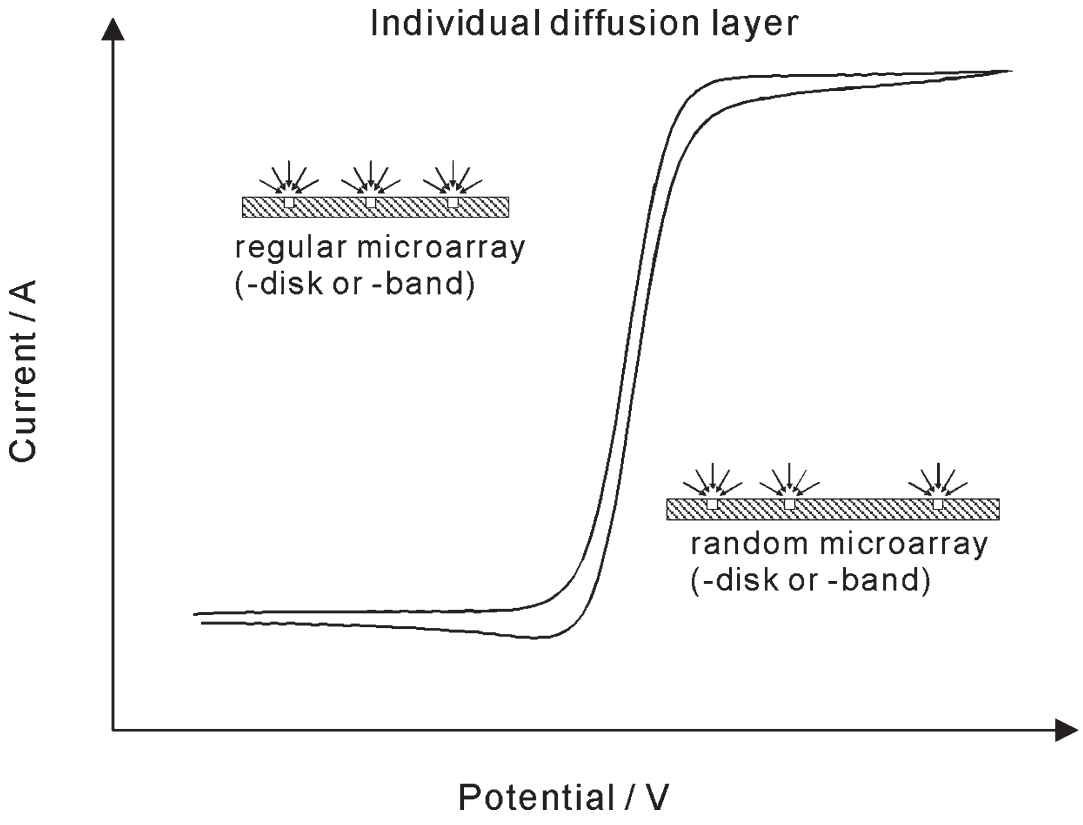
Microelectrode Arrays for Electrochemistry: Approaches to Fabrication

*Xing-Jiu Huang, Aoife M. O'Mahony, and Richard G. Compton**



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Microelectrode arrays have unique electrochemical properties such as small capacitive-charging currents, reduced iR drop, and steady-state diffusion currents. These properties enable the use of microelectrode arrays and have captured much interest in the field of electrochemistry. Techniques for the fabrication of such arrays are reviewed. The relative features and merits of different techniques are also discussed.

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1. Introduction

The size of the electrode affects the mass transport of redox active species to and from the electrode surface and the bulk solution, which consequently influences the observed electrochemical response. In comparison with macroelectrodes (having dimensions greater than 100 μm and commonly on the order of millimeters[1]) and most recently developed nanoelectrodes (having dimensions on the order of a few tens of nanometers[1]), microelectrodes (having at least one dimension less than 100 μm and typically 10–50 μm[1]) have been extensively employed in analytical and physiological applications due to their many advantageous properties, such as small size, low background charging, high current density, and so on. Microelectrode arrays also have gained importance in electrochemical analysis and sensor technology over the past two decades due to their well-known advantages, such as small capacitive-charging currents, reduced *iR* drop, and steady-state diffusion currents.[2,3] They overcome the extremely large current densities yet very small absolute currents of a single microelectrode and have both helpfully high current densities and satisfactory output signals.[4] Several papers concerning the theory and simulation of the microelectrode array behavior of regularly arrayed microdisk and microband electrodes and randomly distributed microband electrode arrays have been published in recent years along with some experimental investigations.[5–12] For example, the use of a regular array of microdisk electrodes wired in parallel can increase the electrochemical window in which one can perform electrochemical experiments while retaining an easily measurable current output;[9] individually addressable microelectrode arrays offer many advantages, such as high spatial resolution, the possibility of sensing multiple analytes using different microelectrodes in the array, and probing signal transmission in a network of biological cells.[13] Owing to this behavior, microelectrode arrays create an opportunity for the integration of living, biological systems into lab-on-a-chip devices, which is very important for in vitro or in vivo biological applications such as enzyme-linked assays and the detection of many other biomolecules.

Microelectrode arrays may be classified as comprising either individually addressable microelectrode arrays[14–16] or as an integrated array[17,18] in terms of how the individual microelectrodes are connected. Various types of array electrodes have been made including planar or recessed microdisk electrode arrays,[18,19] microband electrode arrays,[20,21] interdigitated microelectrode arrays (planar and vertical),[22,23] linear microelectrode arrays,[3] and 3D microelectrode arrays.[24] (Figure 1)

This review examines fabrication techniques for microelectrode arrays developed for electrochemistry. With this work, we complement material in recent reviews on microelectrode arrays mainly concentrated on universal detection platforms,[25,26] applications in environmental analysis,[27] determinations of toxigenic fungi and mycotoxins in foodstuffs,[28] and electroanalytical applications of microelectrode arrays based on vertically aligned multiwalled carbon nanotubes (MWCNTs)[29] or carbon nanofibers.[30] Emphasis is given to fundamental principles and to the features of the different fabrication techniques and related materials. The fabrication techniques included are: i) assembly techniques, such as assemblies of electrode materials and molecular self-assembly; ii) photolithography, such as for metal, carbon, and other electrode arrays; iii) screen-printing technique; iv) direct electrodeposition; and v) modification, such as molecular modification on the array surface or on a hydrophobic block, patterned electrodeposition, and pattern-based carbon nanotube/nanofiber microarrays.

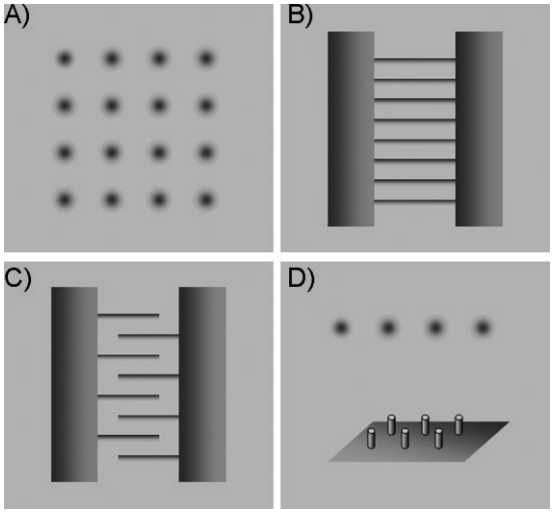

Figure 1. Typical types of microelectrode arrays. A) Microdisk electrode array. B) Microband electrode array. C) Interdigitated microelectrode array (planar and vertical). D) Linear microelectrode array and 3D microelectrode array.

2. Assembly Techniques

Basically, two routes have been explored in this area. One is the assembly of electrode materials (Figure 2), namely, the electrode array is prepared by the assembly of many individual electrode materials (microwire and microband). It is a physical technique. The second one is based on self-assembly of molecules (Figure 3), that is, the array is formed through a chemical self-assembly of molecules on different locations of a flat electrode support.

2.1. Assemblies of Electrode Materials

Compared to other methods for the construction of microelectrode arrays, the assembly of electrode materials has many advantages, such as ready availability of the

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materials (metal: gold, platinum, silver, nickel, etc.; carbon: carbon fiber, carbon paste, graphite, glassy carbon, etc.), relative ease of fabrication, robustness to polishing, and no special laboratory equipment needed. However, it is difficult to create a perfect regular microelectrode array due to the physical nature of the assembly process.

Gold is one of the most frequently used materials for microarray fabrication. For example, Wu[2] fabricated a gold circular microarray by wrapping a piece of gold minigrid (approximately 3×5 mm, the thickness ranges from about 3 to 6 μm, the width is ≈12 μm) of selected size around precast cylinders approximately 3, 4, 5, or 6 mm in diameter (Figure 2B). Bond et al.[31] made an individually addressable 10×10 gold microarray electrode by embedding gold wires in epoxy resin layer-by-layer. Of particular interest is the work of Walt and coworkers,[4,32] who did not directly use gold wire or band to fabricate electrode microarrays. First, a 1-μm layer of gold nanoparticles was deposited around the surface of the individual 25-μm-diameter optical glass fibers. A self-assembled monolayer (SAM) was then formed by immersing the gold-coated fibers into ethanolic solutions containing 11-mercapto-1-undecanol to prevent electrical contact with neighboring ring electrodes. A ring-shaped gold microelectrode array was finally achieved by randomly embedding the above SAM/gold/fibers into an insulating epoxy. As an extension, Walt and Monk[33] sequentially deposited gold in 11-μm-diameter silica capillaries to produce self-assembled 3D gold microtubes and hollow gold microwires. A gold microtube/microwire array was formed by putting many single 11-μm-diameter gold capillaries into 2.2-mm-diameter cylindrical tubing (Figure 2C).

Platinum has also been reported as a material for fabricating electrode microarrays. For example, Evans et al.[34] constructed 10- and 25-μm-diameter microdisk platinum array electrodes using a scale-up of the gold procedure. A platinum wire of 10- or 25-μm-diameter was carefully inserted into a capillary until the platinum reached the end for preparing an individual electrode. Compton et al.[35] fabricated platinum microdisk linear arrays by embedding 29-μm-diameter platinum wires into epoxy resin. Odell and Bowyer[36] fabricated a microband array from metal foil and heat-sealing with fluoropolymer film. Metals such as platinum (25- and 4-μm-thick), gold (10-μm-thick), silver (100- and 25-μm-thick), and nickel (6-μm-thick) foil, glass microscope slides, and Tefzel film were cut with a scalpel and straight edge. The assembly was begun with a glass slide on which were laid four layers of Tefzel film. Then, a strip of foil was laid lengthwise along the top Tefzel film so that 5 mm of the foil extended over each end of the assembly. Alternating layers of Tefzel and foil were used until 10 metal strips had been included.

Carbon electrodes are widely used in electroanalytical chemistry owing to their wide potential window, the availability of surface functional groups for chemical modification, and controllable surface activity resulting from pretreatment.[37–39] Recent works also evaluated the reliability and performance of different methods by assembling carbon materials to form carbon microelectrode arrays. A more efficient preparation of a carbon microdisk array by placing carbon fibers in epoxy resin was highlighted in other works.[40–42] Martin and coworkers[43,44] described a procedure for preparing a carbon microdisk electrode array by filling the pores of microporous host membrane (3, 8, and 13 μm) with carbon paste. O'Hare et al.[45] fabricated a random graphite microelectrode array by mixing graphite powder with epoxy resin. The electrodes were prepared by mounting the composite of graphite and epoxy resin on glass tubing. Magee and Osteryoung[3] fabricated glassy carbon linear array electrodes (≈60-μm-wide) from a glassy carbon plate using a dicing saw. Jin and coworkers[46,47] suggested another way to fabricate carbon microelectrode arrays (Figure 2A). A small amount of mercury was first drawn into a glass capillary. Then about 90 carbon fibers were carefully inserted into the glass capillary at the other end. A low viscosity ethyl α-cyanoacrylate adhesive was applied to the junction of the glass capillary to seal the carbon fiber array to it. The carbon fiber array was connected to a copper wire via the mercury junction by pushing a copper wire down. Ewing et al.[16]

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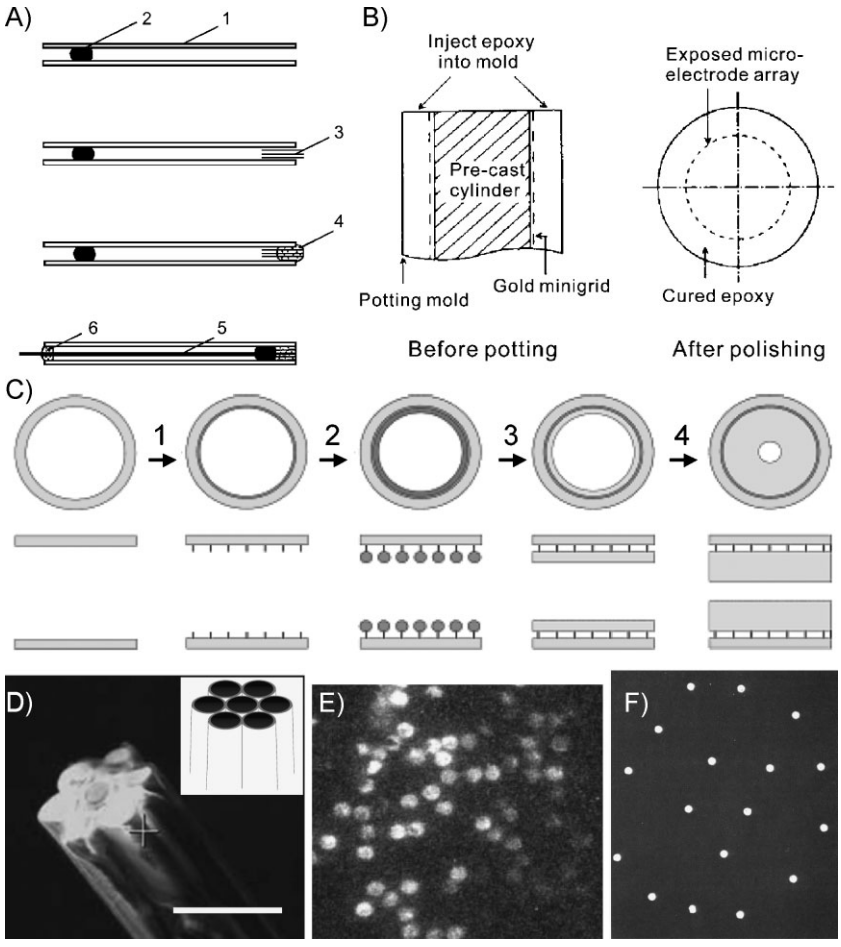

Figure 2. A) Process of manufacturing the carbon fiber microdisk array electrode: 1) glass capillary; 2) mercury; 3) carbon fiber array; 4) ethyl α-cyanoacrylate adhesive; 5) copper wire; 6) epoxy resin. B) Schematic for array construction using gold minigrid. C) Fabrication of a gold μ-tube in a single silica capillary (end and side views): 1) cleaned silica capillaries are modified with a monolayer of bifunctional silane; 2) deposition of a monolayer of colloidal gold on the surface of the capillary; 3) deposition of bulk gold from solution increases the size of the gold colloid, eventually forming a uniform layer; 4) as deposition progresses, the gold thickness approaches the radius of the capillary. D) Scanning electron microscopy (SEM) image of a carbon fiber microelectrode array having seven microdisks. The scale bar is 20 μm. The inset shows a corresponding schematic drawing. E) Microscopy image of white light image of the distal end of gold-coated optical fiber (each fiber is 25 μm), showing a random microring array. F) Microscopy image of 25-μm-diameter platinum disk array (95×). A) Reproduced with permission from Reference [46]. Copyright 1997, Elsevier. B) Reproduced with permission from Reference [2]. Copyright 1993, American Chemical Society. C) Reproduced with permission from Reference [33]. Copyright 2004, American Chemical Society. D) Reproduced with permission from Reference [16]. Copyright 2008, American Chemical Society. E) Reproduced from Reference [32]. F) Reproduced with permission from Reference [34]. Copyright 1990, American Chemical Society.

made a carbon microdisk array by initially inserting carbon fiber into each barrel of a multibarrel glass capillary to create electrodes of two, three, and seven barrels (Figure 2D). The number and the arrangement of the microelectrodes included in the array are preselected by using different multibarrel glass capillaries.

2.2. Molecular Self-Assembly

It is well known that alkanethiols form very stable and well-organized monolayers on gold based on self-assembly and that these monolayers can effectively block electron transfer and mass transport between the electrode and redox couples diffused in the aqueous electrolytes.[48] The array is controllably formed by locations of self-assembly layers of molecules. Based on this principle, the paradigm substrate is gold (Figure 3A). A self-assembled mixed-monolayer of 3-mercaptoproplonic acid (MPA) and hexadecanethiol (HDT) was prepared on a gold electrode substrate by co-adsorption from a mixed ethanol solution of these thiols, and MPA molecules alone can be selectively desorbed from the mixed SAM in a 0.5 M KOH aqueous solution at a scan rate of 0.1 V s^{-1}. This selective desorption has direct application in the fabrication of microelectrode arrays.[49] Liu et al.[50] used the microcontact printing technique to selectively form SAMs on designed areas at the Au electrode surface (Figure 3B). The key step was that the stamp was inked with 10 mM ethanol solution of $HS(CH_2)_{15}CH_3$ and brought into contact with a piece of clean gold substrate for 10 s. A patterned methyl-terminated monolayer was transferred from the stamp onto the gold substrate, leaving an array of bare gold dots that acted as microelectrodes. Homogeneous SAMs (the formation of thiol alkane, $HS(CH_2)_2COOH$) on a gold surface were produced by the inkjet printing technique to form random arrays of disk microelectrodes (Figure 3C) as well as small-band microelectrode arrays (Figure 3D)[51–53].

3. Photolithography

Photolithography refers to a process used in microfabrication to selectively remove parts of a thin film (or the bulk of a substrate). It is based on photoresists (light-sensitive chemicals) and exposure tools equipped with mercury arc lamp illumination sources (producing UV wavelengths of 365 or 436 nm).

3.1. Metal Electrode Arrays

Photolithography is the most widely and currently used technique among several standard lithographic methods to create metal electrode regular arrays. Photolithographic processes require access to a clean room. The detailed procedure is generalized in Figure 4. In order to increase adhesion between the substrate and the electrode materials (100–1000 nm in thickness, Au,[13,19,21,54–72] Pt,[17,18,20,22,62,67,73–78] Ir,[79] etc.), an adhesion layer such as Ti,[20,21,56,57,68,69,71,76,79] Cr,[13,19,22,63–67] Ta,[75,78] Al,[18] Ni–

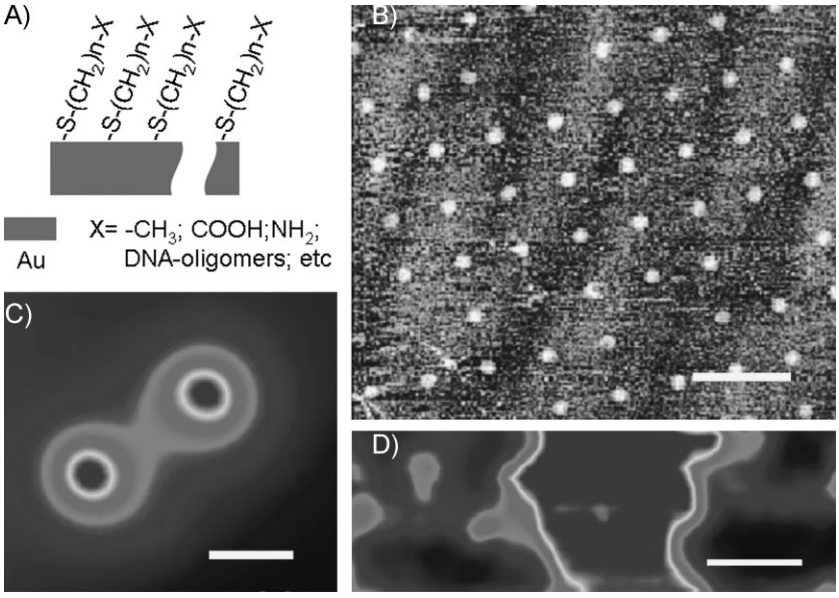

Figure 3. A) Scheme of formation of a SAM. B) Friction force images of the prepared SAM-based microelectrode arrays by microcontact printing. Scale bar: 10 μm. C) Scanning electrochemical microscopy (SECM) images of $HS(CH_2)_2COOH$ ink on gold backfilled with $HS(CH_2)_{15}CH_3$ using 0.5 mM $HS(CH_2)_2COOH$ using an inkjet-printing technique (JPT). Scale bar: 40 μm. D) SECM image of a 300-μm band JPT structure of $HS(CH_2)_{11}NH_2$ embedded in $HS(CH_2)_{15}CH_3$. Scale bar: 200 μm. A,B) Reproduced with permission from Reference [50]. Copyright 2000, American Chemical Society. C,D) Reproduced with permission from Reference [51]. Copyright 2008, American Chemical Society.

Cr,[55] Ti–W,[58] and so on (10–100 nm in thickness) needs to be deposited. The techniques involve thermal vapor or sputter deposition. The layers are patterned using standard photoresist (PR; positive or negative; Figure 4C) with a desired mask (microdisk/microband, linear array, interdigitated array, etc.) and etching (PR: UV light; Au: $4KI/I_2/8H_2O$;[19] Cr: $2K_3Fe(CN)_6/NaOH/8H_2O$;[19] Ti: $10H_2O/HF$; etc.). The PR layer can also be removed by lift-off.[21,80] After removal of the PR, an insulating layer (polymide,[57,65,66] 200–500-nm SiO_2,[20,74] or 600–1000-nm $SiO_2/Si_3N_4/SiO_2$[81]) is evaporated onto the whole surface of the substrate by plasma-enhanced chemical vapor deposition (CVD). The insulating layer is subsequently patterned using another desired mask and etched by reactive ion etching or oxygen plasma. It is worthwhile to point out that smaller structures can be produced using chemical etching rather than using metallo-organics.[62] An alternative way[65,66] to produce an electrode array is to pattern the substrate first and then deposit the adhesion layer and the metal electrode layer (Figure 4B). Dominguez et al.[82] suggested that electrochemical platinum films grown on sputtered platinum contacts can improve the electrochemical performance of microelectrode arrays.

The most important advantage of this technique is that the size, shape, and interparticle spacing of such an electrode array are determined by the requirements of its end application. However, most of the microelectrode arrays were made of metal film, and so their narrow potential window in the negative region may limit their application to reductive electrochemical reactions.[37]

3.2. Carbon Electrodes and Other Arrays

Due to the aforementioned benefits, carbon electrode microarrays have also been constructed using photolithography. In this case, the main problem is the adhesion of the carbon film to the substrate and the low conductivity of carbon film.[23,39] The former results in layers that easily strip off during the microfabrication process and the latter causes a significant *iR* drop after microfabrication.[37] Carbon films are generally radio-frequency (RF) sputter-deposited by the pyrolysis of 3,4,9,10-perylenetetracarboxylic dianhydride in order to improve conductivity.[83–85] Carbon thin films present excellent adhesion to the substrate by a low temperature sputtering deposition process. Because conventional wet-etching procedures on sputter-deposited carbon films have not been successfully developed, a lift-off process or oxygen plasma has been employed.[39] Also of interest is the fabrication of PR-derived carbon post-microarrays by a two-step route including formation of posts of PR (SU-8) under UV exposure and pyrolysis of SU-8 (Figure 5A–C).[24]

Besides a wide potential window, arrays of conductive boron-doped diamond (BDD) electrodes exhibit high stability in the presence of a strong oxidizing species, good chemical and electrochemical stability, and low background current.[86–88] These are especially attractive for electroanalytical applications. A BDD microelectrode array can be fabricated by hot filament/plasma-enhanced CVD and standard photolithography.[86,88–92] Another strategy is to combine microwave-induced plasma growth with laser ablation shaping techniques to prepare and coat a patterned BDD substrate with an intrinsic diamond insulating layer.[87,93] A wide operational potential window is achieved for the BDD microelectrode array with no appreciable redox waves in the potential range −1.50 to +1.70 V versus SCE (a saturated calomel electrode) (Figure 5D).[87] In contrast, the random carbon fiber microelectrode array has a limited potential range in the cathodic region due to oxygen reduction at −0.40 V caused by the copious oxygen evolution at the positive end of the scan, although the cathodic region can be extended to −1.00 V when the anodic potentials are cut at +1.50 V. The cyclic voltammograms show a sigmoidal shape with a constant steady-state limiting current of 1.5 μA across three orders of magnitude of potential scan rates (Figure 5E).[87]

4. Screen-Printed Technique

Unlike photolithography, screen-printing does not need a complicated flow process and its operation is simple.[94] Electrodes are usually made by screen-printing patterns of

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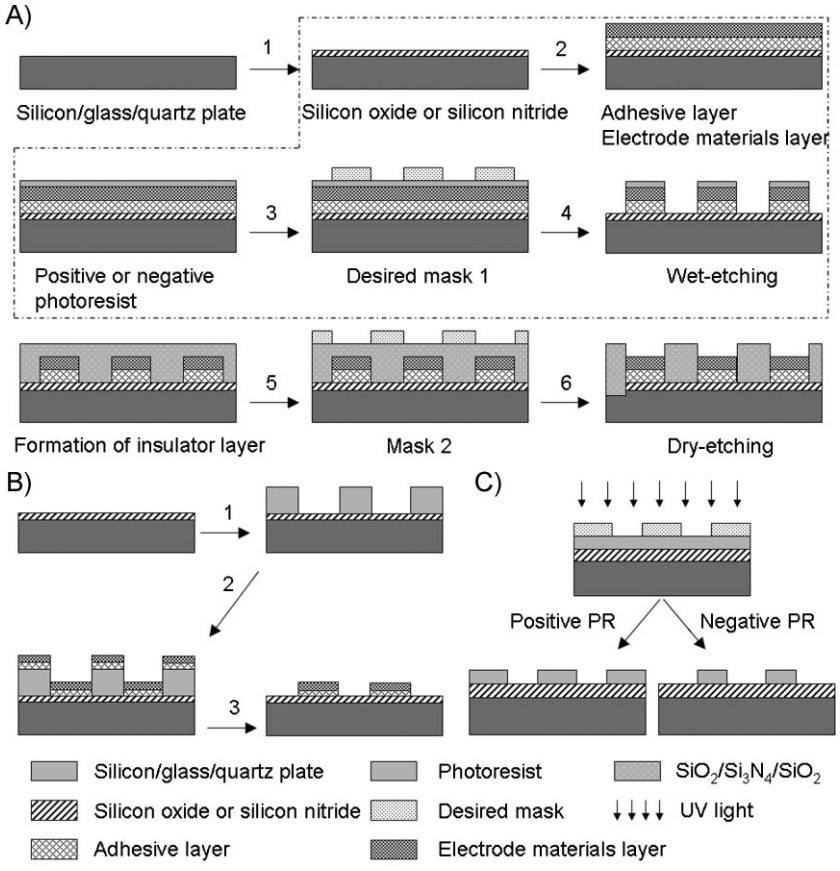

Figure 4. A) Fabrication procedure using standard photolithographic techniques to construct microelectrode arrays: 1) thermal oxidation of silicon in order to obtain a SiO_2 layer for electrical isolation between the substrate and the surface (this step is not necessary if substrates of glass plates are used [55]); 2) an adhesive layer followed by electrode materials was then deposited onto the oxide; 3) after spin-coating the PR, the desired mask 1 containing the pattern for the electrodes and their interconnections covered the surface for the next etching; 4) the wafer was then dipped in successive etching solutions to dissolve metallic electrode materials and adhesive layer; 5) after removal of the PR, an insulating layer was evaporated to the whole surface of the substrate, and the insulating layer was subsequently patterned using a desired mask 2; 6) etching process to create openings of the microelectrode recording sites and the connector pads. B) Alternative way to create a microelectrode array, corresponding to the flow marked by dotted line frame. C) Difference between positive and negative PR under UV light. Reproduced with permission from Reference [55]. Copyright 2006, Elsevier.

conductors and insulators by a special printer. The different desired patterns (microdisk or microband) are defined by precision screens that are made of stainless-steel wire. Ink materials include carbon nanotubes (CNTs),[95] platinum,[96] silver, organo-gold, dielectrics,[94] gold,[97] carbon,[98–105] and graphite.[106–109] Each ink is applied separately with the appropriate screen pattern. The limitation of the screen-printing technique results from the design of a desired pattern and the resulting resolution after photolithography. Screen-printing is also an established technique, however, very few papers have been devoted to the direct fabrication of a microelectrode array.[94] More detailed investigations recently were reported on using commercially available screen-printed electrode arrays.[96,98,99,102–108,110]

5. Electrodeposition

Although electrodeposition is a promising alternative technique for the fabrication of nanostructures such as nanowires,[111] nanotubes,[112] nanorods,[113] nanoflower-like particles,[114] hierarchical nanostructures,[115] and so on, only a few works report on the fabrication of microelectrode arrays in electrochemistry. A random array can be generally created on a prepared substrate by this method. Some of this research has been dedicated to the preparation of an ultramicroelectrode array of gold hemispheres on nanostructured NiAl–Re,[116] gold microhole array electrodes based on a microporous alumina membrane,[117] as well as a random array of silver on a glassy carbon substrate.[118] In comparison with arrays formed by an acoustic streaming directed method, the silver particles are tightly attached to the substrate surface. The advantages of these silver arrays were exemplified in the electroanalytical quantification of halothane (versus silver wire). By considering the importance of electrode supports, patterned electrodeposition has received considerable attention recently, as will be more deeply discussed in Section 6.2.

6. Modification

In order to meet some specific requirements of sensing elements, a modified microelectrode array is often fabricated based on a preformed array. Three kinds of methods can be considered for this scalable fabrication: molecular modification on the surface of a microelectrode array, a hydrophobic block (non-electrode area)-patterned electrodeposition, and pattern-based carbon nanotube/nanofiber arrays.

6.1. Molecular Modification

Even though molecular self-assembly (as described in Section 2.2) and molecular modification possess a similar common feature, namely, a chemical process, unlike molecular self-assembly, molecular modification simply alters a preformed microelectrode array rather than constructs an array on a flat electrode support.

6.1.1. Electrode Array Supports

Molecular modification facilitates the development of a whole range of biosensors and biomicroarray chips. Depending on the end application, the choice of the immobilization technique is extremely important. The control of this step is essential to ensure high reactivity, sensitivity, selectivity, and stability of the surface-confined probe and to avoid nonspecific

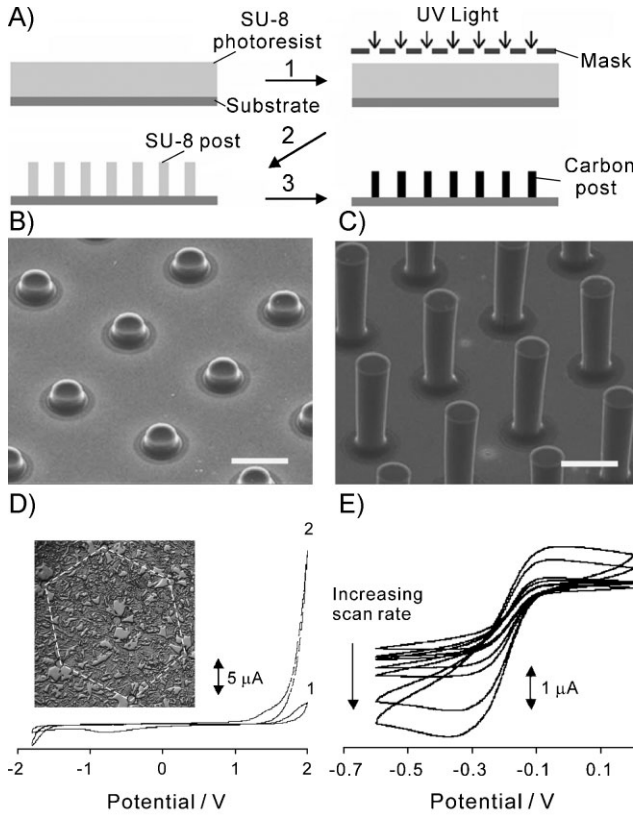

Figure 5. A) Typical process flow for fabricating carbon post-microarrays: 1) after spin-coating on Si substrate, SU-8 is patterned by UV exposure; 2) SU-8 is developed to produce array of posts; 3) SU-8 post-microarrays convert to carbon post-microarrays by pyrolysis. B,C) SEM images of carbon post-microarrays with 20-μm- (B) and 140-μm- (C) high carbon posts. Scale bars: 50 μm. D) Demonstration of the substantially wider electrochemical window on BDD microelctrode array (1) than a random carbon fiber microelectrode array (2). The inset shows a Nomarski contrast optical image of an oxygen-plasma-etched microelectrode array surface showing a well-defined hexagonal unit cell and its polycrystalline nature. The diameter of each conducting BDD disk is 15 μm with a 10× distance between two adjacent conducting elements. E) Cyclic voltammograms of 0.2 mM $(NH_3)_6RuCl_3$ in aqueous solution without added supporting electrolyte, recorded with a BDD microelectrode array at potential scan rates of 0.01, 0.05, 0.1, 0.5, 1, 5, and 10 V s^{-1}, respectively. A–C) Reproduced with permission from Reference [24]. Copyright 2008, Elsevier. D,E) Reproduced with permission from Reference [87]. Copyright 2005, American Chemical Society.

binding of immobilized biomolecules. A general common feature involves two steps: fabrication of the microelectrode array and biomolecule immobilization. Biomolecules can be immobilized on electrode surfaces using electrostatic attraction, covalent immobilization, or ''lock-and-key''-based interactions, such as avidin (streptavidin)-biotin binding (Figure 6). Many different strategies on different supports have been reported in the literature and are briefly described below.

6.1.1.1. Gold Microarray Support: Molecules with thiol end groups can be chemisorbed on gold surfaces. Covalent immobilization uses those molecules with thiol groups as a monolayer to bind many different target molecules on gold supports.[48]

Kraatz et al.[119] used a 20-base-pair double-stranded (ds) DNA and formed equimolar amounts of strands 1 + 2 or 1 + 3 (0.1 mM ds-DNA in 50 mM Tris-ClO_4 buffer, pH 8.7). The 1 + 2 ds-DNA is fully matched, whereas the 1 + 3 ds-DNA contains a single C–A mismatch. The chips proved useful for the detection of single-nucleotide mismatches in unlabeled and prehybridized DNA. Brazill et al.[14] developed a biosensor by electrochemically attaching DNA probes to micrometer-sized regions of the surface of microband gold electrode arrays using biotin-LC-hydrazide (BH). BH was deposited onto each gold electrode through the application of an oxidizing potential. Subsequent attachment of avidin to the biotinylated surface created a ''molecular sandwich'' architecture necessary for further immobilization of biotinylated biomolecules to the surface. A 25-mL drop of 10 mM biotinylated probe DNA was placed over all four electrodes. The probe DNA binds only to the electrodes derivatized with BH and avidin.

Besides DNA, there are a number of other biomolecules (cell, protein, biotin-streptavidin, enzyme, etc.) suitable for modification of gold microarrays. Sheu and coworkers[81,120] plated a 5 × 5 array of gold microdisk electrodes with trypsinized MN9D cells for the in situ temporal detection of dopamine exocytosis from dopaminergic cells, L-dopa-incubated MN9D cells. The gold microelectrode array surface was alternatively coated with collagen solution and subsequently plated with a sample of trypsinized PC12 cell suspension. A real-time detection of the drug effect on dopamine exocytosis from PC12 cells was also studied.[121] Xu et al.[122] selected human IgE and the relative aptamer as a receptor–ligand model system to modify a gold microelectrode array through a hybrid modification by addition of cysteamine, which exhibited rather significant improvements in stereohindrance for binding to the target protein. Chemical modification of aptamers only significantly increases the efficiency of protein binding but also leads to a constant background due to the decrease of nonspecific adsorption. To immobilize XNA on gold microarray surfaces, Xie et al.[123] first modified the gold surface with a SAM that was formed by incubation in a 6-mercaptohexadecanoic acid solution at room temperature overnight. The resulting monolayer was biotinylated using amino-biotin and then saturated with streptavidin. Pishko et al.[124] fabricated glucose, lactate, and pyruvate biosensor arrays based on redox polymer/oxidoreductase nanocomposite thin films deposited on patterned gold microelectrodes. The gold arrays were then functionalized with a negative surface charge through chemisorption of 11-mercaptoundecanoic acid (MUA) followed by the electrostatic assembly of a nanocomposite thin film of cationic osmium redox polymer and anionic oxidoreductases, either glucose oxidase, lactate oxidase, or pyruvate oxidase.

In addition to the aforementioned biomolecule immobilization, research has also focused on non-biomolecule modification. For example, Lopez et al.[125] used two microscopic chemical patterning methodologies (thermodynamic control and electrochemical stripping) to form a SAM of $CH_3(CH_2)_{15}SH$ (C16SH) and $HO(CH_2CH_2O)_6(CH_2)_{11}SH$ (EG6SH) onto a gold microelectrode array. Due to nonspecific adsorption by biomolecules (i.e., EG6S SAMs resist biomolecule adsorption whereas C16S

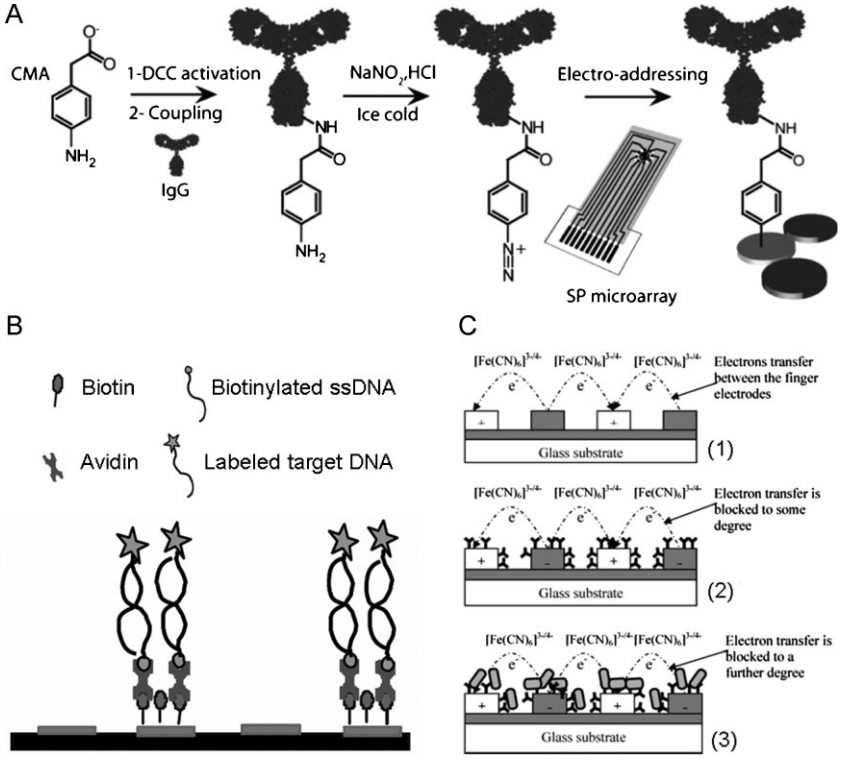

Figure 6. A) Strategy for direct electro-addressing of modified antibody onto graphite electrode surfaces. CMA: 4-carboxymethylaniline; DDC: *N,N′*- dicyclohexylcarbodiimide. B) Schematic representation of the immobilization of biomolecules via BH onto the gold electrode array. BH is selectively electrodeposited, avidin subsequently specifically bound; biotinylated DNA oligonucleotide probes add to the surface-immobilized avidin; fluorescently labeled target DNA specifically hybridizes to complementary probes. C) Principle of the direct impedance immunosensor constructed by ITO interdigitated array microelectrode: 1) bar electrode; 2) antibody immobilization; 3) *E. coli* cell binding. A) Reproduced with permission from Reference [106]. Copyright 2005, American Chemical Society. B) Reproduced with permission from Reference [14]. Copyright 2003, Elsevier. C) Reproduced with permission from Reference [131]. Copyright 2004, American Chemical Society.

SAMs promote biomolecule adsorption), the SAM-based affinity arrays have potential use in chemical and biosensors. Kataky et al.[15] functionalized a gold microelectrode array with thiolated α-, β-, and γ-cyclodextrin nanocavities without spacer groups to ensure close proximity of the cavities to the electrode surface. Hexadecanethiol, dodecanethiol, and hexanethiol monolayers were created on gold microelectrodes array by a series of repeated adsorption and electrochemical desorption steps.[126] A 5,10,15,20-tetrakis-(4-sulphonatophenyl) porphyrin Co(II) modified gold microelectrode array is expected to be a useful tool for electroanalysis and electrocatalysis.[127]

6.1.1.2. Other Microarray Supports

The immobilization of molecules has also been investigated on other microelectrode supports, such as platinum, indium tin oxide (ITO), carbon, and graphite. For example, Uchida et al.[128] modified comb-type platinum microelectrode arrays with Nafion solution. The newly modified microelectrode array exhibited a constant magnitude of direct current under an applied potential and a humidified gas, whereas a drastic change in the current–voltage (*I–V*) profile was observed on exposure to methanol vapor. Bedioui et al.[129] studied NO oxidation on nickel tetrasulfonated phthalocyanine-based film (NiTSPc)-modified platinum microelectrode arrays. An alternative is the immobilization of a mixture containing catalase and glutaraldehyde, or tyrosinase and glutaraldehyde, on a screen-printed platinum electrode array for the amperometric determination of azide.[96]

In another work,[130] Uchida et al. demonstrated the Nafion-modified ITO microelectrode array to be applicable to the selective determination of catecholamines. An anti-*E. coli* antibody-immobilized ITO interdigitated microelectrode array can be used for a label-free electrochemical impedance immunosensor for rapid detection of *E. coli* O157:H7.[131]

Glucose oxidase was immobilized onto carbon post-microarrays via the process of electrochemically polymerized polypyrrole for glucose sensors.[24] A carbon microdisk array served as a host for both glucose oxidase and lactate oxidase.[102] The enzymes are localized electrochemically within the pores of the 15-μm disks of the carbon microarray via co-deposition with rhodium or platinum. Similarly, non-biomolecules can be used for electrode modification. Creasy and Shaw[132] fabricated polishable modified carbon-fiber random microelectrode arrays by matrix modification or ring modification. Matrix-modified electrodes were prepared by copolymerizing vinylferrocene or vinylpyridine along with styrene and divinylbenzene (DVB) to form the composite matrix. For ring-modified electrodes, individual fibers in a bundle were coated with crosslinked poly(vinylferrocene) by electrocopolymerization of vinylferrocene and DVB. The coated fibers were then incorporated into a crosslinked polystyrene matrix. The rings surrounding the disks represent a coating of crosslinked poly(vinylferrocene). An innovative approach is based on the modification of proteins with aniline derivatives (NH_2-Ar-R) and the subsequent diazotation and electro-addressing of the modified proteins at a graphite electrode microarray surface.[106]

6.1.2. Modification of a Hydrophobic Block of a Microelectrode Array

Large amounts of different metals that exhibit signals at electrode surfaces can give rise to one of the biggest difficulties when using an electrochemical technique to measure the quantity of a specific trace metal in solution. The presence of other ''interfering'' metals can lead to unwanted signals. This is of particular relevance in real sample analysis where a wide variety of metals may be present in significant concentrations.[133] A new concept for the preferential removal of these contamination signals is ''diffusional protection'' using liquid–liquid

interfaces as suggested by Compton and coworkers.[133–136] The 5-nonyl-salicylaldoxime,[133,134] *N*,*N*-didodecyl-*N*,*N*-diethylphenylenediamine (DDPD),[135] and dodecane[136] microdroplets were found to immobilize onto the relatively hydrophobic silicon oxinitride blocks rather than the arrayed gold surface to form a partially blocked electrode (Figure 7A and B).[136] Using this partially blocked electrode, the interferant is preferentially absorbed by the regularly spaced droplets on the electrode surface before it reaches the electrode surface, whereas the species of interest is allowed to diffuse unhindered towards the bare electrode surface. Diffusion of interferant towards the electrode is prevented because the droplets act as sinks, setting up concentration gradients that draw interferant to the droplet surface in a Fickian manner, so protecting the electrode from interferant (Figure 7C).[133] A good example is the observation of the reduction peak of Cu(II) at approximately −0.4 V and the corresponding Cu(II) stripping peak at 0 V without interference of As(III) at 5-nonyl-salicylaldoxime-droplet-modified gold electrode arrays, where diffusion of As(III) was effectively blocked towards the electrode surface.[133] The size of dodecane microdroplets of approximately 5-μm diameter immobilized on a regular array and the movement of charge across the surface of the hemispherical DDPD droplets before the bulk material of the droplets is oxidized were further theoretically and experimentally investigated.[136] Figure 7E–H provides another example of cyclic voltammetry of a hemispherical-DDPD-microdroplet-immobilized microelectrode arrays.[135]

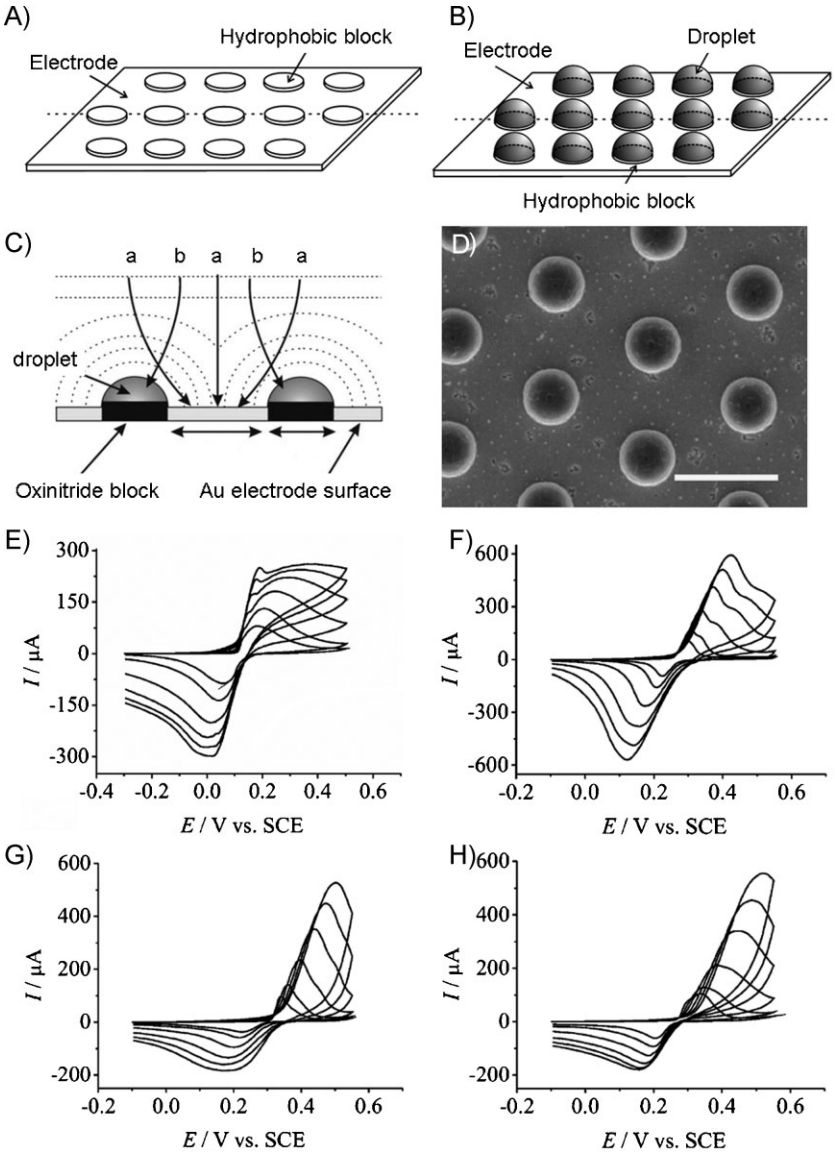

Figure 7. Concept of partially blocked electrode (PBE). A) Schematic illustration of unmodified PBE. B) Schematic illustration of the organic-molecule-modified PBE. C) Scheme showing the "diffusional protection" of a PBE. The interferent *b* is preferentially absorbed into the droplets while the target analyte *a* is left unhindered as it diffuses toward the bare electrode surface between the droplets. The dashed lines indicate the diffusional flux of *b* into the droplets. D) SEM image of a PBE. Scale bar: 10 μm. E–H) Cyclic voltammetry of a DDPD microdroplet on a partially blocked electrode in (E) 0.1 M $NaClO_4$, (F) 0.1 M $NaNO_3$, (G) 0.1 M NaCl, and (H) 0.1 M NaBr at a range of scan rates (0.1, 0.2, 0.5, 1, 1.5, and 2.0 V s^{-1}). A,B) Reproduced with permission from Reference [136]. Copyright 2007, Elsevier. C) Reproduced with permission from Reference [133]. Copyright 2006, Royal Society of Chemistry. D–H) Reproduced with permission from Reference [135]. Copyright 2007, American Chemical Society.

6.2. Patterned Electrodeposition

Patterned electrodeposition (electrodeposition performed on a designed array support) is expected to be a promising technique for fabricating micro-/nanostructures in a "bottom-up" fashion and may have applications in future generations of microelectronics, miniaturized sensors, and microelectromechanical systems.[137] There are generally two ways to achieve patterned electrodeposition. One is via self-organization.[138] The other is template-assisted electrodeposition.[139,140] This review mainly focuses on the latter. After patterned electrodeposition, the new generation of microelectrode arrays exhibit some interesting applications in electrochemistry.

Using a BDD array as a template, a gold-,[141] copper-,[141,142] silver-,[141] and palladium-plated[143] array can be used for arsenic analysis, nitrate analysis, and hydrogen peroxide monitoring. The deposited copper layer is electrocatalytic for nitrate reduction and exhibits an analytically useful range from 1.2 to 124 μM with a marked selectivity for nitrate ion over nitrate salt, with a limit of detection of 0.76 μM,[142] which is possibly the best electrochemical methodology available to date with the analytical range and detection limit being

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equal to or improved in comparison to a number of analytical applications. The palladium-nanoparticle-modified BDD microelectrode array displays a high sensitivity to hydrazine and with a limit of detection of 8 mA mol^{-1} L and 1.8 μM, respectively.[143]

The copper-immobilized gold microarray is electrocatalytic for the electrochemical reduction of sulfur dioxide, which is formed after protonation of sulfite at low pH values (pH < 2).[144] A sensitivity and detection limit of 0.35 nA μM^{-1} and 6 μM, respectively, is shown to be possible at pH 2.5 using linear sweep voltammetry with a linear range observed from 20–500 μM. A similar approach is electrochemical deposition of Zn on TiN microelectrode arrays used for microanodes.[145]

The detection limits of tungsten oxide-modified microdisk arrays of platinum ultramicroelectrodes for the following ions are: $IO_3^- = 0.76$ μM; $BrO_3^- = 2.34$ μM, and $ClO_3^- = 133.2$ μM.[146] The mercury-electroplated, platinum-interdigitated electrode significantly reduces the background current due to hydrogen evolution reaction.[17]

The sensitivity of mercury-plated ITO microelectrode arrays to heavy metal ion Pb^{2+} is 130 nA M^{-1}.[147] The gold-plated iridium nanoband array ultramicroelectrode (6 μm by 0.2 μm, 64-μm interspacing, 100 electrode bands) is capable of the analysis of mercury.[148] For mercury analysis in soil, the detection is in the concentration range of 1–1000 ppm. Each analysis takes about 2–15 min depending on the mercury concentration in the soil. In the case of flue-gas-exposed samples, 8 ppb Hg^{2+} can be reliably measured.

A palladium-particle-modified carbon-fiber microdisk array electrode was employed in capillary electrophoresis for the simultaneous detection of hydrazine, methylhydrazine, and isoniazid.[40] The detection limits for hydrazine, methylhydrazine, and isoniazid were 1.2, 2.1, and 6.2 pg, respectively. The electrochemical deposition of molybdenum oxides by consecutive potential cycles in solutions containing Mo(VI) is a well-established procedure.[55] This oxide film is capable of delivering electrons and mediating the catalytic transfer of oxygen atoms in a highly conductive environment. The efficiency of the modifier in providing catalytic sites for the electrochemical reduction of iodate was demonstrated by voltammetric experiments. Mercury film carbon microelectrode arrays can be used in square wave anodic stripping analysis of lead in blood using indium as internal standard.[105]

The amperometric detection of trace metals in the low or sub-nanomolar range based on a gel-integrated mercury-plated-Ir microelectrode array have been examined by Buffle and coworkers.[149–154] Agarose gel acts as a dialysis membrane, that is, it allows diffusion of small ions and molecules and retains colloidal materials. Chronoamperometry and square wave anodic stripping voltammetry have demonstrated the diffusion properties of heavy metal ions in the agarose gel. It was found that the gel-integrated mercury-plated-Ir microelectrode array enables direct simultaneous determination of the proportion of Zn(II), Cd(II), Pb(II), and Cu(II) in natural waters formed with colloidal complexants and the corresponding complexation parameters by competition with H^+ or metal addition at low added-metal concentrations.

6.3. Pattern-Based Carbon Nanotube/Nanofiber Microarrays

Growing organized carbon nanotubes on large-scale surfaces in a controlled fashion is important for obtaining scaled-up functional devices for use as a microsensor array.[29,155] Combining photolithography with catalytic growth of CNTs via thermal CVD is an effective way to create such a structure (Figure 8). All substrates were patterned with Fe[155,156] or Ni[157–160] films and placed in a cylindrical quartz boat in ethylene gas. The size, geometry, and location of the CNT pillars are precisely defined by lithographic patterning of the catalyst. In vitro stimulation of embryonic rat hippocampal neurons with the CNT microelectrode array after coating with poly(D-lysine) (to enhance cell adhesion to the substrate) has been demonstrated.[156] After selective functionalization of the nanotube ends with primary amine-terminated oligonucleotide probes, the hybridization of less than a few attomoles of oligonucleotide targets can be easily detected. Deducting the upper limit of the number of target DNA molecules, 3.5×10^6 DNA target molecules (≈6 attomoles) are detected.[160] Although excellent results have been obtained, the minimum electrode diameter appears to be 30 μm. As a challenge, Downard and coworkers[161,162] fabricated low-diameter (≤10 μm) vertically aligned CNT microelectrode arrays with controllable

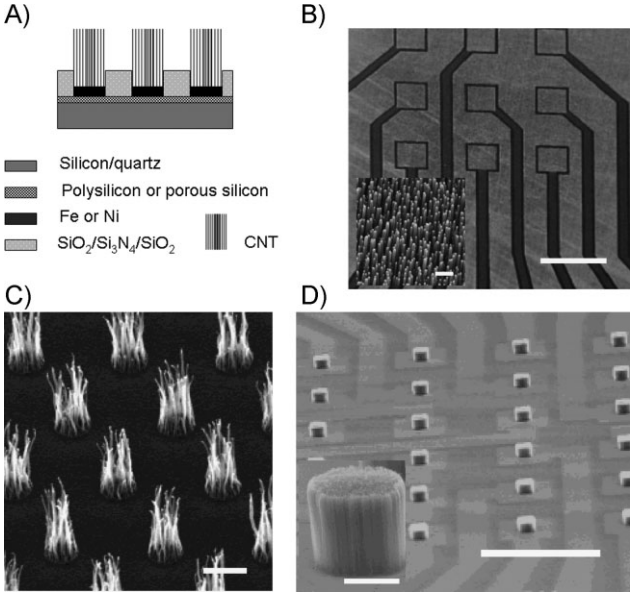

Figure 8. Vertically aligned carbon nanotube microelectrode array. A) Schematic diagram of microelectrode array of vertically oriented carbon nanotubes. B) Perspective view (45 °) of a SEM image of a 3 × 3 microelectrode array, which is ≈200 × 200 μm^2. Scale bar: 50 μm. The inset shows the forest-like vertically aligned MWCNT array on each microelectrode. Scale bar: 1 μm. C) SEM image of array of MWCNTs at Ni spots. D) A 6 × 6 array of 30 × 30 μm^2 CNT pillar microelectrodes. Scale bar: 500 μm. The inset shows a 50-μm-diameter CNT electrode. Scale bar: 25 μm. A,B) Reproduced with permission from Reference [158]. Copyright 2004, American Association for Clinical Chemistry. C) Reproduced with permission from Reference [160]. Copyright 2003, American Chemical Society. D) Reproduced with permission from Reference [156]. Copyright 2006, American Chemical Society.

electrode dimensions and electrode spacing on the conducting carbon film substrate by thermal CVD. Alternatively, Yun et al.[163] synthesized the first high density tower-like MWCNT using water-assisted CVD. The MWCNT tower was then peeled off from the Si substrate and soldered onto pre-patterned printed circuit boards (PCBs). After electrodeposition of gold particles, the CNT microelectrode array can be used for impedance measurements of LNCaP human prostate cancer cells by embedding into fluidic channels. Besides these investigations on pattern-based CNT growth, Keefer et al.[164] found that the CNT-coated ITO microelectrode array enhanced both recording and electrical stimulation of neurons in culture, rats, and monkeys by decreasing the electrode impedance and increasing the charge transfer.

Some recent work has been reported on the use of carbon nanofiber microelectrode arrays made by a similar fabrication process.[30,165,166] Similar studies on electrochemical behaviors show that carbon nanofiber microelectrode arrays can provide a buffering capacity against surface activation/inactivation. Especially for microfluidic-based chemical separation and analysis, the extension of vertical nanofiber elements into a closed channel may offer superior capture efficiency over conventional planar electrodes integrated into the sidewalls of microfluidic separation platforms.[166] Carbon nanofibers consist of stacked curved graphite layers that form cones or "cups," and their chemical properties are quite different from nanotubes. However, at the present time, there is a clear lack of theoretical and experimental data that distinguish the relative electrochemical behaviors of carbon nanotube and carbon nanofiber microelectrode arrays.

7. Summary and Outlook

The different strategies used to fabricate microelectrode arrays for electrochemistry have been reported in this review. When designing an array of microelectrodes, it is often critical to avoid diffusional interference between adjacent electrodes. For microdisk arrays, the center-to-center spacing, d, between individual microelectrodes is crucial and significantly affects the electrochemical behavior. If the interelectrode distance is sufficiently large, the microelectrode array will behave as multiple single electrodes in parallel for a limited period of time. In contrast, when very short interelectrode distances are employed, the individual diffusion fields will merge to form a linear diffusion layer with the entire array structure acting as an electrode. The electrochemical behavior of different arrays with the same relative interelectrode spacing, d/r, where r is the radius, is affected by various parameters including r and the scan rate with the latter dictating in part the time scale of diffusional independence.[167] For optimum performance of a microband array, the array may be designed such that space is used efficiently but the individual microbands behave as isolated electrodes on the time scale of the experiment.[5] Bands must be packed less densely at a random array compared with a regular array to achieve an equivalent level of current sensitivity.[6] The collection efficiency of interdigitated microelectrode arrays is dependent on the average diffusion length of the width of band and gap between adjacent bands.[74]

Finally, it is worth outlining that, although each fabrication method is championed by different groups, in reality there is no "best" method (nor material) for fabrication. All methods have their own specificity and potentials that in many cases do not cover the entire spectrum of the fabrication needs. At the moment, the suitable strategy strictly depends on requirements of electrochemistry (that is, avoidance of diffusional interference) and the surface geometry and features of a particular application (that is, surface modification in electrochemical biosensors). Future development will probably exploit smart combinations of various strategies, which will extend the fabrication potential to a wider class of microelectrode arrays that pave the road to novel devices with excellent electrochemical performance.

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Keywords:

arrays · fabrication · microelectrodes · microtechnology

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