papers with different physical (e.g., thickness, porosity) and chemical properties (e.g., pH, flammability) can be achieved. Among these features, the porosity of paper is a double-edged sword in constructing functional components on paper. For example, papers with high porosity (e.g., filter paper [44,48]) are appropriate for making paper microfluidics, since the highly porous structure eases fluids to flow inside paper under capillary forces [25,49–53]. While on the other hand, papers with low porosity (e.g., printing papers [45,54,55]) are suitable for making paper electronics, since the rough and porous surface could induce reduced electric conductivity of patterned electric traces [56–58]. Thus in some cases, such as making paper-based electrochemical devices, there exists a tradeoff between the fluidity of sample and the electric conductivity of patterned electrodes in terms of selecting papers with specific porous architectures. The structure and composition of three typical types of papers used in POCT, including nitrocellulose (NC) membrane, filter paper and A4 paper, are illustrated in Fig. 2A. As shown in the figure, the NC membrane presents relatively high porosity and uniform pore distribution. The filter paper with high porosity exhibits disordered fiber distribution. While the office paper with low porosity has many impurities distributed around the fibers. So the NC membrane and filter paper are frequently adopted as substrates for lateral flow test strips [59] and microfluidic paper-based devices ( $\mu$ PADs) [60], respectively. While the office paper is usually utilized for deposition of electrodes [61].

### 2.2. Pens

The universal and easily accessible pens have been widely utilized to write functional materials on papers thanks to their superb compatibility with paper [62]. As shown in Fig. 2B, various pens



**Fig. 1. Schematic landscape of the PoP strategies for human health monitoring at point-of-care.** The pen combined with paper has been developed to form the PoP strategies, which includes three steps for fabricating paper-based POCT platforms, i.e., fabrication of paper testing substrate, construction of sensing components on paper, and deposition of reagents. The paper-based POCT platforms fabricated by the PoP strategies are used for human health monitoring, including detecting volatile organic compounds and food contaminations, monitoring human motion and human diseases. Images of pens are reproduced from [62].



**Fig. 2. Pen writing on paper.** (A) SEM images of NC membrane, filter paper and office paper. (B) Optical images of regular pens, a flexible toy pencil and a disassembled self-devised pen. (C) SEM images of various materials deposited on paper through pen writing, i.e., carbon nanofibres deposited on photo paper through fountain pen writing, single-walled carbon nanotubes deposited on weighing paper through pencil writing, graphitic materials deposited on Xerox paper through pristine graphite rod writing. Images are reproduced from [46,54,64,77,79].

including regular pens, a flexible toy pencil and a self-made pen have been involved in the PoP strategies.

Pens that have been utilized in the PoP strategies can be classified into two major categories, i.e., solvent-free pens (e.g., pencil) and solvent-based pens (e.g., ball pen, fountain pen). Pencils, as a representative of the solvent-free tactic, have been used to directly write conductive graphite-based materials on paper, since pencils are made of graphite and additives (e.g., clay/polymer binders) [54]. Different grades of pencils from 9H (hardness) to 9B (blackness) have different graphite contents ranging from 40% to 90% [63]. Higher graphite content in pencils results in higher electric conductivity of written traces. Benefiting from this fact, pure graphite rods have been employed to write graphite traces on paper with improved electric conductivity compared to those from commercial pencil writing [64,65]. However, regular pencils and graphite rods can only be used to write graphite-based materials, limiting their universal applications. To address this, self-made pencils with capability to write diverse materials (e.g., carbon nanotubes (CNTs) [46,47,66], Ag/AgCl [42] and formulated mixtures [43]) have been developed. These complementary pencils endow users with the capability to write more kinds of functional materials on paper in a solvent-free manner, which can also eliminate time-consuming post treatment procedures such as drying. In addition, wax pencil or crayon with the similar structure to regular pencils have also been used to deposit wax on paper through abrasion [38,48], which can be used to construct hydrophobic barrier in paper microfluidics. But this strategy needs a post heating treatment step to melt the deposited solid-phase wax for its penetration into paper.

Ball pen with an ink reservoir, as a typical solvent-processed pen, can transfer ink onto substrate through ball rotation during writing [39]. For writing desired materials on paper using a ball pen, a primary step of developing functional inks is necessarily

needed. Recently, various new formulated inks, including silver-based inks [67,68], copper-based inks [69–71], enzymatic ink [19] and liquid metal inks [72,73], have been developed for ball pen writing, which make it popular in fabrication of diverse functional components on paper. Since the ball pen-writing process involves the potential issue of clogging and leakage, it is noteworthy that the fluid properties of inks (e.g., concentration and viscosity) dramatically affect the writing process of ball pen. For instance, silver-based ink can only be smoothly transferred from ball pen onto paper with a concentration range of 45–55 wt% and a viscosity range of 1–10 Pa s [74]. Similar to ball pen, fountain pen, also resorting to an ink reservoir to store ink with suitable fluid properties, has been employed to write on substrate through synergistic action of gravity and capillarity. And to meet different application demands, a variety of inks have been developed for fountain pens, such as FeCl<sub>3</sub> ink [75], Ag and Au nanoparticle inks [76], carbon nanofiber ink [77] and CNTs ink [45]. However, due to their rigid pen tips, the ball pen and fountain pen-based writing scenarios may not be applicable to rigid substrates. Fortunately, another type of solvent-based pen, commercial marker pen with soft fibrous pen tip connected to the ink reservoir is compatible with both soft and rigid surfaces [35,78]. The ink in the marker pen is usually constituted by water-resistant materials (e.g., hydrophobic resin). Thus the marker pen can be directly used to construct hydrophobic patterns on paper [35]. As the hydrophobic resin remains inside paper after ink evaporation at room temperature, the marker pen-based PoP strategy holds the advantage of avoiding any post treatment step.

Besides the above mentioned commercially available pens, self-made pens loaded with suitable functional ink materials have also been developed, targeting at various using purposes [44,79]. For example, a self-made pen composed of four parts (i.e., a chrome-

plated tip, a polyethylene cartridge, a cap and a holder) was designed for depositing water-resistant materials on paper (Fig. 2B) [79]. A custom-made pen filled with a formulated polydimethylsiloxane (PDMS) ink was developed for building PDMS barriers on paper [44]. These self-made pens are compatible with inks of high viscosity because of their customized pen tips, thus expanding the selection range of ink materials. Furthermore, these self-devised pens can also be integrated with a computer-controlled plotter, which acts as a three-dimensional positioner to realize automatic production, further paving the way for promoting PoP strategies into scalable batch manufacturing [44,79,80].

### 2.3. Pen writing on paper

As introduced above, pens have shown great compatibility with paper substrate to write a wide range of functional materials, such as carbon nanofibers, CNTs and graphites (Fig. 2C). Among various PoP strategies, the solvent-free pencils, including regular pencils and self-made pencils, are mainly used to deposit carbon-based materials (e.g., graphite and CNTs) on paper through abrasion between paper and pencil leads [38,54,81]. Benefiting from such a solid phase processing, there is no need of any post treatment after writing. Because the pencil writing process depends on the mechanical abrasion of pencil leads, it is challenging to precisely control the amount of written materials. Similar issue also exists for the wax pencil writing during depositing wax pattern on paper. Besides, an additional heating treatment after wax pencil writing is needed to melt the solid wax on paper surface and to further enable the wax to permeate into the interior matrix of paper, which complicates the fabrication process [38,48]. On the other hand, the marker pens loaded with permanent ink can simplify the fabrication process through directly depositing hydrophobic materials into paper in a one-step manner [35]. In addition, the solvent-processed pens, such as ball pens and fountain pens, can write uniform lines and patterns through directly depositing inks on paper, owing to the fact that their pen nibs remain intact in structure during writing [45,55,77]. However, as illustrated in Fig. 2C, the meniscus phenomenon occurring during fountain pen writing due to the structure of pen nib may induce uneven surface morphology of written traces. Furthermore, some self-made pens have also been designed to write diverse functional materials on papers, which extend the PoP versatility for fabricating POCT platforms [44].

## 3. PoP strategies for making paper-based POCT platforms

In this section, the PoP strategies used in the three key steps of fabricating paper-based POCT platforms, i.e., fabrication of paper testing substrates, construction of sensing components on the substrates and deposition of reagents, are introduced. The detailed information including the types of pens, writing materials and papers, functions, post treatment step, category and POCT applications is summarized in Table 1.

### 3.1. PoP strategies for fabricating paper testing substrates

Construction of paper-based POCT platforms starts with the fabrication of paper testing substrates, in which building microfluidic channels on paper through patterning hydrophilic/hydrophobic regions to guide fluid flow is an essential process [82]. Several methods have been proposed to construct microfluidic channels on paper, including photolithography [25], inkjet etching [33], plasma treatment [83], cutting [26], contact-printing [51] and wax printing [50,52,84]. However, there are several limitations associated with these methods, such as the engagement of expensive equipment, harmful chemicals and sophisticated

fabrication processes, thus hindering their practicability in fabricating substrates for POCT applications, especially those aiming at the resource-limited regions.

To circumvent these limitations, the PoP strategies have been recently proposed for building microfluidic channels on paper through directly writing hydrophobic materials. The PoP strategies hold the advantages of minimized cost, simplified process, improved portability and rapid prototyping process over the above-mentioned traditional methods [44,48,78,79]. As for the selection of hydrophobic materials, various candidates have been employed to produce water-repellent barriers into paper using the PoP strategies. For instance, wax has been successfully deposited on paper via a commercially available wax pencil to form the microfluidic channels [48]. Two steps are involved in this fabrication process: (1) writing desired wax patterns on both sides of a paper by hand with wax pencil, (2) forming hydrophobic barriers by heating the paper (e.g., in an oven) to melt the wax and facilitate wax penetration into the paper matrix. The whole fabrication process is simple and cost-effective with utilization of ubiquitous and cheap tools (e.g., wax pencil, ruler and heating equipment). Apart from wax, other hydrophobic polymers have also been introduced into the PoP strategies. For example, a pen filled with the mixture of PDMS solution and hexanes was used to build PDMS pattern on paper, where the solid PDMS barrier was formed along the overall thickness direction of paper after curing at 70°C (Fig. 3A) [44]. Since the cured PDMS is elastomeric, the fabricated PDMS/paper hybrid substrate can be folded into three-dimensional structure without damaging the microfluidic channels. Additionally, this self-made pen has realized direct writing of cross-linked PDMS on paper, which cannot be fulfilled by the regular pens because of the high viscosity of PDMS. More recently, commercial marker pens composed of colorant, solvent and resin have also been utilized to write the hydrophobic resin on paper to form hydrophobic barriers after natural evaporation of solvent (Fig. 3B) [35,78,79]. This method can realize one-step fabrication of paper testing substrate without the need for heating process, and demonstrates the compatibility with both rigid (e.g., silica [78]) and soft (e.g., paper [35]) surfaces benefiting from the soft manner of fibrous pen tip, thus holding great potential for widespread POCT applications. These above-introduced pens are mainly dependent on hand-writing process, which are easy to operate but suffer from poor repeatability and slow prototyping. A self-made pen loaded with either commercial permanent ink or special custom-made ink was then developed to make microfluidic channels on paper [79]. Moreover, such self-devised pens can be further integrated with a software-controlled plotter to realize automatic and mass production of paper microfluidic substrates (Fig. 3C), which is beneficial to improve manufacturing speed and repeatability from batch to batch [79].

### 3.2. PoP strategies for constructing sensing components on paper

The sensing components functioning as collection and conversion of detection signals are pivotal units of the paper-based POCT platforms. Utilizing the PoP strategies in construction of sensing components on paper can minimize manufacturing cost, simplify fabrication process, improve portability, promote rapid prototyping ability and facilitate the process of DIY fabrication. Therefore, the PoP strategies have ignited many research interests for manufacturing a variety of functional components for piezoresistive sensing [85], chemiresistive sensing [66] and electrochemical sensing [42] in recent years.

#### 3.2.1. PoP strategies for making piezoresistive sensors

Piezoresistive sensors are widely used in many fields, such as pressure sensing [86] and disease detection [87]. The working

**Table 1**  
Summary of the PoP strategies for making paper-based POCT platforms.

Pen type	Materials	Paper type	Functions/Objectives	Post-treatment	Category	POCT applications	Refs.
Regular pencils (HB, 2B, 6B, 9B)	Graphite	Whatman chromatography paper #1, office paper	Acting as electrodes of electrochemiluminescence device or strain sensing elements	None	Paper electronics	Human motion monitoring	[38,54,81]
Flexible toy pencil	Graphite/polymer composites	Office paper	Acting as sensing elements of chemiresistors	None	Paper electronics	VOCs monitoring	[54]
Custom-made pencils	Carbon nanotubes	Copy paper, weighing paper	Acting as sensing elements for chemiresistive gas sensors	None	Paper electronics	VOCs monitoring	[46,47,66]
Doped pencils	Horseradish peroxidase, glucose oxidase	Whatman chromatography paper #1	deposition of enzymes on paper	None	Paper microfluidics	Human diseases monitoring	[99]
	Graphite powder doped with either redox compounds or Ag and AgCl	Whatman chromatography paper #1	Acting as modified electrodes or reference electrodes for paper-based electrochemical detectors	None	Paper electronics	–	[42,43]
Ball pens	Silver/carbon ink	A4 paper	To write electrodes for paper-based electrochemical detectors	Heating in an oven at 70°C, 30 min for carbon ink and 120°C, 30 min for silver ink	Paper electronics	Food contaminations monitoring	[55]
	Capture and control probe solution, Au nanoparticle probe solution	Nitrocellulose membrane and conjugate pad of a lateral flow test strip	To make test and control lines on the nitrocellulose membrane and deposit gold nanoparticle probe on the conjugate pad	Heating in an oven at 37°C for 2 h	–	Human diseases monitoring	[39]
Fountain pens	Carbon nanotubes	Copier paper	Acting as sensing elements for chemical sensor	None	Paper electronics	VOCs monitoring	[45]
	Saturated FeCl <sub>3</sub> solution	A4 paper	To pattern oxidizing agent on paper	None	Paper electronics	VOCs monitoring	[75]
	Plasmonic nanoparticles	A4 paper	Surface enhanced Raman scattering sensor	None	Paper electronics	Food contaminations monitoring	[76]
Crayon	Solid wax	Whatman chromatography paper #1	To form the hydrophobic wax into paper	Baking in an oven at 130°C for 150 s	Paper microfluidics	Human diseases monitoring	[38]
Wax pencil	Solid wax	Filter paper	To form the hydrophobic wax into paper	Heating in an oven at 150°C for 5 min	Paper microfluidics	Human diseases monitoring	[48]
Marker pen	Commercial permanent ink containing hydrophobic resin	Chromatography paper	To form the hydrophobic resins into paper	None	Paper microfluidics	Human diseases monitoring	[35]
Self-devised pen	PDMS	Whatman filter paper	To create the hydrophobic PDMS into the paper	Curing at 70°C after 1 h	Paper microfluidics	Human diseases monitoring	[44]
	Formulated inks	Whatman qualitative filter paper grade 1	To form the hydrophobic barriers into paper	None	Paper microfluidics	Food contaminations monitoring	[79]

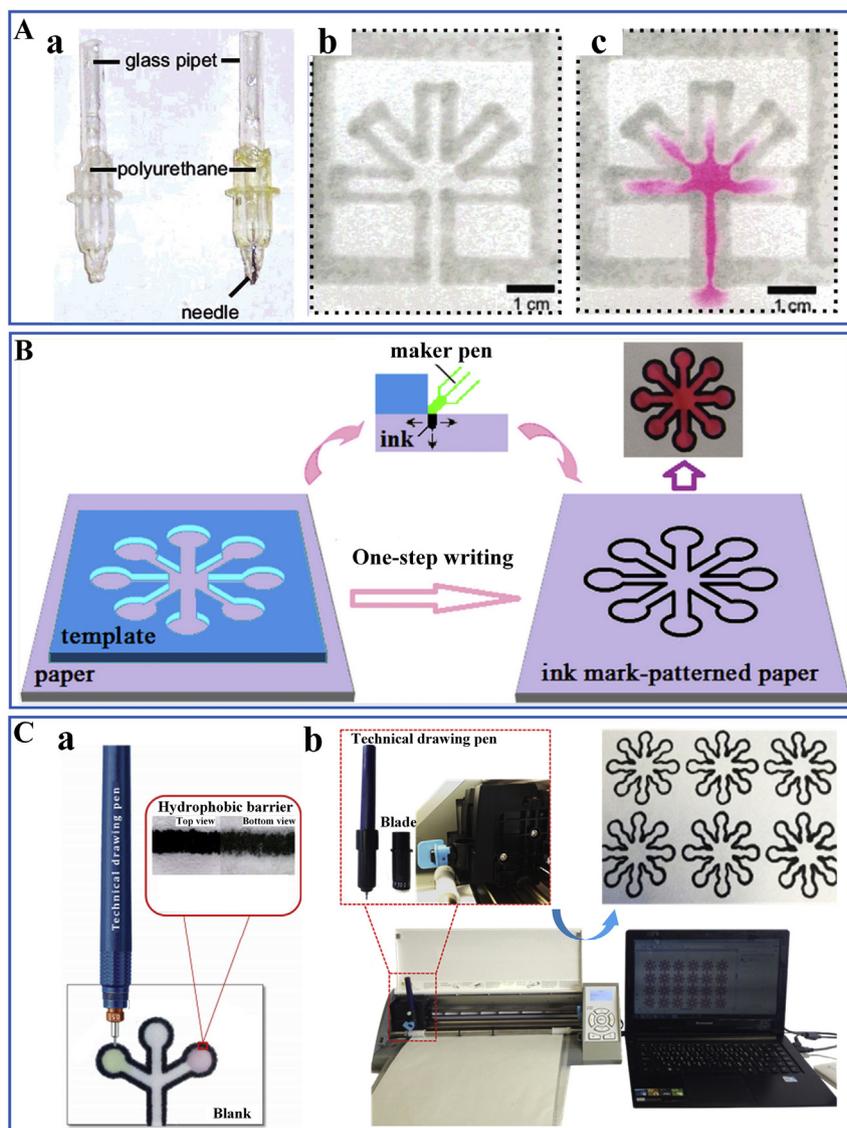
principle of piezoresistive sensors is dependent on the resistance change induced by the mechanical tensile/compressive strain applied on the sensors, which is usually due to substrate deformation (i.e., tension or compression). Specifically, stretching the substrate deposited with conductive sensing components can increase the resistance because the gap between coated conductive particles is widened, and compressing the substrate can decrease the resistance conversely. In general, piezoresistive sensors are formed by a cantilever beam deposited with conductive materials as the sensing elements. Silicon is a traditional substrate of piezoresistive sensors, but its rigid format makes it not appropriate for flexible applications, such as wearable devices. To address this, paper as a promising flexible substrate has been alternatively used to construct piezoresistive sensors for flexible applications.

Recently, the PoP strategies have been introduced for the fabrication of paper-based piezoresistive sensors. A typical example is pencil-writing compact and conductive graphite particles on paper as pressure sensing elements [88]. So far, commercially available pencils with a variety of hardness and blackness grades, such as 9H, 6H, 2H, HB, 2B, 6B and 9B, have experienced uses in depositing graphite traces on paper for realizing piezoresistive sensors (Fig. 4) [54,85,89]. Based on the tunneling effect between the adjacent graphite particles in traces varying with graphite/

additives ratios, the sensors written by various grades of pencils show tunable piezoresistive properties. It has been demonstrated that the piezoresistive sensors written by harder pencils (with lower graphite/additives ratio) present better sensitivity to strain loading [85]. This fact could be due to that the volume fraction of graphite particles in written traces by harder pencils is closer to the conductive percolation threshold, which is a critical impact factor affecting the electric conductivity of particle-based conductive composites [54,85]. In short, the pencils used for making piezoresistive sensors on paper are very cost-effective and can be accessible at local stores, which is crucial to expand the application of the piezoresistive sensors written by pencils. However, due to their complex components and unknown ratio, pencil leads made by different manufacturers may show inferior repeatability when used to fabricate piezoresistive sensors.

### 3.2.2. PoP strategies for making chemiresistive sensors

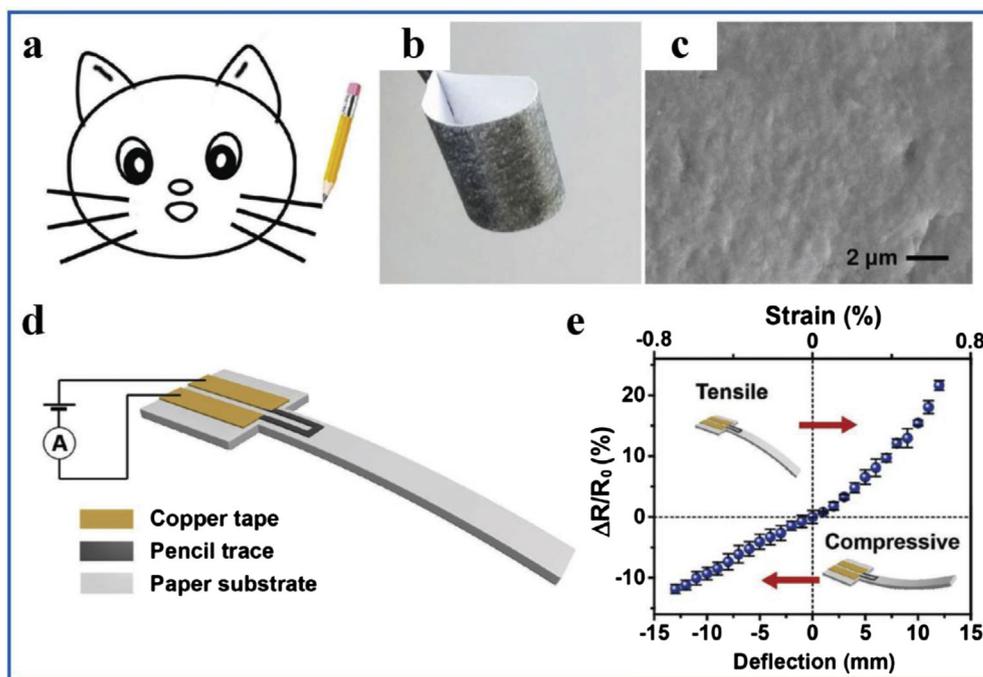
Chemiresistive sensors are designed to detect chemicals in surrounding environment. Their working principle relies on the change of electric conductivity (reflected by resistance or current) in response to chemical reaction with target analytes. The chemiresistive sensors are composed of two main components, i.e., the conductive elements and the sensing elements. Owing to the



**Fig. 3.** Pen-on-paper strategies for making paper testing substrates. (A) A self-devised writing pen filled with PDMS for making paper microfluidic devices: (a) optical image of the devised pen, (b) a microfluidic system in filter paper, in which hydrophilic channels bounded by hydrophobic PDMS barriers, (c) a sample of red ink that wicks along the channels. (B) Schematic of one-step writing strategy for making paper-based microfluidic devices using a marker pen. (C) A self-devised writing pen for making paper microfluidic devices: (a) writing hydrophobic barriers on paper using the developed pen, (b) the developed pen was integrated on a desktop software-controlled plotter for mass production of paper microfluidics. Images are reproduced from [35,44,79].

capability of writing both conductive and sensing materials on paper in a simple and cost-effective manner, the PoP strategies have been utilized to produce chemiresistive sensors on paper in a fully written way. For instance, an HB pencil and a flexible toy pencil were respectively employed to write conductive graphite and polymer sensing materials on paper to form a paper-based chemiresistive sensor for detection of volatile organic compounds (VOCs) (Fig. 5) [54]. As demonstrated in the figure, this sensor consisted of two layers of pencil-written traces: the first layer composed of graphite particles and polyvinyl chloride (PVC)-based binders (acting as the sensing element) was written by a flexible toy pencil; the second layer composed of graphite (acting as the conductive electrodes) was written by an HB pencil. Upon exposure to VOCs, the polymer binders in pencil traces swelled, widening the gap between graphite particles and thus leading to an increased resistance of the sensor. However, due to that the flexible toy pencil is not accessible at all cases, the sensors written by this type of pencil are hard to be applied widely.

Besides the application in fabricating the resistance change-based chemiresistive sensors, the PoP strategies have also been employed to fabricate the paper-based chemiresistive sensors that are based on electric current change through applying a constant voltage on the sensor during testing [46]. Considering that CNTs are desirable materials for chemical sensing owing to their high sensitivity to chemical analytes (e.g.,  $\text{NH}_3$  [90,91]), CNTs acting as the sensing materials have been utilized in making chemiresistive sensors with the PoP strategies. For instance, Swager's group devised a home-made pencil to write CNTs (as the sensing element) between gold electrodes (as the conductive element) to form paper-based chemiresistive sensors [46,47,66]. The pencil was manufactured by adding the mixture containing CNTs into a die (i.e., a special mold) and extruding the mixture through adding a constant pressure ( $\sim 0.4$  GPa) [46]. For realizing fully-written CNTs-based chemiresistive sensors on paper, both conductive elements and sensing elements were written on paper by using different pencils [47,66]. Furthermore, this strategy makes it possible to



**Fig. 4.** Pen-on-paper strategies for making paper-based piezoresistive sensor. A bioinspired paper-based piezoresistive sensor made by pencil writing: (a) sketch map of cat's whiskers, (b) optical image of pencil trace on paper, (c) SEM image of the pencil trace on paper, (d) schematic structure of the piezoresistive sensor, (e) normalized resistance change as a function of substrate deflection. Images are reproduced from [81].

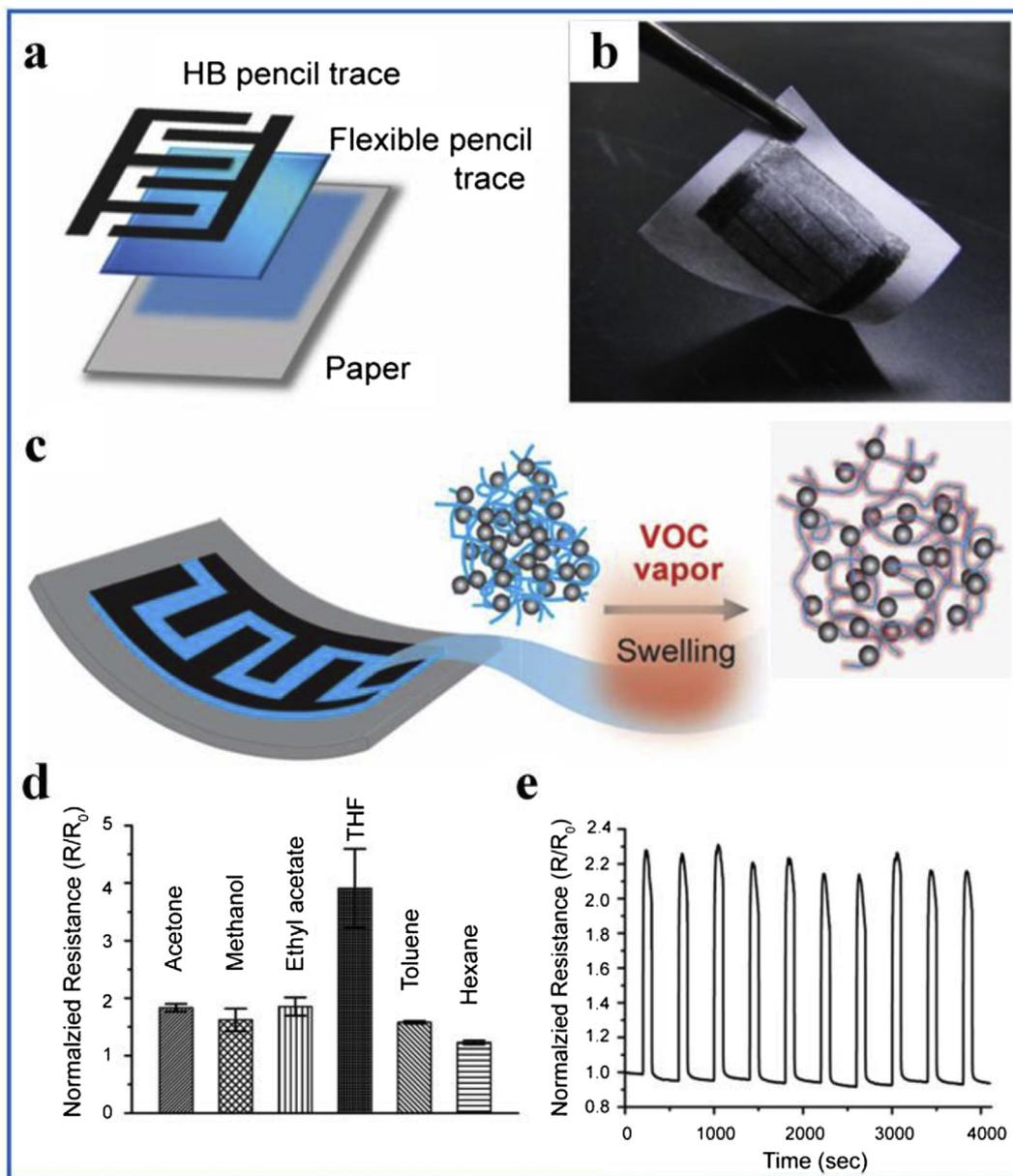
fabricate CNTs-based sensors in a solvent-free manner, which avoids the slight solubility of CNTs in most solutions. But on the other hand, this strategy is not compatible with the substrates with smooth surface, which may fail to supply sufficient friction to peel off conductive materials from pencil leads.

### 3.2.3. PoP strategies for making electrochemical sensors

Electrochemical sensors, typically consisting of a two- or three-electrode system, are mainly used to detect targets through redox reactions on electrode surfaces. Integration of electrodes on paper to form the paper-based electrochemical sensors has been employed to realize POCT in a quantitative and sensitive manner [22]. Conventional methods involved in the fabrication of electrodes on paper mainly include sputtering [92], sintering [93], screen printing [94] and inkjet printing [95], which are subjected to the disability in rapid prototyping and DIY. To address this, the PoP strategies have been introduced to establish electrodes on paper through writing with pencils and ball pens. For instance, Dossi et al. used diverse grades of commercial pencils (HB, B, 2B, 3B, 4B, 6B and 8B) to write electrodes on paper, and proved that the electrodes written by 3B pencils presented optimum electrochemical performance, which is probably due to the favorable proportion of graphite and additives (clay and polymers) [36,37]. Although this method is simple and rapid to manufacture electrodes, the written electrodes may suffer from relatively low electron transfer capability due to the limited content of graphite in commercial pencil leads. Also, there may exist a disturbance for electrochemical response to analytes because of impurities. To address this, self-made pencils have also been developed to fabricate both modified electrodes and Ag/AgCl reference electrodes on paper (Fig. 6A). Herein, pencils were made by doping the mixtures of graphite powder and binders (e.g., sodium bentonite and sodium silicate) with electrode modifiers (e.g., decamethylferrocene or cobalt (II) phthalocyanine), or by mixing the Ag/AgCl-electrodeposited graphite powder with binders [42,43]. But

in this approach, the modification of working electrode was obtained during pencil fabrication and the modifiers were physically bonded with graphite particles, which may not be stable for long-term testing. Besides pencils, the ball pen-based PoP strategies have also been applied to fabrication of paper-based electrochemical sensors. For instance, Bandothkar et al. created a ball pen loaded with an enzymatic ink composed of graphite powder and enzyme, and used it to directly write enzyme-modified working electrodes of electrochemical sensors [19]. This PoP strategy shows the merit of eliminating additional sensor modification steps and endowing the user sufficient freedom to make DIY sensors. However, to prevent clogging and leakage during writing, the pretreatment step to adjust the concentration and viscosity of the ink is needed as the ball pen writing is solvent processing. To simplify the fabrication process, our group developed a pressure-assisted ball pen to directly write carbon working electrode and silver reference electrode on paper without the ink pretreatment step (e.g., dilution) [55], which can enhance the versatility of the ball pen-based PoP strategy for making electrochemical sensors on paper (Fig. 6B).

In short, the application of PoP strategies in manufacturing piezoresistive sensors, chemiresistive sensors and electrochemical sensors has been demonstrated. Moreover, PoP strategies have also been applied in making paper-based surface enhanced Raman scattering (SERS) sensors, due to their ultrahigh sensitivity for detection. As an example, Polavarapu et al. employed a fountain pen filled with metallic nanoparticles to directly write SERS arrays on A4 paper and acquired expected SERS activity and efficiency [76]. Further, a pen-written SERS sensor combined with a portable Raman spectrometer was proposed to improve its practicality for field use [96]. Hence, the PoP strategies, circumventing the limitations of time consumption or equipment dependence involved in conventional methods for paper-based SERS sensors fabrication, are expected to transform SERS technologies toward real life applications.

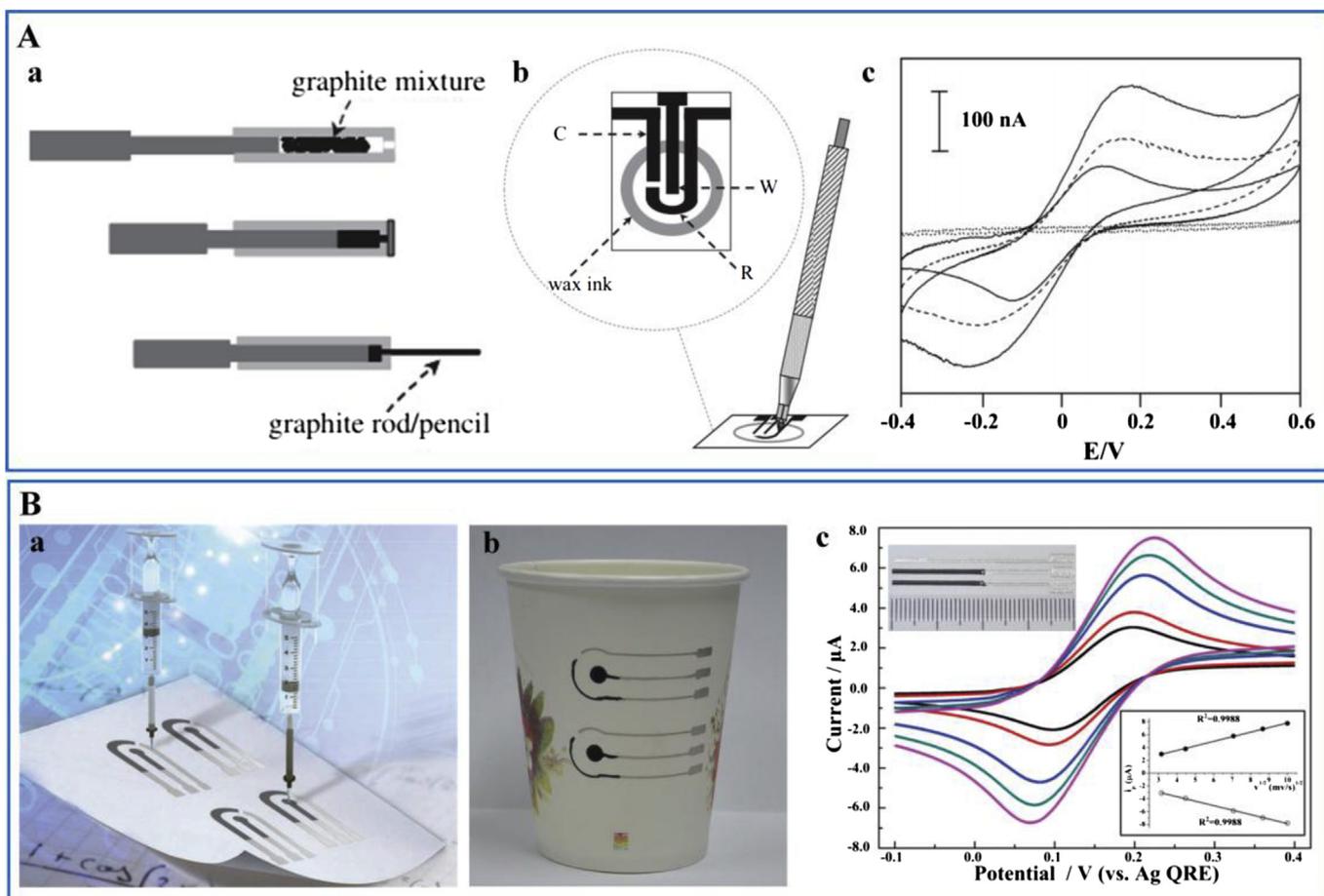


**Fig. 5.** Pen-on-paper strategies for making paper-based chemiresistive sensor. A bilayer chemiresistor written by an HB pencil and a flexible toy pencil: (a) schematic structure of the chemiresistor, (b) photograph of the pencil-written chemiresistor, (c) schematic diagram illustrating the mechanism of the chemiresistor responding to VOCs, (d) normalized resistance changes of the chemiresistor upon exposure to different VOCs, (e) real-time normalized resistance changes of the sensor upon repeated cycles, showing good reversibility. Images are reproduced from [54].

### 3.3. PoP strategies for deposition of reagents

Deposition of reagents onto the POCT platforms can enhance their specific identification capability to targets, therefore playing an important role in the POCT platform construction. Traditional methods for deposition of reagents are mainly achieved through coating [97], electrochemical deposition [98] or inkjet printing [31,33], which are subjected to either non-flexibility for desired pattern or high cost. Alternatively, the PoP strategies have shown the feasibility of depositing reagents in a simple, rapid and cost-effective way. For instance, a ball pen filled with the ink mixture of glucose oxidase, graphite powder and additives (including polyethylene glycol, chitosan, xylitol, methylene green) has been employed to deposit enzyme on the working electrode surface of electrochemical glucose sensor (Fig. 7A) [19]. The enzyme-modified electrodes were achieved by directly writing the enzymatic ink onto the fresh carbon

working electrode of the sensor. This process is simple and rapid, but exhibits low repeatability in modification of different sensors. Generally, the deposition of enzymes on paper is mainly carried out in a solvent-processed manner through dissolution and ready for use after drying. However, the unexpected denaturation of enzymes occurs during drying process. To address this limitation, a customized pencil was created to deposit enzymes onto paper in a solvent-free manner (Fig. 7B) [99]. Firstly, a certain amount of enzymes (horseradish peroxidase and glucose oxidase) mixed with polyethylene glycol (PEG) and graphite were pressed into the shape of a pencil lead. And then, the pencil lead integrated with a holder was applied to deposition of enzymes on paper surface through direct writing. Finally, the written enzymes dissolved and reacted with targeted analytes after the introduction of aqueous sample containing analytes. This PoP strategy has been demonstrated to improve the enzyme stability during its storage on paper in



**Fig. 6.** Pen-on-paper strategies for making paper-based electrochemical sensors. (A) A self-devised pencil for directly writing paper electrochemical sensors: (a) schematic illustration of the fabrication process of the pencil leads, (b) the pencil leads were inserted in a commercial holder to write the sensor, (c) cyclic voltammograms recorded to reflect the electrochemical performance of the sensor. (B) A pressure-assisted ball pen to write electrochemical sensors on paper: (a) schematic of the written electrodes on paper using the pen refilled with carbon ink and silver ink, (b) photograph of a fabricated electrochemical sensor on a paper cup to depict the versatility of the strategy, (c) cyclic voltammograms showing good electrochemical performance of the sensor. Images are reproduced from [36,42,43,55].

comparison with traditional solution-based deposition methods. Furthermore, this reagent pencil is applicable to the deposition of different kinds of reagents on paper, such as glucose and Erioglau-line, by using various PEGs with different molecular weights [100]. In addition, our group has developed a “Biopen” loaded with functional inks to modify a lateral flow test strip for detecting human immunodeficiency virus type 1 (HIV-1) nucleic acid [39]. The “Biopen” integrated three ink reservoirs which were filled with solutions of capture probe, control probe and gold nanoparticle probe, respectively. Correspondingly, the capture and control probes, acting as the test line and the control line, were easily written on the NC membrane of the test strip, while the gold nanoparticle probe was written on the conjugate pad of the test strip. This method shows great potential for deposition of testing probes during preparation of lateral flow test strips benefiting from its requirement for relatively low amount of reagents. On the other hand, although the PoP strategies for deposition of reagents in preparing POCT platforms have shown many attractive features (e.g., low cost, simplicity and portability), some challenges still exist, such as deficiency in precise control of the amount of reagents.

#### 4. PoP strategies for human health applications

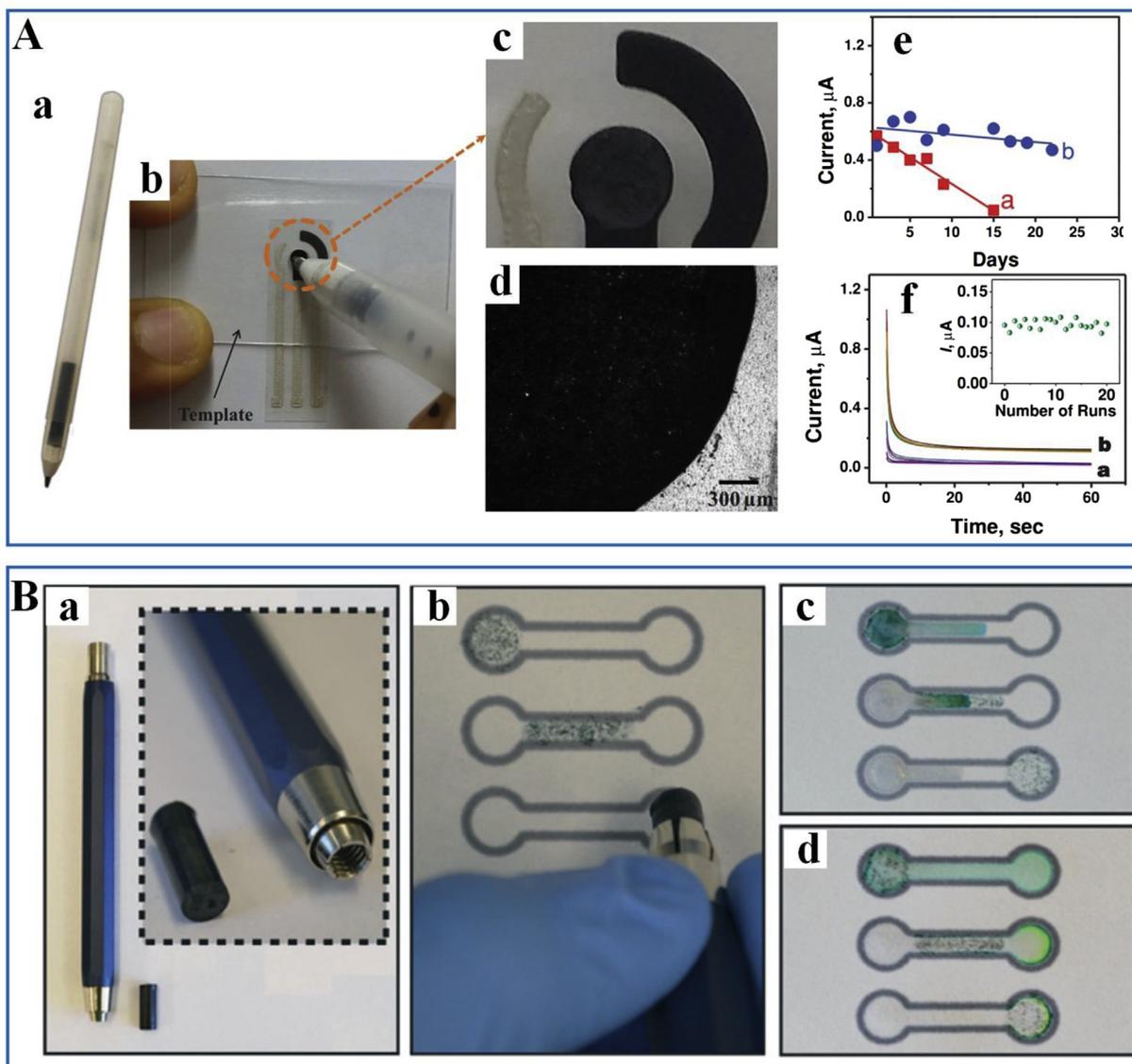
Human health refers to a safe ambient environment that human beings live in and a healthy human body. For monitoring and evaluation of human health status, POCT techniques possessing

reliable, affordable and accessible characteristics are preferred. By now, the PoP strategies as emerging POCT techniques have been widely applied in human health testing due to their unparalleled inexpensiveness and easy accessibility. In this section, we summarize the applications of the PoP strategies in the human health-oriented POCT field.

##### 4.1. Human ambient environment monitoring

###### 4.1.1. Volatile organic compounds monitoring

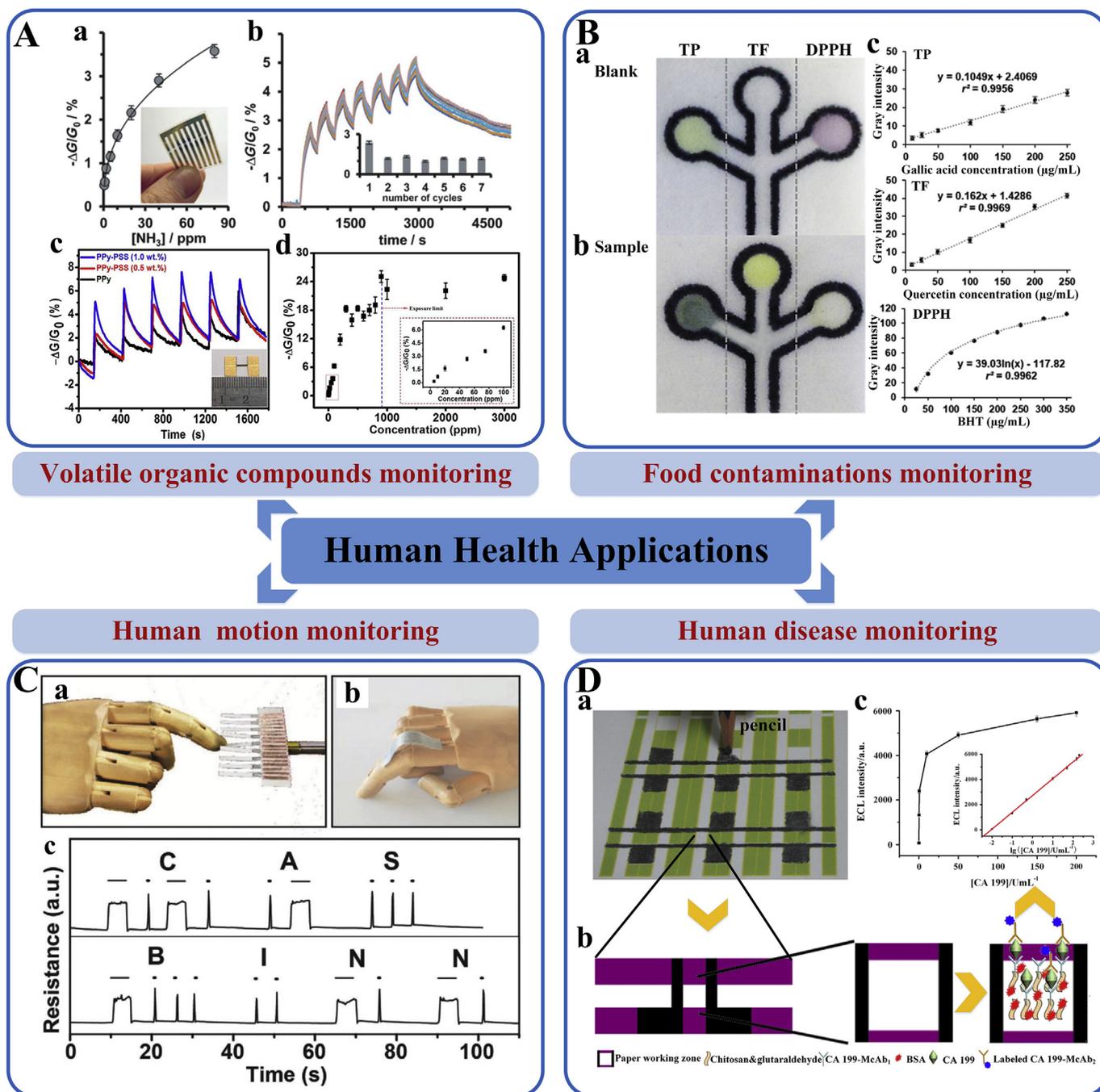
VOCs (e.g., acetone and  $\text{NH}_3$ ) as a kind of harmful gases pose a great threat to human health. Therefore, rapid, sensitive and in-situ monitoring of VOCs in human ambient environment is critically demanded. Gas chromatography-mass spectrometry (GC-MS) technology is traditionally used for monitoring VOCs with high sensitivity and specificity. But GC-MS requires high operating cost, bulky instrument and skilled operator, making it not appropriate for POCT applications. To circumvent these limitations, the sensors based on electric signal changes in response to VOCs absorption have been developed for monitoring VOCs. Moreover, to fabricate these sensors in an easy and rapid manner, the PoP strategies have been applied. For instance, Lin et al. used a flexible toy pencil to write graphite-based chemiresistive sensor on paper, which was successfully engaged in the detection of six types of VOCs, including acetone, methanol, ethyl acetate, tetrahydrofuran (THF), toluene and hexane [54]. This sensor exhibits good detection reversibility



**Fig. 7. Pen-on-paper strategies for deposition of reagents.** (A) the deposition of enzymes with a ball pen: (a) photograph of the ball pen, (b) writing of enzymatic ink onto a fresh sensor using the pen and a template, (c) a close-up view and (d) microscopic image of the sensor surface after writing, (e) stability test of electrochemical ink, (f) amperometric response obtained at 0 mM and 2 mM glucose concentrations. (B) the deposition of enzymes with a reagent pencil: (a) photograph of the reagent pencil, (b) the reagents written on paper by using this pencil, (c) the dissolution of the written-reagents after water introduction, (d) the transformation of the dissolved reagents to detection zone. Images are reproduced from [19,99].

for each of VOCs, attributing to the reversible resistance changes caused by the rapid absorption of VOCs when exposed to VOCs and the rapid desorption of VOCs when re-exposed to fresh air. In addition, the CNTs-based sensors have been demonstrated to be well suitable for monitoring VOCs, due to their extremely high sensitivity to VOCs [90,101]. For example, Swager's group developed a PoP strategy to write CNTs-based sensors on paper for detecting various VOCs, including  $\text{NH}_3$ , acetone, THF and dimethyl methylphosphonate (DMMP) (Fig. 8A) [46,47,66]. In their work, they firstly cast the CNTs powders into the shape of pencils and then mechanically abraded the pencils on paper to make sensors in a solvent-free manner. In comparison to the traditional solvent processing of CNTs, their method can eliminate the concern of sparing solubility of CNTs in most solvents. Then, the selectors designed to specifically identify VOCs were mixed with CNTs during the pencil preparation process, which helps to dramatically improve the detection sensitivity and specificity [66].

Apart from the pencil-based PoP strategies, fountain pens could also find applications in making  $\text{NH}_3$  sensor through writing polypyrrole arrays on paper, in which the detection results were demonstrated by the electric current changes of the sensors (Fig. 8A) [75]. To further improve the detection sensitivity of the  $\text{NH}_3$  sensor, poly (sodium-p-styrenesulfonate) was added into polypyrrole to form a polymer mixture during the ink preparation process, through which the interaction between the sensor with  $\text{NH}_3$  could be enhanced, further resulting in an increased sensitivity with an electric current change of 6.25%–100 ppm concentration. In summary, the sensors made by the PoP strategies show great prospect in monitoring VOCs owing to their high sensitivity and selectivity. But there is still a bit far away to apply these sensors into practical applications, as peripheral devices (such as gas collectors) and portable readers are yet to be integrated with these sensors so far as investigated.



### Volatile organic compounds monitoring

### Food contaminations monitoring

## Human Health Applications

### Human motion monitoring

### Human disease monitoring

**Fig. 8.** Pen-on-paper strategies for POCT in human health applications. Human ambient information monitoring: (A) Chemiresistive sensors for monitoring volatile organic compounds: (a) the change in conductance in response to  $NH_3$  at various concentrations, (b) the plot showing repeated exposure of sensor to a certain concentration of  $NH_3$ , (c)  $NH_3$  (100 ppm) response of paper chemiresistors, (d) normalized conductance change as a function of  $NH_3$  concentrations. (B) A PoP microfluidic device for monitoring food contaminations (e.g., antioxidants): (a) the device before determination of total phenols (TP), total flavonoids (TF) and 2,2-diphenyl-1-picrylhydrazyl (DPPH), (b) the device after sample introduction, (c) the detection results for each antioxidant testing. Human body information monitoring: (C) A PoP piezoresistive sensor for human motion monitoring: (a) schematic image of pencil-written piezoresistive sensor as human-machine interface, (b) sketch map of a pencil-written sensor for monitoring human finger motion, (c) signs of “CAS” and “BINN” realized through finger bending. (D) A PoP electrochemiluminescence device for human diseases monitoring: (a) hand-written PoP electrodes using a 6B pencil (b) schematic representation of the procedure for immunoassay, (c) calibration curves for immunoassay of CA 199. Images are reproduced from [38,46,75,79,81].

#### 4.1.2. Food contaminations monitoring

Nowadays, food safety is of great importance for human health all over the world. In recent years, monitoring food contaminations (e.g., melamine [102]) has attracted increasing interests especially in developing countries. Traditional methods for detecting illegal food additives are mainly based on assays operated in central laboratory, which are dependent on complex instruments and are

time- and energy-consuming. Thus, there exists a great need for detecting food contaminations in a simple, reliable, rapid and sensitive way.

For this purpose, the POP strategies have been introduced to establish paper-based POCT platforms for monitoring food contaminations. For example, our group have developed a pressure-assisted ball pen to write electrochemical sensors with

conductive inks (e.g., carbon and silver inks) on paper to realize electrochemical detection of melamine with detection limit of  $1 \mu\text{M}$  [55]. Polavarapu et al. created a fountain pen loaded with silver plasmonic ink and used it to write SERS arrays to detect thiabendazole with detection limit of 20 ppb [76]. In addition, during food processing and for long-term storage, antioxidants are normally added in food samples to prevent food from spoilage. Recently, Nuchtavorn et al. manufactured a paper-based colorimetric microfluidic chip using a self-made pen for detection of phenolic and flavonoid contents in food samples (Fig. 8B) [79]. In their method, the colorimetric results can be easily read by naked eyes and further quantitatively analyzed by a cell phone. In the above examples, monitoring food contaminations based on electrochemical and colorimetric methods has been realized through the PoP strategies with merits of simplified fabrication process and rapid results readout. By and large, researchers are devoting to bringing these PoP strategies to the real world for practical monitoring of food contaminations.

#### 4.2. Human body monitoring

The vigorously rising tendency of personalized medicine, in which patients are pledged to learn insight of their health situation by themselves, is triggering advances in wearable human health monitoring systems (i.e., the front-end of personalized medicine) to ensure gradual perfection of this emerging healthcare industry. Among all the strategies for realizing body-worn health monitoring, the PoP strategies have recently drawn increasing interests mainly due to its easy accessibility. The operation process of PoP strategies is simple and cheap enough to be competent for DIY purposes. In addition, such PoP strategies can be scaled up to further drop the cost for making wearable healthcare monitoring systems.

##### 4.2.1. Human motion monitoring

Monitoring of human motion can provide useful information for human health, especially for disabled and old people, where human-friendly wearable sensors are demanded for improved user experience. For instance, Liao et al. fabricated a wearable strain sensor via pencil writing graphite sensing materials on paper [103], which was successfully utilized to detect human finger motion through monitoring the regular resistance change responding to the finger bending–stretching motion. Besides, the sensor offers the advantages of being human-friendly and the capability of direct and conformable attachment on human skin. More recently, inspired by the tactile feedback function of mammals' (e.g., cat) facial whiskers, Hua et al. developed a bioinspired strain sensor made by a pencil and attached the fabricated paper-based sensor on a finger to monitor the finger motion [81]. As an example, the signs of “CAS” and “BINN” produced by finger bending were successfully detected (Fig. 8C). The final signal based on the resistance change of the sensor can be easily monitored. The above examples indicate that the strain sensors fabricated by the PoP strategies show promising prospect in the field of monitoring human motion [81]. At the present stage, the wearable sensors can be easily fabricated by the PoP strategies and conformably attached onto body. But the peripheral signal acquisition systems are sophisticated and inaccessible, which would be the main challenge to expand wearable sensors into real applications.

##### 4.2.2. Human diseases monitoring

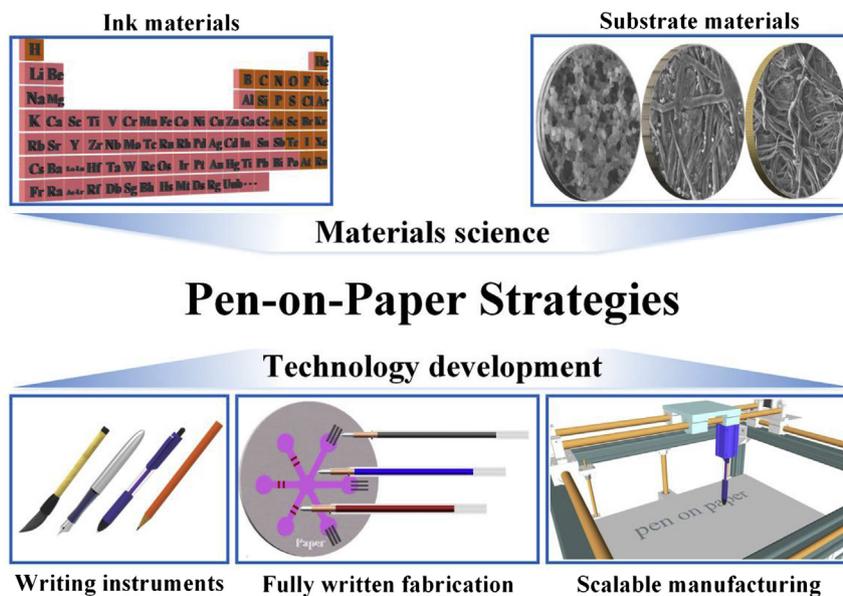
At present, many people are afflicted by infectious diseases (e.g., viral hepatitis) and chronic diseases (e.g., diabetes). Thus monitoring these diseases is utterly important for improving human health. The POCT platforms characterized by moderate cost, user-

friendly operation and quick result readout are highly demanded for early screening of serious diseases and routine monitoring of chronic diseases. Recently, the PoP strategies have found wide applications for making POCT platforms in monitoring human diseases. For example, Yang et al. developed a PoP strategy to manufacture electrochemiluminescence immunosensor constructed by hydrophilic regions and conductive electrodes through writing hydrophobic barriers with a crayon and writing electrodes with a regular 6B pencil on paper (Fig. 8D) [38]. The immunosensor was reliably used to detect Carbohydrate antigen 199 (CA 199), which is the highest sensitive tumor marker of pancreatic cancer, in real serum samples. The detection results agreed well with those obtained from the commercial enzyme-linked immunosorbent assay (ELISA), demonstrating its practical feasibility for screening tumor marker. Further, prostate-specific antigen (PSA), a tumor marker for identifying prostate cancer [104] and breast cancer [105], in real clinical serum samples was successfully detected using a colorimetric paper platform fabricated by a marker pen with detection limit of  $0.3602 \text{ ng mL}^{-1}$  [35]. In this work, the assay was performed in a circular detection zone on paper realized by marker pen writing. During testing, the repeated washing steps were involved before each reagent introduction, which is complicated, time-consuming and user-unfriendly. Another valuable example is the detection of HIV-1 with detection limit of  $\sim 10 \text{ nM}$  using a lateral flow test strip prepared by a Biopen [39]. The achievement of this strategy is close to practical application, as the preparation of test strip via Biopen writing is easy to achieve and the final assay needs minimum user intervention. In addition, the PoP strategies have also been employed to make paper-based colorimetric devices for glucose monitoring [44]. Herein, the PoP strategies were devised to write hydrophobic materials (e.g., PDMS [44], wax [48]) on paper to define the microfluidic channels for transferring the sample to the detection zone. The detection results were obtained through color change once the sample reached the detection zone, which could be directly read by naked eyes. Hence, such PoP strategies show great practicability for monitoring biomarkers of both serious diseases and chronic diseases.

## 5. Conclusions, current challenges and future perspectives

The PoP strategies, characterized by writing desired functional materials on paper using pens, have been widely used in the POCT field for human health monitoring owing to their advantages of simplicity, accessibility, low cost, user-friendliness and rapid prototyping capability. Regular pens including pencils, ball pens and fountain pens have been employed to write various functional elements on paper targeting at different POCT application purposes. Moreover, some self-made pens with a wide range of formulated inks have also been developed to meet specific personalized demands, further reinforcing the versatility of the PoP strategies in fabrication of POCT platforms. Most importantly, these PoP strategies have shown satisfactory feasibility in human health monitoring applications through monitoring both human ambient environment they live in and human body.

The PoP strategies have been undergoing unprecedented development in recent years aiming at the most advanced and urgently needed POCT applications. However, they are also facing some challenges. The limited selection range of ink materials available for PoP strategies due to the fastidious selection standard, requiring potential inks to be of proper surface tension, viscosity and concentration, may restrict the practical functionality of the written elements. Similarly, the limitation that only a few paper substrates with suitable wettability to write inks are capable for realizing PoP scenarios is going against the vista of their extensive applications. Additionally, the tedious and energy-consuming post-



**Fig. 9. Future perspectives of PoP strategies.** They mainly refer to materials science (i.e., ink and substrate materials selection) and technology development (i.e., writing instruments, fully written fabrication and scalable manufacturing. Images of pens are reproduced from [62].

treatments necessary for most solvent-based writing methods are unexpectedly tarnishing the reputation of PoP strategies of being easily accessible and rapid prototyping. Besides, due to manual errors from different operators, the repeatability of written patterns needs to be further improved, which is crucial for the commercialization of the written paper-based platforms. Another key challenge associated with PoP strategies is their poor capability for mass production [106]. Until now, most PoP strategies are exploited to write mono-functional ink for making single component, which are not satisfactory for commercialized paper-based products generally constituted by multi-components. On the basis of these challenges, the PoP strategies are highly active in laboratory, but limited in practical applications. To eventually ensure the PoP strategies to be feasibly used in practical applications, these disturbing hurdles require to be circumvented in a near future.

Based on the literatures of PoP strategies summarized in this review, the future perspectives of the PoP strategies can be oriented in two main directions, i.e., the materials science and the technology development (as shown in Fig. 9). For the materials science, the development of varying novel ink materials for pen writing is highly needed, which means that more functional components can be realized by simply hand writing. More kinds of substrate materials with unique structural porosity, roughness and wettability are also anticipated to collaborate with pens in specific applications of human health monitoring. The recently emerging paper materials composed of carbon derivatives (e.g., graphene paper, carbon fiber paper and CNT paper) are nominated as promising substitutes to enrich the army of paper materials for POCT uses. For the technology development, it is expected to introduce more writing instruments (e.g., marker pen) with reinforced functionality to fabricate POCT platforms through one-step writing without any need for tedious post-treatment procedure. In addition, integrating PoP strategies with digitally controlled plotters is a prospective way to eliminate human factor during writing and achieve scalable batch manufacturing. Due to the simplicity of deploying different pens or cartridges with a plotter (like a revolver), this next-generation all-in-one device could write all functional inks needed onto paper substrates, thus showing enormous potential to make fully written POCT platforms. We envision that these

improvements will facilitate the commercialization of pen-writing paper-based platforms. Another key element that deserves intensified attention is the combination with the cutting-edge wearable technology to output wearable POCT platforms and devices [107]. Benefiting from the simplicity of pen writing and human friendliness of paper materials, this wearable vision can be a big hit in offering real-time, on-site human physiological monitoring and disease diagnosis, moving a giant step forward to the ultimate goal of precise and personalized healthcare.

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### References

- [1] A.D. Warren, G.A. Kwong, D.K. Wood, K.Y. Lin, S.N. Bhatia, Point-of-care diagnostics for noncommunicable diseases using synthetic urinary biomarkers and paper microfluidics, *Proc. Natl. Acad. Sci. U. S. A.* 111 (2014) 3671–3676.
- [2] V. Gubala, L.F. Harris, A.J. Ricco, M.X. Tan, D.E. Williams, Point of care diagnostics: status and future, *Anal. Chem.* 84 (2011) 487–515.
- [3] C.P.Y. Chan, W.C. Mak, K.Y. Cheung, K.K. Sin, C.M. Yu, T.H. Rainer, R. Renneberg, Evidence-based point-of-care diagnostics: current status and emerging technologies, *Annu. Rev. Anal. Chem.* 6 (2013) 191–211.
- [4] M. Zhang, G. Feng, Z. Song, Y.-P. Zhou, H.-Y. Chao, D. Yuan, T.T.Y. Tan, Z. Guo, Z. Hu, B.Z. Tang, B. Liu, D. Zhao, Two-dimensional metal-organic framework with wide channels and responsive turn-on fluorescence for the chemical sensing of volatile organic compounds, *J. Am. Chem. Soc.* 136 (2014) 7241–7244.
- [5] M.C. Janzen, J.B. Ponder, D.P. Bailey, C.K. Ingison, K.S. Suslick, Colorimetric sensor arrays for volatile organic compounds, *Anal. Chem.* 78 (2006) 3591–3600.
- [6] J. Yoon, S.K. Chae, J.-M. Kim, Colorimetric sensors for volatile organic compounds (VOCs) based on conjugated polymer-embedded electrospun fibers, *J. Am. Chem. Soc.* 129 (2007) 3038–3039.

- [7] P.D. Patel, (Bio)sensors for measurement of analytes implicated in food safety: a review, *TrAC Trends Anal. Chem.* 21 (2002) 96–115.
- [8] R.C. Alves, M.F. Barroso, M.B. González-García, M.B.P.P. Oliveira, C. Delerue-Matos, New trends in food allergens detection: toward biosensing strategies, *Crit. Rev. Food Sci. Nutr.* 56 (2016) 2304–2319.
- [9] C. Cháfer-Pericás, Á. Maquieira, R. Puchades, Fast screening methods to detect antibiotic residues in food samples, *TrAC Trends Anal. Chem.* 29 (2010) 1038–1049.
- [10] E. Roh, B.-U. Hwang, D. Kim, B.-Y. Kim, N.-E. Lee, Stretchable, transparent, ultrasensitive, and patchable strain sensor for human-machine interfaces comprising a nanohybrid of carbon nanotubes and conductive elastomers, *ACS Nano* 9 (2015) 6252–6261.
- [11] Y. Wang, L. Wang, T. Yang, X. Li, X. Zang, M. Zhu, K. Wang, D. Wu, H. Zhu, Wearable and highly sensitive graphene strain sensors for human motion monitoring, *Adv. Funct. Mater.* 24 (2014) 4666–4670.
- [12] M. Amjadi, K.-U. Kyung, I. Park, M. Sitti, Stretchable, skin-mountable, and wearable strain sensors and their potential applications: a review, *Adv. Funct. Mater.* 26 (2016) 1678–1698.
- [13] D.C.H. Burgess, J. Wasserman, C.A. Dahl, Global health diagnostics, *Nature* 444 (2006) 1–2.
- [14] C.D. Chin, T. Laksanasopin, Y.K. Cheung, D. Steinmiller, V. Linder, H. Parsa, J. Wang, H. Moore, R. Rouse, G. Umvilighozo, E. Karita, L. Mwambarangwe, S.L. Braunstein, J. van de Wijgert, R. Sahabo, J.E. Justman, W. El-Sadr, S.K. Sia, Microfluidics-based diagnostics of infectious diseases in the developing world, *Nat. Med.* 17 (2011) 1015–1019.
- [15] P. Yager, G.J. Domingo, J. Gerdes, Point-of-care diagnostics for global health, *Annu. Rev. Biomed. Eng.* 10 (2008) 107–144.
- [16] A. Niemi, T.M. Ferguson, D.S. Boyle, Point-of-care nucleic acid testing for infectious diseases, *Trends Biotechnol.* 29 (2011) 240–250.
- [17] J.R. Choi, J. Hu, S. Wang, H. Yang, W.A.B. Wan Abas, B. Pingguan-Murphy, F. Xu, Paper-based point-of-care testing for diagnosis of dengue infections, *Crit. Rev. Biotechnol.* 37 (2017) 100–111.
- [18] D. Mabey, R.W. Peeling, A. Ustianowski, M.D. Perkins, Tropical infectious diseases: diagnostics for the developing world, *Nat. Rev. Micro.* 2 (2004) 231–240.
- [19] A.J. Bandodkar, W. Jia, J. Ramirez, J. Wang, Biocompatible enzymatic roller pens for direct writing of biocatalytic materials: “do-it-yourself” electrochemical biosensors, *Adv. Healthcare Mater.* 4 (2015) 1215–1224.
- [20] J. Hu, S. Wang, L. Wang, F. Li, B. Pingguan-Murphy, T.J. Lu, F. Xu, Advances in paper-based point-of-care diagnostics, *Biosens. Bioelectron.* 54 (2014) 585–597.
- [21] A.W. Martinez, S.T. Phillips, G.M. Whitesides, E. Carrilho, A. Chem, Diagnostics for the developing world: microfluidic paper-based analytical devices, *Anal. Chem.* 82 (2010) 3–10.
- [22] E.J. Maxwell, A.D. Mazzeo, G.M. Whitesides, Paper-based electroanalytical devices for accessible diagnostic testing, *MRS Bull.* 38 (2013) 309–314.
- [23] D.M. Cate, J.A. Adkins, J. Mettakoonpitak, C.S. Henry, Recent developments in paper-based microfluidic devices, *Anal. Chem.* 87 (2015) 19–41.
- [24] R.H. Tang, H. Yang, J.R. Choi, Y. Gong, S.S. Feng, B. Pingguan-Murphy, Q.S. Huang, J.L. Shi, Q.B. Mei, F. Xu, Advances in paper-based sample pretreatment for point-of-care testing, *Crit. Rev. Biotechnol.* 37 (2017) 411–428.
- [25] A.W. Martinez, S.T. Phillips, M.J. Butte, G.M. Whitesides, Patterned paper as a platform for inexpensive, low-volume, portable bioassays, *Angew. Chem. Int. Ed.* 46 (2007) 1318–1320.
- [26] E.M. Fenton, M.R. Mascarenas, G.P. López, S.S. Sibbett, Multiplex lateral-flow test strips fabricated by two-dimensional shaping, *ACS Appl. Mater. Interfaces* 1 (2009) 124–129.
- [27] M. Santhiago, J.B. Wydallis, L.T. Kubota, C.S. Henry, Construction and electrochemical characterization of microelectrodes for improved sensitivity in paper-based analytical devices, *Anal. Chem.* 85 (2013) 5233–5239.
- [28] C. Renault, M.J. Anderson, R.M. Crooks, Electrochemistry in hollow-channel paper analytical devices, *J. Am. Chem. Soc.* 136 (2014) 4616–4623.
- [29] L. Ge, S. Wang, J. Yu, N. Li, S. Ge, M. Yan, Molecularly imprinted polymer grafted porous Au-paper electrode for an microfluidic electro-analytical origami device, *Adv. Funct. Mater.* 23 (2013) 3115–3123.
- [30] W. Kit-Anan, A. Olarnwanich, C. Sriprachuabwong, C. Karuwan, A. Tuantranont, A. Wisitsoraat, W. Srituranvich, A. Pimpin, Disposable paper-based electrochemical sensor utilizing inkjet-printed polyaniline modified screen-printed carbon electrode for Ascorbic acid detection, *J. Electroanal. Chem.* 685 (2012) 72–78.
- [31] C. Sriprachuabwong, C. Karuwan, A. Wisitsoraat, D. Phokharatkul, T. Lomas, P. Sritongkham, A. Tuantranont, Inkjet-printed graphene-PEDOT:PSS modified screen printed carbon electrode for biochemical sensing, *J. Mater. Chem.* 22 (2012) 5478–5485.
- [32] K. Crowley, E. O'Malley, A. Morrin, M.R. Smyth, A.J. Killard, An aqueous ammonia sensor based on an inkjet-printed polyaniline nanoparticle-modified electrode, *Analyst* 133 (2008) 391–399.
- [33] K. Abe, K. Suzuki, D. Citterio, Inkjet-printed microfluidic multianalyte chemical sensing paper, *Anal. Chem.* 80 (2008) 6928–6934.
- [34] Z. Li, F. Li, Y. Xing, Z. Liu, M. You, Y. Li, T. Wen, Z. Qu, X. Ling Li, F. Xu, Pen-on-paper strategy for point-of-care testing: rapid prototyping of fully written microfluidic biosensor, *Biosens. Bioelectron.* 98 (2017) 478–485.
- [35] J. Nie, Y. Zhang, L. Lin, C. Zhou, S. Li, L. Zhang, J. Li, Low-cost fabrication of paper-based microfluidic devices by one-step plotting, *Anal. Chem.* 84 (2012) 6331–6335.
- [36] N. Dossi, R. Toniolo, A. Pizzariello, F. Impellizzeri, E. Piccin, G. Bontempelli, Pencil-drawn paper supported electrodes as simple electrochemical detectors for paper-based fluidic devices, *Electrophoresis* 34 (2013) 2085–2091.
- [37] N. Dossi, R. Toniolo, E. Piccin, S. Susmel, A. Pizzariello, G. Bontempelli, Pencil-drawn dual electrode detectors to discriminate between analytes comigrating on paper-based fluidic devices but undergoing electrochemical processes with different reversibility, *Electroanalysis* 25 (2013) 2515–2522.
- [38] H. Yang, Q. Kong, S. Wang, J. Xu, Z. Bian, X. Zheng, C. Ma, S. Ge, J. Yu, Hand-drawn/written pen-on-paper electrochemiluminescence immunodevice powered by rechargeable battery for low-cost point-of-care testing, *Biosens. Bioelectron.* 61 (2014) 21–27.
- [39] Y.L. Han, J. Hu, G.M. Genin, T.J. Lu, F. Xu, BioPen: direct writing of functional materials at the point of care, *Sci. Rep.* 4 (2014) 4872.
- [40] Y. Yang, E. Noviana, M.P. Nguyen, B.J. Geiss, D.S. Dandy, C.S. Henry, Paper-based microfluidic devices: emerging themes and applications, *Anal. Chem.* 89 (2017) 71–91.
- [41] Y. Zhang, L. Zhang, K. Cui, S. Ge, X. Cheng, M. Yan, J. Yu, H. Liu, Flexible electronics based on micro/nanostructured paper, *Adv. Mater.* (2018), <https://doi.org/10.1002/adma.201801588>.
- [42] N. Dossi, R. Toniolo, F. Terzi, F. Impellizzeri, G. Bontempelli, Pencil leads doped with electrochemically deposited Ag and AgCl for drawing reference electrodes on paper-based electrochemical devices, *Electrochim. Acta* 146 (2014) 518–524.
- [43] N. Dossi, R. Toniolo, F. Impellizzeri, G. Bontempelli, Doped pencil leads for drawing modified electrodes on paper-based electrochemical devices, *J. Electroanal. Chem.* 722 (2014) 90–94.
- [44] D.A. Bruzewicz, M. Reches, G.M. Whitesides, Low-cost printing of poly(dimethylsiloxane) barriers to define microchannels in paper, *Anal. Chem.* 80 (2008) 3387–3392.
- [45] J.-W. Han, B. Kim, J. Li, M. Meyyappan, Carbon nanotube ink for writing on cellulose paper, *Mater. Res. Bull.* 50 (2014) 249–253.
- [46] K.A. Mirica, J.G. Weis, J.M. Schnorr, B. Esser, T.M. Swager, Mechanical drawing of gas sensors on paper, *Angew. Chem. Int. Ed.* 51 (2012) 10740–10745.
- [47] K.M. Frazier, K.A. Mirica, J.J. Walsh, T.M. Swager, Fully-drawn carbon-based chemical sensors on organic and inorganic surfaces, *Lab Chip* 14 (2014) 4059–4066.
- [48] Y. Lu, W. Shi, L. Jiang, J. Qin, B. Lin, Rapid prototyping of paper-based microfluidics with wax for low-cost, portable bioassay, *Electrophoresis* 30 (2009) 1497–1500.
- [49] A.W. Martinez, S.T. Phillips, G.M. Whitesides, Three-dimensional microfluidic devices fabricated in layered paper and tape, *Proc. Natl. Acad. Sci.* 105 (2008) 19606–19611.
- [50] C. Renault, J. Koehne, A.J. Ricco, R.M. Crooks, Three-dimensional wax patterning of paper fluidic devices, *Langmuir* 30 (2014) 7030–7036.
- [51] K.L. Dornelas, N. Dossi, E. Piccin, A simple method for patterning poly(dimethylsiloxane) barriers in paper using contact-printing with low-cost rubber stamps, *Anal. Chim. Acta* 858 (2015) 82–90.
- [52] E. Carrilho, A.W. Martinez, G.M. Whitesides, Understanding wax printing: a simple micropatterning process for paper-based microfluidics, *Anal. Chem.* 81 (2009) 7091–7095.
- [53] Y. Lu, W. Shi, J. Qin, B. Lin, Fabrication and characterization of paper-based microfluidics prepared in nitrocellulose membrane by wax printing, *Anal. Chem.* 82 (2009) 329–335.
- [54] C.-W. Lin, Z. Zhao, J. Kim, J. Huang, Pencil drawn strain gauges and chemiresistors on paper, *Sci. Rep.* 4 (2014) 3812.
- [55] Z. Li, F. Li, J. Hu, W. Wee, Y. Han, B. Pingguan-Murphy, T. Lu, F. Xu, Direct writing electrodes using ball pen for paper-based point-of-care testing, *Analyst* 140 (2015) 5526–5535.
- [56] L. Hu, J.W. Choi, Y. Yang, S. Jeong, F. La Mantia, L.-F. Cui, Y. Cui, Highly conductive paper for energy-storage devices, *Proc. Natl. Acad. Sci. U. S. A.* 106 (2009) 21490–21494.
- [57] Y.H. Jung, T.-H. Chang, H. Zhang, C. Yao, Q. Zheng, V.W. Yang, H. Mi, M. Kim, S.J. Cho, D.-W. Park, H. Jiang, J. Lee, Y. Qiu, W. Zhou, Z. Cai, S. Gong, Z. Ma, High-performance green flexible electronics based on biodegradable cellulose nanofibril paper, *Nat. Commun.* 6 (2015) 7170.
- [58] J. Lessing, A.C. Glavan, S.B. Walker, C. Keplinger, J.A. Lewis, G.M. Whitesides, Inkjet printing of conductive inks with high lateral resolution on omniphobic “RF paper” for paper-based electronics and MEMS, *Adv. Mater.* 26 (2014) 4677–4682.
- [59] W.C. Mak, V. Beni, A.P. Turner, Lateral-flow technology: from visual to instrumental, *TrAC Trends Anal. Chem.* 79 (2016) 297–305.
- [60] M.M. Gong, D. Sinton, Turning the page: advancing paper-based microfluidics for broad diagnostic application, *Chem. Rev.* 117 (2017) 8447–8480.
- [61] D. Tobjörk, R. Österbacka, Paper electronics, *Adv. Mater.* 23 (2011) 1935–1961.
- [62] Z. Li, H. Liu, C. Ouyang, W. Hong Wee, X. Cui, T. Jian Lu, B. Pingguan-Murphy, F. Li, F. Xu, Recent advances in pen-based writing electronics and their emerging applications, *Adv. Funct. Mater.* 26 (2016) 165–180.
- [63] N. Dossi, F. Terzi, E. Piccin, R. Toniolo, G. Bontempelli, Rapid prototyping of sensors and conductive elements by day-to-day writing tools and emerging manufacturing technologies, *Electroanalysis* 28 (2016) 250–264.
- [64] G. Zheng, L. Hu, H. Wu, X. Xie, Y. Cui, Paper supercapacitors by a solvent-free drawing method, *Energy Environ. Sci.* 4 (2011) 3368–3373.

- [65] V. Brus, P. Maryanchuk, Photosensitive Schottky-type heterojunctions prepared by the drawing of graphite films, *Appl. Phys. Lett.* 104 (2014) 173501.
- [66] K.A. Mirica, J.M. Azzarelli, J.G. Weis, J.M. Schnorr, T.M. Swager, Rapid prototyping of carbon-based chemiresistive gas sensors on paper, *Proc. Natl. Acad. Sci. U. S. A.* 110 (2013) 3265–3270.
- [67] L.Y. Xu, G.Y. Yang, H.Y. Jing, J. Wei, Y.D. Han, Pressure-assisted low-temperature sintering for paper-based writing electronics, *Nanotechnology* 24 (2013) 355204.
- [68] W. Yang, C. Liu, Z. Zhang, Y. Liu, S. Nie, Paper-based nanosilver conductive ink, *J. Mater. Sci. Mater. Electron.* 24 (2013) 628–634.
- [69] W. Li, W. Li, J. Wei, J. Tan, M. Chen, Preparation of conductive Cu patterns by directly writing using nano-Cu ink, *Mater. Chem. Phys.* 146 (2014) 82–87.
- [70] W. Li, M. Chen, Synthesis of stable ultra-small Cu nanoparticles for direct writing flexible electronics, *Appl. Surf. Sci.* 290 (2014) 240–245.
- [71] W. Li, M. Chen, J. Wei, W. Li, C. You, Synthesis and characterization of air-stable Cu nanoparticles for conductive pattern drawing directly on paper substrates, *J. Nanopart. Res.* 15 (2013) 1–10.
- [72] Y. Gao, H. Li, J. Liu, Direct writing of flexible electronics through room temperature liquid metal ink, *PLoS One* 7 (2012) e45485.
- [73] Y. Zheng, Q. Zhang, J. Liu, Pervasive liquid metal based direct writing electronics with roller-ball pen, *AIP Adv.* 3 (2013) 2117.
- [74] A. Russo, B.Y. Ahn, J.J. Adams, E.B. Duoss, J.T. Bernhard, J.A. Lewis, Pen-on-paper flexible electronics, *Adv. Mater.* 23 (2011) 3426–3430.
- [75] H. Jia, J. Wang, X. Zhang, Y. Wang, Pen-writing polypyrrole arrays on paper for versatile cheap sensors, *ACS Macro Lett.* 3 (2013) 86–90.
- [76] L. Polavarapu, A.L. Porta, S.M. Novikov, M. Coronado-Puchau, L.M. Liz-Marzán, Pen-on-paper approach toward the design of universal surface enhanced Raman scattering substrates, *Small* 10 (2014) 3065–3071.
- [77] H. Warren, R. Gatley, H. Moffat, Conducting carbon nanofibre networks: dispersion optimisation, evaporative casting and direct writing, *RSC Adv.* 3 (2013) 21936–21942.
- [78] X. Fang, H. Chen, X. Jiang, J. Kong, Microfluidic devices constructed by a marker pen on a silica gel plate for multiplex Assays, *Anal. Chem.* 83 (2011) 3596–3599.
- [79] N. Nuchtavorn, M. Macka, A novel highly flexible, simple, rapid and low-cost fabrication tool for paper-based microfluidic devices ( $\mu$ PADs) using technical drawing pens and in-house formulated aqueous inks, *Anal. Chim. Acta* 919 (2016) 70–77.
- [80] Y. Zheng, Z.-Z. He, J. Yang, J. Liu, Personal electronics printing via tapping mode composite liquid metal ink delivery and adhesion mechanism, *Sci. Rep.* 4 (2014) 4588.
- [81] Q. Hua, H. Liu, J. Zhao, D. Peng, X. Yang, L. Gu, C. Pan, Bioinspired electronic whisker arrays by pencil-drawn paper for adaptive tactile sensing, *Adv. Electron. Mater.* 2 (2016) 1600093.
- [82] X. Li, D.R. Ballerini, W. Shen, A perspective on paper-based microfluidics: current status and future trends, *Biomicrofluidics* 6 (2012) 011301.
- [83] X. Li, J. Tian, T. Nguyen, W. Shen, Paper-based microfluidic devices by plasma treatment, *Anal. Chem.* 80 (2008) 9131–9134.
- [84] A. Nilghaz, D.H. Wicaksono, D. Gustiono, F.A.A. Majid, E. Supriyanto, M.R.A. Kadir, Flexible microfluidic cloth-based analytical devices using a low-cost wax patterning technique, *Lab Chip* 12 (2012) 209–218.
- [85] T.-K. Kang, Tunable piezoresistive sensors based on pencil-on-paper, *Appl. Phys. Lett.* 104 (2014) 073117.
- [86] V. Mosser, J. Suski, J. Goss, E. Obermeier, Piezoresistive pressure sensors based on polycrystalline silicon, *Sens. Actuat. A* 28 (1991) 113–132.
- [87] K.W. Wee, G.Y. Kang, J. Park, J.Y. Kang, D.S. Yoon, J.H. Park, T.S. Kim, Novel electrical detection of label-free disease marker proteins using piezoresistive self-sensing micro-cantilevers, *Biosens. Bioelectron.* 20 (2005) 1932–1938.
- [88] X. Liu, M. Mwangi, X. Li, M. O'Brien, G.M. Whitesides, Paper-based piezoresistive MEMS sensors, *Lab Chip* 11 (2011) 2189–2196.
- [89] T.-L. Ren, H. Tian, D. Xie, Y. Yang, Flexible graphite-on-paper piezoresistive sensors, *Sensors* 12 (2012) 6685–6694.
- [90] J. Kong, N.R. Franklin, C. Zhou, M.G. Chapline, S. Peng, K. Cho, H. Dai, Nanotube molecular wires as chemical sensors, *Science* 287 (2000) 622–625.
- [91] D.R. Kauffman, A. Star, Carbon nanotube gas and vapor sensors, *Angew. Chem. Int. Ed.* 47 (2008) 6550–6570.
- [92] L.Y. Shiroma, M. Santhiago, A.L. Gobbi, L.T. Kubota, Separation and electrochemical detection of paracetamol and 4-aminophenol in a paper-based microfluidic device, *Anal. Chim. Acta* 725 (2012) 44–50.
- [93] D.D. Liana, B. Raguse, L. Wiecek, G.R. Baxter, K. Chuah, J.J. Gooding, E. Chow, Sintered gold nanoparticles as an electrode material for paper-based electrochemical sensors, *RSC Adv.* 3 (2013) 8683–8691.
- [94] Z. Nie, C.A. Nijhuis, J. Gong, X. Chen, A. Kumachev, A.W. Martinez, M. Narovlyansky, G.M. Whitesides, Electrochemical sensing in paper-based microfluidic devices, *Lab Chip* 10 (2010) 477–483.
- [95] A. Määttä, U. Vanamo, P. Ihalainen, P. Pulkkinen, H. Tenhu, J. Bobacka, J. Peltonen, A low-cost paper-based inkjet-printed platform for electrochemical analyses, *Sens. Actuat. B* 177 (2013) 153–162.
- [96] C. Han, Y. Li, Q. Jia, L.H. Bradley, Y. Gan, Y. Yao, L. Qu, H. Li, Y. Zhao, On-demand fabrication of surface-enhanced Raman scattering arrays by pen writing, and their application to the determination of melamine in milk, *Microchim. Acta* 184 (2017) 2909–2917.
- [97] F. Tian, H. Li, M. Li, C. Li, Y. Lei, B. Yang, A tantalum electrode coated with graphene nanowalls for simultaneous voltammetric determination of dopamine, uric acid, L-tyrosine, and hydrochlorothiazide, *Microchim. Acta* 184 (2017) 1611–1619.
- [98] Z. Zhao, Y. Sun, P. Li, W. Zhang, K. Lian, J. Hu, Y. Chen, Preparation and characterization of AuNPs/CNTs-ErGO electrochemical sensors for highly sensitive detection of hydrazine, *Talanta* 158 (2016) 283–291.
- [99] H.T. Mitchell, I.C. Noxon, C.A. Chaplan, S.J. Carlton, C.H. Liu, K.A. Ganaja, N.W. Martinez, C.E. Immoos, P.J. Costanzo, A.W. Martinez, Reagent pencils: a new technique for solvent-free deposition of reagents onto paper-based microfluidic devices, *Lab Chip* 15 (2015) 2213–2220.
- [100] C.H. Liu, I.C. Noxon, L.E. Cuellar, A.L. Thraen, C.E. Immoos, A.W. Martinez, P.J. Costanzo, Characterization of reagent pencils for deposition of reagents onto paper-based microfluidic devices, *Micromachines* 8 (2017) 242.
- [101] S. Ammu, V. Dua, S.R. Agnihotra, S.P. Surwade, A. Phulgirkar, S. Patel, S.K. Manohar, Flexible, All-organic chemiresistor for detecting chemically aggressive vapors, *J. Am. Chem. Soc.* 134 (2012) 4553–4556.
- [102] J.R. Ingelfinger, Melamine and the global implications of food contamination, *N. Engl. J. Med.* 359 (2008) 2745–2748.
- [103] X. Liao, Q. Liao, X. Yan, Q. Liang, H. Si, M. Li, H. Wu, S. Cao, Y. Zhang, Flexible and highly sensitive strain sensors fabricated by pencil drawn for wearable monitor, *Adv. Funct. Mater.* 25 (2015) 2395–2401.
- [104] J.-M. Nam, C.S. Thaxton, C.A. Mirkin, Nanoparticle-based bio-bar codes for the ultrasensitive detection of proteins, *Science* 301 (2003) 1884–1886.
- [105] M.H. Black, M. Giai, R. Ponzzone, P. Sisoni, H. Yu, E.P. Diamandis, Serum total and free prostate-specific antigen for breast cancer diagnosis in women, *Clin. Cancer Res.* 6 (2000) 467–473.
- [106] K. Yamada, H. Shibata, K. Suzuki, D. Citterio, Toward practical application of paper-based microfluidics for medical diagnostics: state-of-the-art and challenges, *Lab Chip* 17 (2017) 1206–1249.
- [107] H. Liu, H. Qing, Z. Li, Y.L. Han, M. Lin, H. Yang, A. Li, T.J. Lu, F. Li, F. Xu, Paper: a promising material for human-friendly functional wearable electronics, *Mater. Sci. Eng. R* 112 (2017) 1–22.