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Micropatterning of Functional Conductive Polymers with Multiple Surface Chemistries in Register

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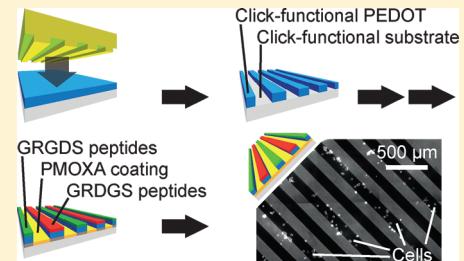
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Supporting Information

ABSTRACT: A versatile procedure is presented for fast and efficient micropatterning of multiple types of covalently bound surface chemistry in perfect register on and between conductive polymer microcircuits. The micropatterning principle is applied to several types of native and functionalized PEDOT (poly(3,4-ethylenedioxythiophene)) thin films. The method is based on contacting PEDOT-type thin films with a micropatterned agarose stamp containing an oxidant (aqueous hypochlorite) and applying a nonionic detergent. Where contacted, PEDOT not only loses its conductance but is entirely removed, thereby locally revealing the underlying substrate. Surface analysis showed that the substrate surface chemistry was fully exposed and not affected by the treatment.

Click chemistry could thus be applied to selectively modify re-exposed alkyne and azide functional groups of functionalized polystyrene substrates. The versatility of the method is illustrated by micropatterning cell-binding RGD-functionalized PEDOT on low cell-binding PMOXA (poly(2-methyl-2-oxazoline)) to produce cell-capturing microelectrodes on a cell nonadhesive background in a few simple steps. The method should be applicable to a wide range of native and chemically functionalized conjugated polymer systems.



1. INTRODUCTION

Micropatterned conductive polymers are exciting active materials for low-cost microsystems with a number of attractive unique characteristics. These include their ability to act both as an ionic and an electronic conductor and the potential for altering the chemical appearance of the polymers by simply altering the monomer unit.^{1–6} For biomedical applications, conductive polymers have further valuable features such as the ability to capture biomolecules on or within the polymer and specifically release these molecules upon electrical stimuli^{7,8} and as a vehicle for electrochemically controlled cellular adhesion.^{9,10} These applications rely on the ability to engineer the surface chemistry of the conductive polymer as well as its surroundings to control biomolecule and cell adhesive properties. PEDOT (poly(3,4-ethylenedioxythiophene)) is a particularly interesting conductive polymer due to its ease of handling, high conductivity, chemical stability, and cellular compatibility.^{1,11,12}

Conductive polymers are conventionally micropatterned using photolithography and other clean room processes.^{13,14} Such processes are versatile but expensive and may additionally use harsh chemical conditions that adversely affect the surface chemistry of the final product. Alternative inexpensive micropatterning methods are therefore in demand. Such methods

should ideally preserve the surface chemical properties and even permit engineering of the surface chemistry. We address this need by demonstrating a simple method for producing defined functionalized PEDOT microelectrodes on functionalized polymer substrates. The method allows the introduction of multiple types of patterned surface chemistries, both onto the electrodes and to the gaps in between. These in-register surface chemistries are covalently bound, and local functionalities can thus be chosen to fit a given task. Notably, no alignment steps are required and the presented “printed dissolution” method is inexpensive, since it largely avoids clean room processes.

The central concept of the method is to locally remove the conductive polymer film to expose a chemically unaffected underlying functional substrate (Figure 1). It is well-known that a strong oxidant, e.g. aqueous sodium hypochlorite (NaOCl), can overoxidize PEDOT to disrupt the conjugated system in the polymer backbone and further degrade the polymer and thus remove its conductivity.¹⁵ The local removal is initiated by physically contacting a PEDOT thin film with a bas-relief structured agarose stamp containing the oxidizing agent (Figure

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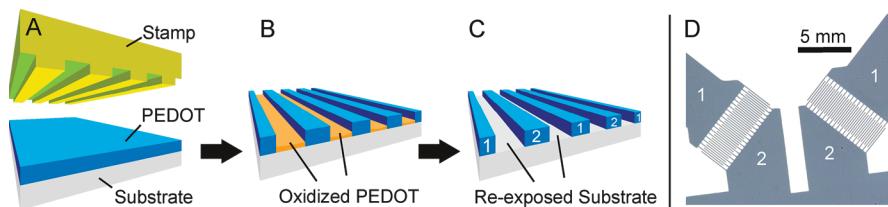


Figure 1. Schematic of conductive polymer micropatterning by printed dissolution. (A) An agarose hydrogel stamp with a predefined microstructure in bas-relief is soaked in an oxidant-containing solution (aqueous NaOCl) and brought into contact with a conductive polymer (PEDOT) thin film on a substrate. (B) Overoxidized and nonconducting PEDOT remains in the contacted areas after stamping. (C) The overoxidized PEDOT is removed by washing in aqueous detergent (Triton X-100) or by adding detergent directly to the aqueous oxidant. (D) Optical micrograph of a PEDOT thin film on a polymer (COC) substrate patterned into two sets of interdigitated arrays of 100 μm wide electrodes (digits “1” and “2” mark connectors for independently addressable electrodes, as shown in (C)).

1A), as we reported earlier using aqueous NaOCl as oxidant.¹⁶ The patterning procedure leaves a stable film of overoxidized PEDOT in the gaps between the electrodes (Figure 1B). Here, we report that this remaining overoxidized PEDOT can be removed from the supporting substrate by applying a nonionic detergent either directly in the agarose stamp or in a subsequent washing step (Figure 1C). Equally important, we show that various functional chemical groups are not influenced by the oxidative environment used in the patterning procedure. These findings open a simple route to fabricate polymeric microsystems with controlled surface chemistries both on and between PEDOT electrodes by “hiding” polymer thin films containing specific functional groups below the PEDOT film. This aspect distinguishes our method from standard micropatterning techniques such as reactive ion etching (RIE) that normally destroys any predefined organic chemistry below the etched film. Our procedure is shown to be applicable for patterning several functionalized PEDOT types, poly(3,4-(1-azidomethylethylene)dioxythiophene) (PEDOT-N₃) and poly(3,4-(1-hydroxymethylethylene)dioxythiophene) (PEDOT-OH), in addition to regular PEDOT. Consequently, multiple types of localized chemistries can easily be introduced into an all-polymer microsystem by combining functional substrates with functional PEDOT films of orthogonal chemical reactivity.

We first demonstrate the general principle by locally removing PEDOT thin films from injection molded cyclic-olefin-copolymer (COC) substrates. We then proceed to illustrate how multiple in-register surface chemistries can be introduced through the process. Combining a click-reactive substrate (PS-N₃, poly(4-azidomethylstyrene)) with PEDOT-OH allows the introduction of two distinct types of surface chemistries, and the click-functional PEDOT-N₃ in combination with an alkyne-modified polystyrene substrate can provide three types of locally directed surface chemistries in register. The latter is achieved using electroclick reactions.^{17–19} Finally, we show that a high degree of biological specificity can be achieved by introducing coatings of poly(2-methyl-2-oxazoline) (PMOXA) or poly(ethylene glycol) (PEG), both having low cell-binding properties, below PEDOT-N₃ microelectrodes selectively modified with RGD-containing peptides, to achieve localized cell attachment in an all-polymer microfluidic device.

2. EXPERIMENTAL SECTION

Chemicals and Materials. EDOT-OH, 10–15 wt % aqueous NaOCl (sodium hypochlorite), Triton-X100, agarose, and all small halogenated marker molecules were purchased from Sigma-Aldrich. Clevios M (EDOT monomer) and Clevios C-B 40 (40 wt % iron(III)tosylate in *n*-butanol) were acquired from Heraeus Clevios GmbH (Germany). PEG-alkyne (750 Da, art. no. PEG2840) was

obtained from IRIS Biotech GmbH (Germany). EDOT-N₃ was synthesized as described in our previous report.⁵ Alkyne-modified polystyrene (PS-alkyne) was synthesized as outlined in the Supporting Information, following an earlier established route.²⁰ Azide-modified polystyrene (PS-N₃), alkyne-PEG-GRGDS, and alkyne-PEG-GRGDS were synthesized and characterized as described in the Supporting Information. Alkyne-PMOXAs were synthesized and characterized as described in the Supporting Information, combining earlier reported schemes.^{21–26} Disk-shaped (diameter 50 mm; thickness 2 mm) cyclic olefin copolymer (COC) substrates were injection-molded on an Engel Victory 80/45 (Schwertberg, Austria) using TOPAS 5013 (TOPAS Advanced Polymers, Frankfurt-Höchst, Germany).

Thin Film Preparations. PS-N₃ and PS-alkyne thin films were prepared by spin-coating a solution of 5 mg/mL polymer in 1,4-dioxane onto COC substrates at 1000 rpm. The samples were heated briefly on a hot plate at 60 °C to remove residual solvent. PMOXA films used for the cellular studies of Figure 7 resulted from overnight reaction of a PS-N₃ covered COC substrate with a PMOXA(4000)-alkyne solution of 1 mM CuSO₄, 15 mM sodium ascorbate, 2 mM PMOXA-alkyne dissolved in 64/36 v/v DMSO/H₂O. The following day the substrate was backfilled by reaction for 4 h with a PMOXA(2000)-alkyne reactant solution of 1 mM CuSO₄, 15 mM sodium ascorbate, 2 mM PMOXA-alkyne dissolved in 64/36 v/v DMSO/H₂O. Following the reaction, the sample was rinsed in Milli-Q water. PEDOT, PEDOT-N₃, and PEDOT-OH thin films with tosylate counterions were prepared by *in situ* polymerization on their respective substrate surfaces.^{5,12} PEDOT films were prepared by spin-coating a solution of 6.5 mL of Clevios C-B40, 2 mL of *n*-butanol, 220 μL of EDOT monomer, and 150 μL of pyridine at 700–1000 rpm followed by >2 min baking on a hot plate at 65 °C. Following polymerization the film was rinsed in Milli-Q water and ethanol. PEDOT-OH films were fabricated on top of a premade PEDOT film using the same methodology (PEDOT-OH/PEDOT). PEDOT-N₃ was likewise spin-coated onto PEDOT (PEDOT-N₃/PEDOT) by using 45 mg of EDOT-N₃, 700 μL of *n*-butanol, and 700 μL of Clevios C-B40 as precursor solution. Both PEDOT-OH and PEDOT-N₃ solutions were spin-coated at 1000 rpm. The resulting conducting polymer films had a thickness of ~150 nm.²⁷

Agarose Stamp Preparation. A silicon mold was fabricated by standard photolithography and deep reactive ion etching. The mold fabricated in this manner proved more stable over time than our earlier reported method using SU-8.¹⁶ Also, this method allowed deeper features to be produced in the stamp, which facilitated the patterning of large areas. Prior to each use, the mold was rinsed in ethanol and occasionally rinsed in air plasma to remove any residual organic material. The silicon mold was placed on a hot plate set to 65 °C. A 10 wt % solution of agarose in Milli-Q water was mixed thoroughly. The solution was heated in a microwave oven to remove air bubbles from the solution. To prevent the solution from boiling, this was done using a series of multiple short heating cycles. The hot agarose solution was poured directly onto the silicon mold, contained inside a 5 cm diameter polystyrene Petri dish with its bottom removed. The container was covered with a lid and kept on the hot plate for 10 min. The mold was then transferred to a fridge and left for minimum 10 min to cool down.

After the fabrication the agarose stamp was usually cut with a scalpel to a smaller size for improved handling.

Agarose Stamping Procedure. The agarose stamp was soaked for 15 min in a stamping solution, and excess solution was blown off using an air gun. The stamp was gently pressed onto the sample surface to establish contact, left for 4 min (unless stated otherwise) before removing the stamp, and then immediate rinsing of the sample in Milli-Q water. Between each stamping cycle, the stamp was soaked for 5 min in the stamping solution. For stamping PEDOT films, a solution of 1:10 solution of NaOCl stock in Milli-Q water was used, resulting in a concentration of 1–1.5 wt % NaOCl while for the samples containing PEDOT-OH on PEDOT or PEDOT-N₃ on PEDOT 1/6 of the NaOCl stock was used leading to a concentration of 1.7–2.5 wt % NaOCl. Stamping solutions also included 0.1 vol % Triton-X100 where indicated.

Poststamping Washing Procedure. Following the stamping, the samples were washed for 10 min in an aqueous solution of 0.1 vol % Triton-X100 and 1 wt % sodium ascorbate at 50 °C (except where stated otherwise). All samples were washed twice for 10 min in Milli-Q water at 50 °C and 10 min in 80/20 v/v DMSO/H₂O at room temperature, before rinsing in ethanol, Milli-Q water, and reoxidation of the PEDOT by rinsing in 10/90 v/v Clevios C-B40/H₂O, and rinsing in Milli-Q water.

Ester Coupling of 5-Bromopentanoic Acid on PEDOT-OH. PEDOT-OH was reacted for 45 min using 180 mM 5-bromopentanoic acid, 150 mM 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC), 150 mM 4-(dimethylamino)pyridine (DMAP) in dry DMSO. The sample was rinsed in Milli-Q water followed by reoxidation of the PEDOT by rinsing in 10/90 v/v Clevios C-B40/H₂O and rinsing in Milli-Q water.

Click Reaction Conditions. Poststamping click reactions were all done overnight in water–DMSO mixtures and stopped by rinsing in deionized water followed by reoxidizing the PEDOT by rinsing in 10/90 v/v Clevios C-B40/H₂O and rinsing in Milli-Q water. Clicking of 5-iodopentyne to a substrate of PEDOT on PS-N₃: 65/35 v/v DMSO/H₂O, 5 mM CuSO₄, 20 mM sodium ascorbate, 25 mM 5-iodopentyne. Clicking of 5-iodopentyne to a substrate of PEDOT-OH (ester coupled to bromopentanoic acid)/PEDOT on PS-N₃: 65/35 v/v DMSO/H₂O, 1 mM CuSO₄, 10 mM sodium ascorbate, 5 mM 5-iodopentyne. Clicking of perfluorononyl azide to a substrate of PEDOT-N₃/PEDOT on PS-alkyne: 70/30 v/v DMSO/H₂O, 1 mM CuSO₄, 10 mM sodium ascorbate, 5 mM 4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoronyl azide.

Electroclick Reaction Conditions. Electroclick reactions were conducted using a copper plate top electrode, in a setup similar to that of our earlier report.¹⁹ The top electrode was used to ensure a uniform functionalization of the electrodes. The spacing to the top electrode was ~330 μm. One set of PEDOT-N₃/PEDOT electrodes was set to 0.5 V potential and the other electrode set to −0.5 V vs the copper top electrode. For the second reaction the potentials on the electrode sets were swapped. 1 mM alkyne reactant and 1 mM CuSO₄ in 90/10 v/v DMSO/H₂O were used. The reactions proceeded for 5 min using halogen-alkyne marker reactions and for 20 min using alkyne-PEG-(GRGDS) and alkyne-PEG-(GRGDS). Reactions were stopped by rinsing in Milli-Q water followed by reoxidization of the PEDOT by rinsing in a 10/90 Clevios C-B40/H₂O and rinsing in Milli-Q water.

XPS Analysis. XPS experiments were conducted on a Thermo Fisher Scientific K-Alpha (East Grinstead, UK). Large area surface analysis used a 400 μm spot of monochromatized aluminum K α radiation, and survey (pass energy 200 eV) and high-resolution (pass energy 50 eV) spectra of relevant elements were acquired. Line-scan investigations proceeded using a nearly circular X-ray spot of 40 μm diameter and a step size of 30 μm with acquisition of high-resolution (pass energy 50 eV) spectra of relevant elements. This implies that on each 100 μm wide electrode, as well as in each 100 μm wide space between electrodes, there will be at least one measurement point where the detected elemental composition originates entirely from the electrode or the space between electrodes, respectively. Charge compensation was used on all samples. Data analyses of the XPS spectra obtained were performed using the Avantage software package

supplied by the manufacturer. For the line-scan measurements, the elemental composition of each spot was determined from the high-resolution spectra using a fitted peak with a linear background and a signal-to-noise threshold of 0.9.

Contact Angle Measurements. All contact angles were measured using a Data Physics OCA20 contact angle system and dedicated software. Contact angles were measured on at least three different areas of each sample using Milli-Q water as probe liquid. Prior to all measurements, any dust on the samples was blown off by inert gas.

Fibroblast Attachment Studies. Cellular adhesion was tested in a homemade all-polymer microfluidic chamber. 3T3 fibroblast cells were allowed to adhere for 1 h, and unattached cells washed away at a shear rate of 20 Pa. See Supporting Information for further details.

3. PRINTED DISSOLUTION CAN LOCALLY REEXPOSE UNPERTURBED SUBSTRATE CHEMISTRY

Exposure of PEDOT films to an agarose stamp containing aqueous hypochlorite (NaOCl) results in the formation of a chemically stable, transparent, and nonconducting material. We reported earlier how this can be used for making micrometer sized patterns of PEDOT and nonconductive PEDOT.¹⁶ Here, we show that the overoxidized material can be dissolved when a nonionic detergent is added to the stamp or to a subsequent washing step, thereby exposing the chemistry of the underlying substrate. Figure 2 presents the efficiency in removing PEDOT on COC hydrocarbon substrates using unstructured stamps. The effect of applying the detergent Triton-X100 was examined using X-ray photoelectron spectroscopy (XPS) and contact

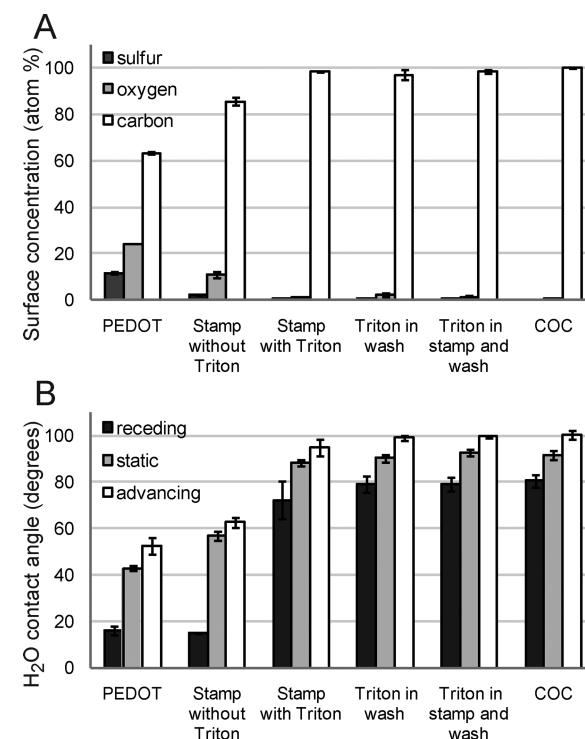


Figure 2. Efficiency in removing PEDOT from polymer (COC) substrates by printed dissolution using planar (unstructured) agarose stamps with or without added detergent (Triton X100) in the oxidant-containing stamping solution or/and in the washing step. (A) Surface elemental composition determined by XPS analysis. (B) Advancing, receding, and static water contact angle analysis. Error bars show the standard deviation of three independent experiments. The left-most and right-most data points represent analysis performed on untreated PEDOT films or on uncoated COC, respectively.

angle analysis. PEDOT-on-COC samples stamped without the use of detergent were found to be hydrophilic and to contain significant amounts of oxygen and sulfur. These properties were observed to be largely invariable over macroscopic length scales (centimeters). The addition of detergent either in the stamp and/or in a subsequent wash resulted in the dissolution and removal of the stamped films. The surface chemical characteristics of the samples then closely resembled those of the underlying COC.

Various solvents were also assessed for their ability to dissolve the overoxidized PEDOT-type films. The films were observed to be resistant to a number of commonly used polar solvents such as water, ethanol, isopropanol, *n*-butanol, acetone, acetonitrile, and 1,4-dioxane. Overoxidized PEDOT-N₃ films, being light-brown in visual appearance, could be thinned by immersion in DMF or DMSO as evidenced by a gradual decrease in light absorption. XPS confirmed that a majority of the overoxidized film was indeed removed. This corresponds well to our earlier finding that PEDOT and especially PEDOT-N₃ undergoes strong swelling in DMSO.²⁷ The fabrication of all-polymer microsystems requires a dissolution system that dissolves the overoxidized material without affecting other polymer components. Since DMF and DMSO dissolve a wide range of polymers, including the functionalized polystyrenes used later in this work, their generic applicability for removing the overoxidized PEDOT material is limited. Addition of just small amounts of water to the DMSO prevented the modified polystyrenes from dissolving. This possible solution was investigated by measuring the ability of DMSO/water mixtures with up to 90 vol % DMSO to remove the overoxidized PEDOT and PEDOT-N₃ material (see Supporting Information Table S1). Higher DMSO concentrations dissolved the overoxidized PEDOT more effectively, but measurable amounts of overoxidized PEDOT remained on the substrates even at 90/10 v/v DMSO/water. In addition, the use of DMSO/water mixtures may not be applicable to other polymer materials with higher solubility in DMSO.

The mild reducing agent sodium ascorbate was added to the Triton-X100 wash to maintain the PEDOT films in a partially reduced state in which tosylate could be observed by XPS to be removed from the film and replaced by other anions. This was found to aid the dissolution of the overoxidized PEDOT on some substrates. Following this reductive wash, the non-contacted PEDOT film was easily reoxidized to restore the native fully p-doped state containing tosylate counterions by immersion in an aqueous solution of Fe(III) tosylate.^{5,18,27}

Triton-X100 washing solutions without this reducing agent, or even containing a mild oxidizing agent, in most cases had an equivalent effect. The reducing agent was found mainly to be of importance for removing overoxidized PEDOT-N₃ (see Figures S4 and S5), but for analytical consistency the same washing procedure was used for all samples. An additional 80/20 v/v DMSO/water wash was also applied to all samples for consistency in comparing the results, although this step was generally only required in the absence of detergent (see Tables S1 and S2 and Figures S4 and S5). Figure 2 shows that the detergent may be introduced with equal success during stamping or during washing for the PEDOT-on-COC system. This indicates that the detergent is simply aiding the dissolution of the overoxidized product, rather than directly influencing the oxidation process. For other polymer substrates such as PS-N₃ (poly(4-(azidomethyl)styrene)), the addition of Triton-X100 in the stamp was found to be superior to applying it in a

subsequent wash (see Figure S5). This might suggest that the Triton-X100 plays a role in aiding the oxidation of the PEDOT at the PEDOT/PS-N₃ interface, possibly by solvating the overoxidized products during the etching process. In the remainder of this work Triton-X100 was used both in the stamp as well as in a subsequent washing step, unless noted.

The optimized printed dissolution method was employed for producing conductive polymer microelectrode arrays by locally removing PEDOT using a microstructured agarose stamp. The targeted microelectrode design consisted of dual sets of interdigitated 100 μm wide and 3.5 mm long PEDOT electrodes with 100 μm spacing on a COC substrate. The same structural motif was used for all microstructuring in this work. The resulting PEDOT pattern is displayed in Figure 1D, while Figures S1 and S2 show photographs of the tools and samples used, respectively. XPS line scans were performed across the electrodes to analyze their elemental composition, using an analysis spot of nominally 40 μm in diameter. The elemental composition in the middle of each electrode (Figure 3, positions with highest oxygen and sulfur content)

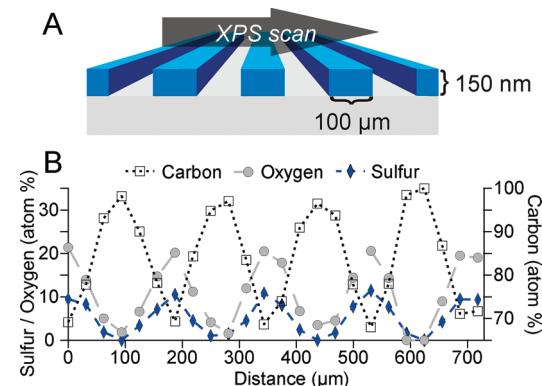


Figure 3. (A) Sketch of PEDOT on polymer (COC) substrates micropatterned by printed dissolution to fabricate 100 μm wide and 150 nm high electrodes (blue) with 100 μm spacing exposing the underlying substrate (gray). (B) Elemental composition across five PEDOT microelectrodes and the exposed substrate between electrodes, as determined by an XPS line scan. Note that the aspect ratio of the sketched microelectrodes is not to scale.

corresponds closely to the elemental composition measured on untreated PEDOT (Figure 2A, “PEDOT”), indicating that the PEDOT electrodes are not influenced by the stamping process. Correspondingly, the elemental compositions measured in the points between the electrodes match that of pure COC (Figure 2A, “COC”). The XPS results confirm that printed dissolution can also be used for locally removing PEDOT on microscopic length scales. PEDOT structures much smaller than 100 μm in width can be made using hypochlorite-loaded agarose stamps as demonstrated for line widths down to 2 μm in our previous work without the use of detergent.¹⁶ Reproducible fabrication of similarly sized features using our current approach may require shorter stamping times and lower NaOCl concentrations than presented here. The studies presented in Tables S3 and S4 show that a stamp contact time of 1 min is equally effective for the detergent aided removal of overoxidized PEDOT on COC as the 4 min generally used in this work. For a stamping time of 4 min, equally good PEDOT removal can be achieved for a 10 times lower NaOCl concentration, while the concentration can be reduced by at least 4 times for a stamping time of 1 min.

Polymer substrates with functional chemical groups can also be locally re-exposed using printed dissolution and subsequently covalently functionalized. Figure 4A shows schemati-

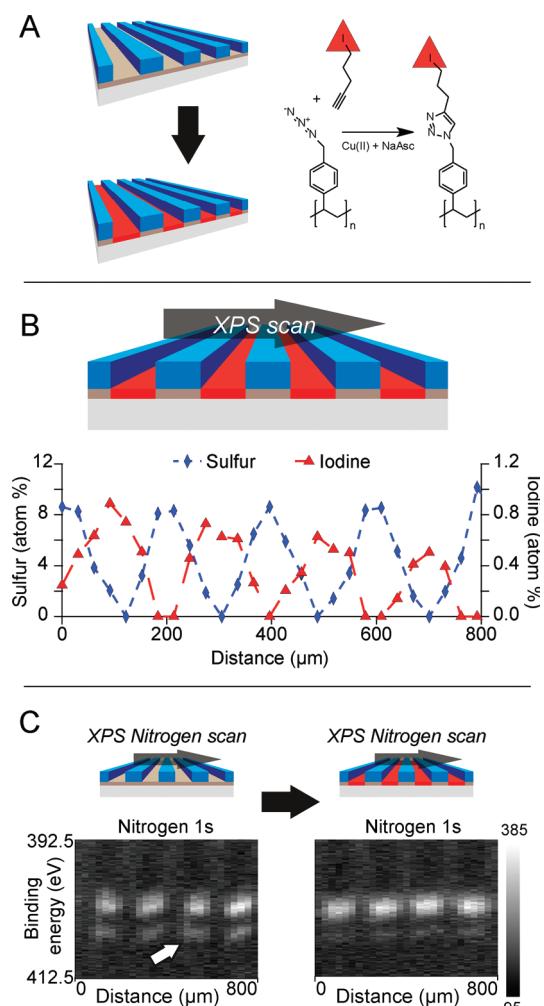


Figure 4. Chemical modification of a re-exposed functional polymer substrate. (A) Re-exposed poly(azido styrene) (PS-N₃) is covalent modified by 5-iodopentyne using click chemistry after patterning a PEDOT film on PS-N₃ into 100 μm wide electrodes. (B) XPS line scan of the elemental composition across five electrodes (for clarity, only the surface concentrations of sulfur from PEDOT and iodine from 5-iodopentyne are presented). (C) High-resolution XPS line scans of the nitrogen peak before (left) and after (right) the click reaction. The initial presence of azides (left) and subsequent reaction into triazoles (right) is revealed by the reduction in intensity of the high binding energy doublet peak (404 eV, white arrow).

cally how the re-exposed azido groups of a PS-N₃ substrate beneath a micropatterned PEDOT film can be coupled to an organic alkyne (5-iodopentyne containing iodine as heteroatom for selective detection by XPS) through click chemistry. XPS line scan analysis of the variation in elemental composition across a number of microelectrodes (Figure 4B) confirmed the successful confinement of the click reaction to the re-exposed areas between PEDOT electrodes by showing spatially alternating peaks from iodine (reacted 5-iodopentyne) and sulfur (PEDOT electrodes). The azido groups of exposed PS-N₃ give rise to a characteristic doublet peak (intensity ratio 1:2) in the high-resolution XPS nitrogen 1s spectra. XPS line scans of the micropatterned PEDOT showed the presence of this

doublet between the PEDOT electrodes (Figure 4C, left), which strongly indicates that the PS-N₃ was exposed without damaging the functional chemical groups. After subsequent reaction with the 5-iodopentyne, the high binding energy peak was observed to decrease in intensity (Figure 4C, right) as expected for the successful click reaction of an azide and an alkyne to form a triazole.

4. MICROPATTERNEDE ORTHOGONAL SURFACE CHEMISTRIES CAN SPATIALLY DIRECT CHEMICAL REACTIVITY

One of the major advantages of PEDOT-type conductive polymers is that small chemical groups can easily be introduced in the monomer unit without disrupting the conductance of the polymer.^{4–6,18,27,28} One example is the commercially available 3,4-(1-hydroxymethylethylene)dioxythiophene (EDOT-OH). We tested the patterning procedure on PEDOT-OH films and found that it was equally effective as for PEDOT. This opens the possibility for covalently attaching chemical functionalities directly to the electrodes as well as to the spaces between the electrodes. Figure 5A illustrates this concept, where a thin film of PEDOT-OH on PEDOT was deposited on a PS-N₃ substrate and then coupled to 5-bromopentanoic acid using standard ester coupling conditions. The modified PEDOT-OH/PEDOT film was subsequently micropatterned using patterned dissolution to locally expose the underlying PS-N₃ that was further coupled to 5-iodopentyne by click chemistry. XPS line scans on the resulting surfaces showed spatially alternating signals from bromine (modified PEDOT-OH electrodes) and iodine (modified PS-N₃ substrate) (Figure S8).

Functionalizing the conductive polymer film before micropatterning has advantages and disadvantages. The major advantages are the simplicity of this scheme and the very low risk of molecules designated for the electrodes to bind unspecifically to the areas between the electrodes. Another advantage is that the same reaction chemistry can be used in series to functionalize both the electrodes and the underlying substrate. Figure S8 shows an example of this approach to provide two different types of chemical functionality to PEDOT-N₃ electrodes on a PS-N₃ background, i.e., two materials with equal surface reactivity. In Figure S8, cell-binding electrodes on a cell nonbinding background resulted from coupling a cell-binding oligopeptide–alkyne onto the unstructured PEDOT-N₃, patterning the film into microelectrodes using patterned dissolution, and final grafting of PEG-alkyne to the areas between the electrodes. The major disadvantage of the approach is that the functionalization of the film with certain types of molecules may influence the stamping procedure, especially if a bulk functionalization is performed.²⁷ Bulk modification of PEDOT-N₃ with hydrophilic molecules such as PEG-alkynes appeared to significantly increase the rate of oxidant diffusion from the stamp into the film. The increase in diffusion rate made the process faster and more difficult to control. Conversely, prior reaction with hydrophobic molecules (a fluorocarbon alkyne) slowed the diffusive process and could prevent the agarose stamp from adsorbing properly onto the film (data not shown).

The use of orthogonal reactive chemistries to add separate surface chemistry on the electrodes and on the substrate was illustrated in Figure 5A. Figure 6A shows a schematic of how to add separate covalently bound functionalities to the substrate and to either set of microelectrodes: A thin film of PEDOT-N₃

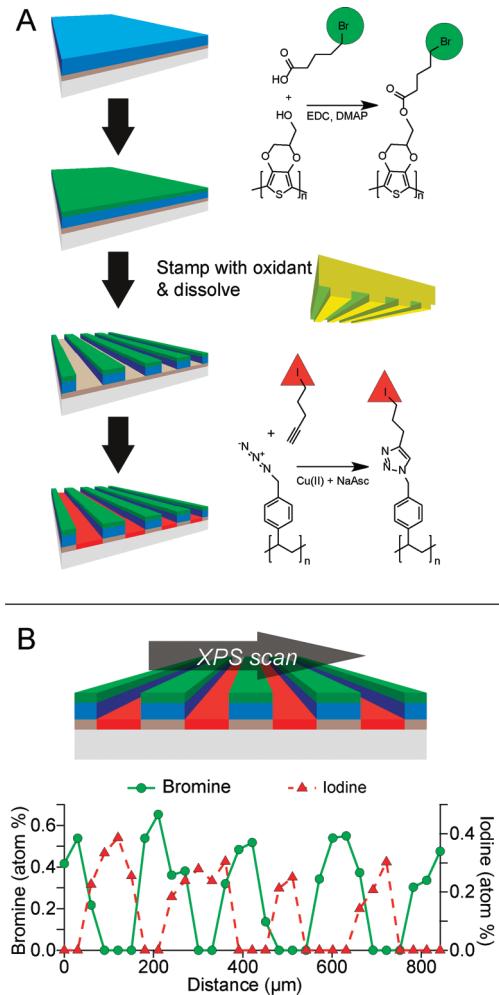


Figure 5. Chemical micropatterning of two types of covalently bound surface chemistry in register. (A) PEDOT-OH/PEDOT on PS-N₃ is modified with 5-bromopentanoic acid (bromine as tracer) using standard ester coupling chemistry. Subsequent micropatterning of the PEDOT-OH/PEDOT film into 100 μm wide electrodes exposes the underlying PS-N₃ substrate for click chemistry coupling of 5-iodopentyne (iodine as tracer) between the electrodes. (B) XPS line scan of the elemental composition across five electrodes (for clarity, only bromine and iodine concentrations are presented).

on PEDOT was deposited on an alkyne-containing polystyrene copolymer substrate (PS-alkyne). The PEDOT-N₃/PEDOT film was micropatterned by patterned dissolution, and the re-exposed alkynes of the PS-alkyne substrate were reacted with perfluoronyl azide to provide fluorine as heteroatom for XPS analysis. Next, electroclick chemistry^{18,19} was sequentially employed to couple 1-bromo-4-ethynylbenzene (bromine as heteroatom) onto one set of electrodes and couple 5-iodopentyne (iodine as heteroatom) onto the other set of electrodes. Thus, in total, three types of localized surface chemistry were introduced. XPS line scans on the resulting surfaces showed spatially alternating signals from fluorine (modified PS-alkyne substrate) and either bromine (modified PEDOT-N₃ electrode set 1) or iodine (modified PEDOT-N₃ electrode set 2) (Figure 6B).

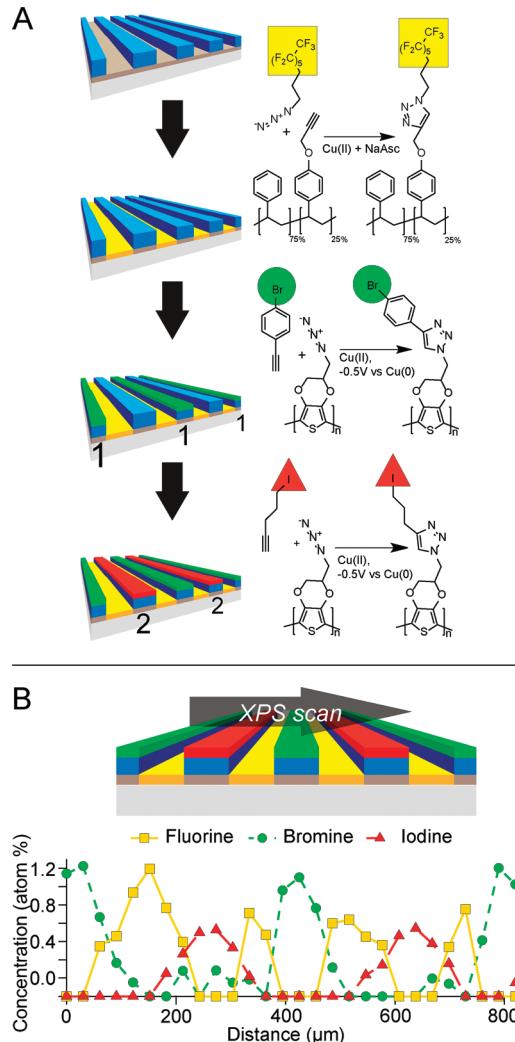


Figure 6. Chemical micropatterning of three types of covalently bound surface chemistry in register. (A) Re-exposed alkyne-functional polystyrene (PS-alkyne) is covalently modified by tridecafluorononyl azide (fluorine as tracer) using click chemistry after patterning a PEDOT-N₃/PEDOT film on PS-alkyne into 100 μm wide electrodes. One set of electrodes (marked "1") is then "electroclicked" with 1-bromo-4-ethynylbenzene (bromine as tracer) followed by electroclicking of the other set of electrodes (marked "2") using 5-iodopentyne (iodine as tracer). Electroclic chemistry is based on the electrochemical reduction of inactive Cu(II) into catalytically active Cu(I) locally at the targeted electrodes. (B) XPS line scan of the elemental composition across five electrodes (for clarity, only fluorine, bromine, and iodine concentrations are presented).

5. MULTIPLE MICROPATTERNED CELL-AFFECTING CHEMISTRIES CAN SPATIALLY CONTROL CELL ADHESION

Macromolecules can also be covalently attached and used for introducing e.g. biological specificity to the systems. We illustrate this by showing how cellular adhesion can be locally and specifically controlled in an all-polymer microsystem. Many cells have been shown to adhere and proliferate on PEDOT-type polymers, and the adhesion is known to be influenced by the redox state of the PEDOT.^{1,9,10} Our aim was to minimize such unspecific adhesion on and between the PEDOT electrodes while presenting specific cell anchoring motifs on designated PEDOT electrodes only.

PEG coatings are widely applied to reduce protein adsorption and cellular adhesion to surfaces. Nevertheless, there are alternatives to PEG and recently (poly(2-methyl-2-oxazoline)) (PMOXA) has received a lot of attention as a promising candidate.^{29–32} Some benefits of PMOXA compared to PEG are greater hydrophilicity and better resistance to oxidative degradation and chain cleavage, thus offering higher resistance to long-term nonspecific protein adsorption.^{29–33}

We anticipated that the stability of PMOXA in oxidative environments would be sufficient to allow a preformed PMOXA film present below a PEDOT film to be exposed and remain functional after stamping. First, the oxidative environment of the printed dissolution process was tested on PMOXA coatings made by reacting PS-N₃ films with an alkyne-terminated PMOXA. XPS analysis showed almost identical elemental compositions of the films before and after stamping (see Table S7). Second, such PMOXA films were coated by PEDOT films and re-exposed upon patterning. The PMOXA films were found to be intact and to contain only small amounts of overoxidized PEDOT, based on contact angle and XPS analysis (see Figure S9 and Table S7). Importantly, the resulting PMOXA films exhibited low binding of cells compared to unmodified PS-N₃ (Figure 7A, top). We also investigated if a similar approach of coupling PEG-alkynes to PS-N₃, followed by PEDOT coating and re-exposure could be employed, but this was not possible. Notably, the failure of PEG coatings apparently did not originate in oxidation of the PEG upon contact with NaOCl: Table S7 shows that the elemental compositions of the PEG films before and after stamping are identical. This suggests that PMOXA and PEG may interact differently with PEDOT either during PEDOT polymerization or during the stamping procedure, which apparently prevents re-exposure of PEG. Useful low cell-binding PEG coatings were instead obtained by coupling a re-exposed PS-N₃ surface with PEG-alkyne after the patterning procedure (see Figure 7A, bottom, and Figure S7).

We used peptides containing the amino acid sequence Arg-Gly-Asp (RGD) that is known to induce specific cellular attachment through the appropriate type(s) of integrin membrane proteins.³⁴ The amino acid sequence Gly-Arg-Gly-Asp-Ser (GRGDS) has been reported to be effective when the RGD motif is placed at the C-terminal of a peptide.³⁴ We synthesized molecules containing this amino acid sequence connected via a short PEG spacer to an alkyne group, the latter being used for coupling the molecule to azide-containing surfaces. Additionally, we synthesized equivalent molecules containing the scrambled amino acid sequence GRDGS. This scrambled sequence is not expected to induce specific cell attachment. The cell binding efficiency of the modified surfaces was evaluated by allowing 3T3 fibroblast cells to adhere for 1 h under stationary flow conditions in a microfluidic setup followed by applying a defined flow for a specified time to detach and remove weakly bound cells. Coupling of the GRGDS-containing peptide to PEDOT-N₃ resulted in a larger number of 3T3 fibroblasts adhering to the surface compared to native PEDOT-N₃ (Figure 7B, top). In contrast, coupling of the scrambled GRDGS-containing peptide resulted in much fewer cells adhering than on native PEDOT-N₃ (Figure 7B, bottom).

We employed the outlined processes to produce an all-polymer microsystem with three types of biofunctional surface chemistries in register, i.e., one electrode set with high cell-binding peptide chemistry, a second electrode set with low cell-

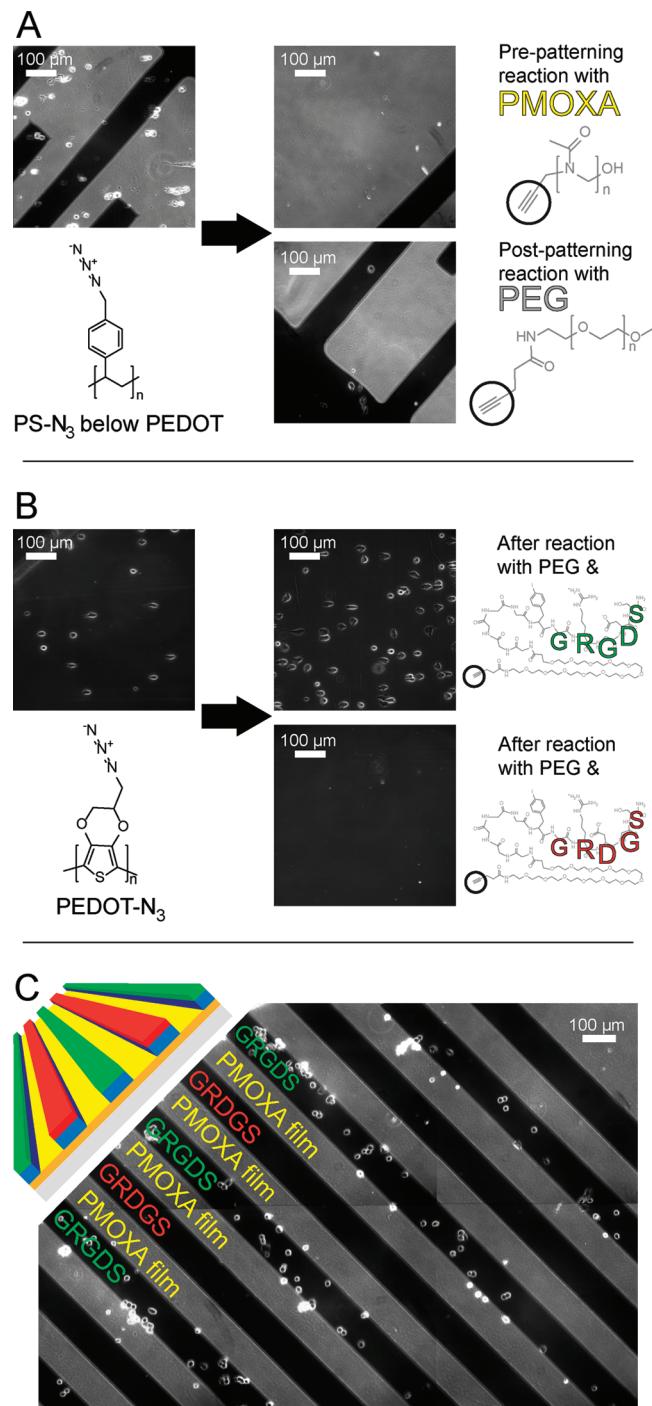


Figure 7. Triple micropatterned biofunctional surface chemistries in register controlling the adhesion of 3T3 fibroblast cells in a microfluidic system. (A) Low cell-binding surface chemistries resulting either from click chemistry coupling of PMOXA-alkyne to a PS-N₃ substrate (left) before PEDOT coating and subsequent reexposure by stamping (upper right) or from click chemistry coupling of PEG-alkyne to a PS-N₃ substrate after PEDOT coating and reexposure by stamping (lower right). (B) Cell adhesion to PEDOT-N₃ films (left) chemically reacted with a mixture of PEG-alkyne and the cell specific peptide alkyne-PEG-GRGDS (upper right) versus a mixture of PEG-alkyne and the scrambled peptide alkyne-PEG-GRDGS (lower right). (C) Specific cellular adhesion to PEDOT-N₃/PEDOT microelectrodes electroclicked with alkyne-PEG-GRGDS versus corresponding PEDOT-N₃/PEDOT microelectrodes electroclicked with alkyne-PEG-GRDGS as well as PMOXA-alkyne re-exposed between the electrodes.

Figure 7. continued

The PMOXA-alkyne was reacted onto an underlying PS-N₃ substrate before coating with the PEDOT-N₃/PEDOT thin film.

binding peptide chemistry, and low cell-binding PMOXA chemistry between the electrode sets. A PMOXA-alkyne functionalized PS-N₃ substrate was coated by a PEDOT-N₃/PEDOT film. The latter film was then microstructured by patterned dissolution to re-expose PMOXA between the resulting microelectrodes. Electroclick chemistry was used to functionalize one set of electrodes with the active GRGDS peptide followed by functionalizing of the other set with the inactive scrambled GRDGS peptide. Figure 7C shows that 3T3 fibroblast cells attached specifically to the GRGDS peptide-coated electrodes while showing no adhesion to the other functionalized sample areas, when the cells were allowed to adhere for 1 h before washing. Control experiments were also performed with GRGDS peptides on both electrodes on a PMOXA background (Figure S6) and on samples without any added functionalities (Figure S8).

6. DISCUSSION

The printed dissolution PEDOT patterning scheme is a simple but versatile tool that enables fabrication of all-polymer microsystems systems with incorporated electrically conductive circuits and various types of in-register localized (bio)-chemistry. The method should also applicable for patterning PEDOT films on nonpolymer substrates. Preliminary tests showed that it can be used, for instance, for patterning PEDOT and re-exposing azide groups on glass substrates that had initially been covered with azides using silane chemistry. On such nonpolymer substrates, and for polymers with high resistance to organic solvents such as DMSO or DMF, our early investigations suggest that the use of detergent can be avoided by washing away the overoxidized material using organic solvents. Substrates presenting other functional chemical groups than the click-reactive azide and alkyne groups used in this work should also have the potential to be “hidden” below PEDOT films and re-exposed upon stamping. The main requirement is that the groups do not oxidize when exposed to hypochlorite during stamping. This should not be the case for e.g. carboxylate groups. Another concern can be strong interactions between the substrate and the (overoxidized) PEDOT, which makes the removal of PEDOT more difficult. Our failure to hide and re-expose PEG-functionalized PS-N₃ may be caused by such strong interfacial interactions.

Patterned dissolution may have other limitations. Previous reports showed that PEDOT can be integrated into a range of polymer substrates by washing with appropriate solvents to induce swelling of the substrate.^{35,36} In our work, all PEDOT-type films resulted from in situ polymerization of an *n*-butanol containing solution of the respective PEDOT precursor. Accordingly, PEDOT is expected to be partially integrated into polymer substrates that undergo significant swelling in *n*-butanol, thereby making it more difficult to remove the PEDOT by patterned dissolution. Polystyrene has been reported to take up 10 wt % *n*-butanol at 65 °C.³⁷ In agreement with this, we observed that spin coating of polystyrene substrates with Fe(III)tosylate in *n*-butanol (the EDOT oxidant solution) resulted in notably more hydrophilic surfaces, even after rinsing with water. This suggests that partial

integration of PEDOT into the outermost part of polystyrene surfaces may occur during EDOT polymerization. Such integration could explain why it was generally more difficult to remove PEDOT from polystyrenes than from COC, this being reflected in the requirement for using detergent directly in the stamp (see Figures S4 and S5). From a practical point of view PEDOT can be removed from the polystyrene surfaces sufficient well to allow introduction of a range of complex surface chemistries, as exemplified in this work. For other types of polymer substrates, PEDOT integration could be a larger problem. We suggest to circumvent this by polymerizing PEDOT from other solvents or at lower temperatures or by polymerizing PEDOT from the vapor phase.³⁸

The conductivity of the pristine PEDOT film was found to be reduced by <25% after patterning and washing with detergent (data not shown), as also observed in our former work on patterned deactivation using a hypochlorite loaded agarose stamp without detergent wash.¹⁶ Thus, the improvement in pattern quality offered by the detergent wash did not affect the conductivity of the remaining PEDOT. The observed reduction in conductivity, still being in the hundreds of S/cm after patterning, is most likely caused by the presence of chlorine vapor in the immediate stamp vicinity. We did not investigate if the covalent functionalization of the PEDOT films leads to an additional decrease in the conductivity. However, in a recent publication²⁷ we found that significant amounts of material could be introduced even into the bulk of the PEDOT-N₃ film, without compromising the conductivity.

The conjugated backbone of PEDOT is a universal feature of (intrinsically) conductive polymers. Correspondingly, over-oxidation of the conductive backbone has been used in numerous other patterning/local deactivation schemes of a variety of conductive polymers.^{13,14,39,40} Our printed dissolution concept essentially exploits that the overoxidation changes the solubility parameters of the conductive polymer, thus likely making the approach applicable for locally removing other conductive polymers and other PEDOT type polymers than those tested here.

Photolithography-based patterning techniques were mentioned in the Introduction as one example of a multitude of other methods to pattern conductive polymers, as recently reviewed by Feng et al.¹³ We will only discuss a few approaches of particular interest to polymer systems with spatially defined surface chemistries. Numerous printing techniques are available for locally adding the conductive polymer to a surface, as opposed to removing it. Prepolymerized conductive polymers or precursors for initiating polymerization have been transferred to various substrates by additive printing, e.g., using microcontact printing.^{13,41} Additive printing requires a substrate surface with high affinity for the printed material, being either an initiator or a conductive polymer. Polymer substrates are typically hydrophobic and nonpolar, which generally results in low affinity for polar conductive polymer materials and associated problems in printing the latter class of materials. In contrast, our approach only requires wetting of the substrate surface by the PEDOT precursor solution during spin-coating and polymerization, and wetting is possible on most substrate materials given an appropriate choice of solvent. Additive printing has a further challenge in achieving high accuracy overlay alignment, i.e., to deposit multiple areas of different types of chemistry in register with sharply defined boundaries between neighboring chemistries. Printed dissolution meets this challenge by actively removing chemically

poorly defined boundary zones between neighboring areas during the dissolution step. The benefits of additive printing techniques and of printed dissolution could possibly be combined, for example, by using high-resolution inkjet printing of an oxidant and a detergent to perform subtractive rather than additive printing of the conductive polymer.⁴²

7. CONCLUSIONS

Printed dissolution is an easy and versatile method for making microelectrodes of PEDOT-type polymers that can be used as a vehicle for in-register micropatterning of multiple types of covalently bound surface chemistry. The method was shown to be applicable for diverse reaction schemes through the introduction of various defined surface chemistries on PEDOT-OH and PEDOT-N₃ electrodes as well as on PS-alkyne and PS-N₃ substrates, either before or after the patterning step. The method was further used as an enabling technology in the fabrication of an all-polymer microfluidic demonstrator system, in which fibroblast cells could be specifically captured onto designated electrodes. We suggest that the general concept of overoxidizing PEDOT and dissolving the overoxidized material is not limited to polymer substrates and that the concept is likely applicable to patterning of other conjugated organic materials than PEDOT-type materials.

■ ASSOCIATED CONTENT

Supporting Information

Quantification by contact angle analysis and XPS of the removal of PEDOT-type films by patterned dissolution on different substrates and for varying process conditions, including different solvents, detergents, stamping times, and oxidant concentrations; XPS analysis of low cell-binding coatings exposed to stamping; optical micrographs of the parts used for electrode fabrication and for the homemade microfluidic chamber; detailed description of cell adhesion experiments and optical micrographs of cell adhesion to other combinations of surface modified materials; experimental details for synthesis of the compounds used. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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