Organic Bionics: A New Dimension in Neural Communications

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This manuscript is dedicated to the memory of Professor Alan G. MacDiarmid

The term "bionics" is synonymous with the term "biomimetics" and in this context refers to the integration of human engineered devices to take advantage of functional mechanisms and structures resident in nature. The use of electrical conductors to transmit charge into and out of biological systems to affect biological processes has been the source of great scientific interest. This has inspired many to explore the possible use of electrical stimulation in promoting positive health outcomes. Advances in medical bionics technology are dependent upon eliciting precise control of the electrical energy to deliver beneficial health outcomes. The advent of carbon-based organic conductors now provides the platform for unprecedented possibilities by which the electrical energy can be used to modulate the function of medical devices. The use of organic conductors in the field of bionics, and in particular medical bionics, as that involved with the development of devices that enable the effective integration of biology (nature) and electronics to achieve a targeted functional outcome is explored.

1. Introduction

Since the early experiments of Galvani[1] and Volta[2], the use of electrical conductors to transmit charge into and out of biological systems has inspired many to explore the possible use of electrical stimulation to influence biological events. What has evolved in the two hundred or so years since Galvani and Volta's experiments is the sophisticated world of medical bionics wherein we strive to build effective connectivity between the biological world and that of electronics. Due to this research field being multidisciplinary, researchers have adopted different terminology to define the convergence of biology and electronics, including bioelectronics, neurotechnology, and bionics. For the purpose of this review, we use the term bionics and explore the use of organic conductors in this exciting field of research.

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Medical bionic devices have been largely targeted towards the primary "excitable cell" systems, muscle and nerve, since it is known that electrical stimulation influences biological events within these systems. Electrical stimulation of nerve tissue has now become widely employed in the treatment of acquired or hereditary neural defects by prosthetic neural implants such as the Cochlear electrode,[3] which has now restored hearing in more than 180 000 people. In addition, deep brain stimulation electrode protocols have emerged for neutralizing aberrant neural activity in the central nervous system for the treatment of movement disorders[4–6] and more recently, for treatment-resistant neuropsychiatric illness.[7,8]

The electrical stimulation of nerve cells is also employed in neural prostheses for vision[9–11] and limb movement restoration,[12] in clinical therapies for treatment of Parkinson's disease, dystonia, and chronic pain.[13,14] Since the studies on the electrical stimulation of the Vagus nerve,[15,16] there has been increasing clinical interest in the possibility of using this approach for controlling epileptic seizures.[17–20] In all of these applications, an implanted microelectrode array stimulates the neurons and modulates their behavior.

A bionic device consists of several integrated technologies such as electrodes to record and/or stimulate the appropriate cells or tissue, electronics to control the recording and stimulating protocols, and power sources (i.e., batteries). For example, the bionic ear (**Figure 1**) consists of a microphone to pick up sound, a speech transducer to translate the sound into a train of electrical impulses, and electrode housing that hosts the stimulating electrodes. It is the effectiveness of this latter component that determines the performance of all bionic devices. The nature of the stimulating electrodes dictates the construction of the electrode/cellular interface by the biological system and subsequently the ability to effectively transmit charge across that interface.[21,22]

The electrode must be able to effectively and efficiently transfer charge to the appropriate biological target. Furthermore, it must be compatible with the surrounding biological environment, not causing inflammation or infection, and ideally the composition structure of the electrode should be such that the development of an appropriate low impedance injection and inflammation free electrode/cellular interface is encouraged and in fact facilitated.

The electrode materials used for bionic devices are traditionally metallic. For example, platinum (Pt) has been employed in cochlear implant electrodes[3] as well as in most other functional stimulation such as deep brain stimulation (DBS) electrodes[23] and vision stimulator applications.[24] Gold, iridium (Ir) oxide,[25] and alloys of Pt and Ir have also been used for a range of applications.[26–28] Tungsten electrodes have been used for over 50 years to study brain function.[29] Research into utilizing carbon as an electrode material has resulted in a large number of publications outlining the usefulness of carbon nanotubes[30–32] and carbon fibers.[33] Carbon fiber electrodes can provide a lower impedance across the electrode/cellular interface and they are also readily fabricated as electrodes with micrometer dimensions. Further decreases in electrode dimensions can be achieved by etching the carbon fiber tip.[34,35]

While both metallic and carbon electrodes have served us well in the development of bionic devices, their properties are fixed at the time of implantation and they provide little scope in terms of assisting the development of an appropriate electrode/cellular interface.[21]

2. Inherently Conducting Polymers

Another group of conductors, the inherently conducting polymers (ICPs), are organic in nature and have emerged as promising materials for bionic applications.[21,36,37–39] ICPs provide versatility in composition unavailable with traditional conducting materials. This versatility arises from the choice of polymer backbone as well as the diversity in the molecular anionic dopant (A^-) incorporated.

As far as the polymer backbone is concerned, the most studied of the ICPs are the polyanilines (**1**), polypyrroles (**2**), and the polythiophenes (**3**,**4**). The ability to produce the polypyrroles at neutral pH from aqueous media and the fact that they maintain conductivity under physiological conditions (pH = 7 in aqueous media) has meant that, to date at least, this conducting polymer backbone has attracted most attention towards the development of new electrode materials for medical bionics.

Conducting polyanilines are usually prepared from an acidic aqueous media and must be maintained in a protonated state to retain electronic conductivity. This has limited their application in bionic studies. However, at least one functionalized polyaniline (**5**) has proven useful as an integral component in a bionic electrode: when functioning as a dopant in polypyrrole (PPy) (see later).

Unfunctionalized polythiophenes are usually prepared from organic solvents, and they spontaneously de-dope to the more insulating form under physiological conditions rendering them less suitable for bionic electrodes. However, modification of polythiophenes by attaching functional groups (R) to modify solubility and their de-doping and electrochemical properties is readily achievable.[40,41] The polythiophene backbone is more readily functionalized than the polypyrroles or the polyanilines, and with polythiophenes the functionalization can often result in improved processability with a concomitant improvement in mechanical and electronic properties. This is usually not the case for polypyrroles and polyanilines. Given the rich chemistries available with the polythiophene backbone, they are poised to gain more widespread application in bionic studies. Significant progress has already been achieved using poly(3,4-ethylenedioxythiophene) (PEDOT; structure 4) that is electronically stable under physiological conditions.[42–45]

Numerous studies report on the culture of various types of cells such as PC12 cells, fibroblasts, endothelial cells, neuroblastoma cells, glial cells, and a cortical neuron cell line on PEDOT films. Richardson-Burns et al.[42] demonstrated the successful polymerization of PEDOT around living neuronal cells. They showed that the SH-SY5Y neuroblastoma-derived cells remained viable in the presence of 3,4-ethylenedioxythiophene (EDOT) monomer prior to polymerization. Upon electrochemical polymerization, the PEDOT grew around the adhered neural cells forming an intimate connection to the living cells. Peramo et al.[43] successfully deposited PEDOT on acellularized tissue showing smooth, tubular PEDOT structures completely

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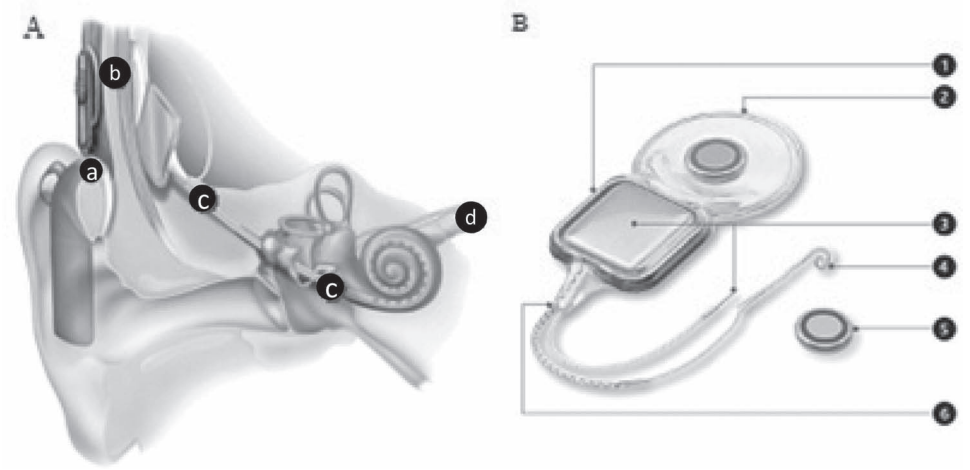

Figure 1. Cochlear implant (bionic ear). Schematic of the internal components of the implant showing the electrode array sitting inside the cochlea (A): a) the sound processor captures sound and converts it into digital code; b) the sound processor transmits the digitally coded sound through the coil to the implant; c) the implant converts the digitally coded sound to electrical impulses and sends them along the electrode array, which is positioned in the cochlea; and d) the implant's electrodes stimulate the cochlea's hearing nerve, which then sends the impulses to the brain where they are interpreted as sound. The CI512 implant showing the internal components of the Nucleus 5 system (B): 1) receiver stimulator in titanium casing; 2) implant coil which enables telemetry; 3) two extracochlear electrodes; 4) precurved perimodiolar electrode array with 22 platinum electrodes; 5) removable magnets for magnetic resonance imaging (MRI) safety, and 6) symmetrical exit leads from casing. Reproduced with permission.[46] Copyright 2011, Bionics Institute.

penetrating and surrounding the tissue fibers. Their results indicate that in situ polymerization occurs throughout the tissue, converting it into an extensive acellular, non-antigenic substrate of interest for in vivo experiments related to nerve repair neural sensing and bioartificial prosthesis. These studies highlight the cytocompatible nature of PEDOT and represent an exciting step towards fully integrated electrode/cellular interfaces.

The molecular dopant A^- makes up a large percentage of the composition of any conducting polymer and so provides a convenient means to manipulate the chemical and biological properties. For example, polypyrrole can be rendered "biological" in nature through the incorporation of appropriate biomaterials such as biological polyelectrolytes.[47,48] Some of the biological polyelectrolytes incorporated into conducting polymers during synthesis are shown in **Figure 2**. In all cases, electrically conductive polymers are produced. An interesting and beneficial consequence of incorporating polyelectrolytes as the dopant is that often gel-like (high water content) electronic materials are formed spontaneously upon formation of the conducting polymer.[49] Polymer structures with lower modulus, as a result of high water content, have an inherent compatibility with living cells.

An interesting approach has been to incorporate a complementary conducting polymer, in particular poly(2-methoxyaniline-5-sulfonic acid) (PMAS), into PPy as the dopant.[50] This system is particularly interesting in that it also provides "softer" gel-like PPy substrates[51,52] and access to multiple electrochemically switching scenarios (via the conducting backbone and the conducting dopant) that can be used to manipulate properties in situ. To date, PPy/PMAS substrates have proven to be highly effective for supporting the differentiation of both primary (muscle) myoblasts[53] and nerve cells,[54] of which the latter can be enhanced by electrical stimulation.

Another exciting feature of the organic conductors is the ability to create the electrode assembly under physiological conditions, permitting fabrication in the presence of living cells to enable their integration into the conducting polymer structures. For example, we have developed protocols that enable integration of intact red blood cells into conducting polymers during assembly of the material.[55] The approach uses a polyelectrolyte dopant that plays a dual role: enabling function of a gel-like (high water content) conducting polymer and acting as a molecular chaperone to facilitate incorporation of the red blood cells. Martin and co-workers developed an ingenious protocol that allows formation of a conducting polymer (PEDOT) in the presence of living cells (neuroblastoma-derived cells) in

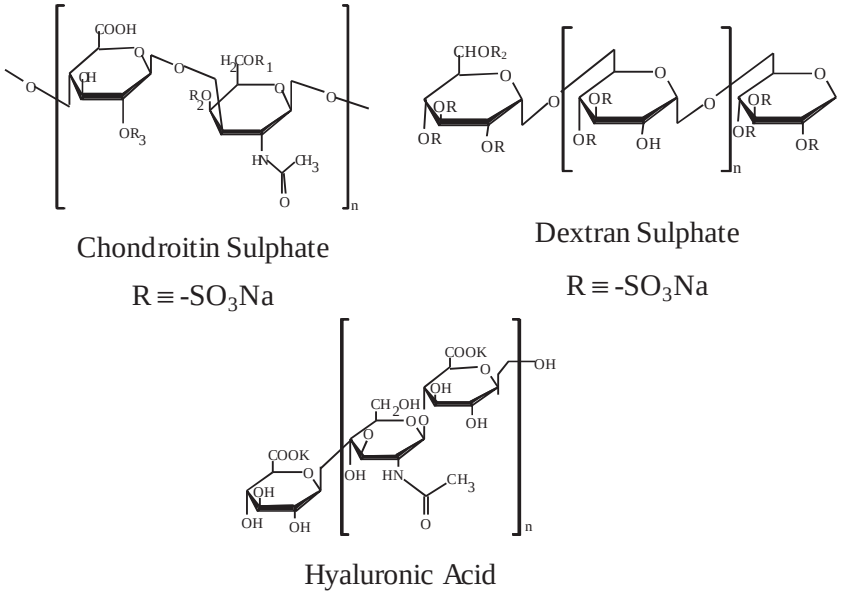

Figure 2. Biological molecules used as dopants for synthesis of conducting polymers.

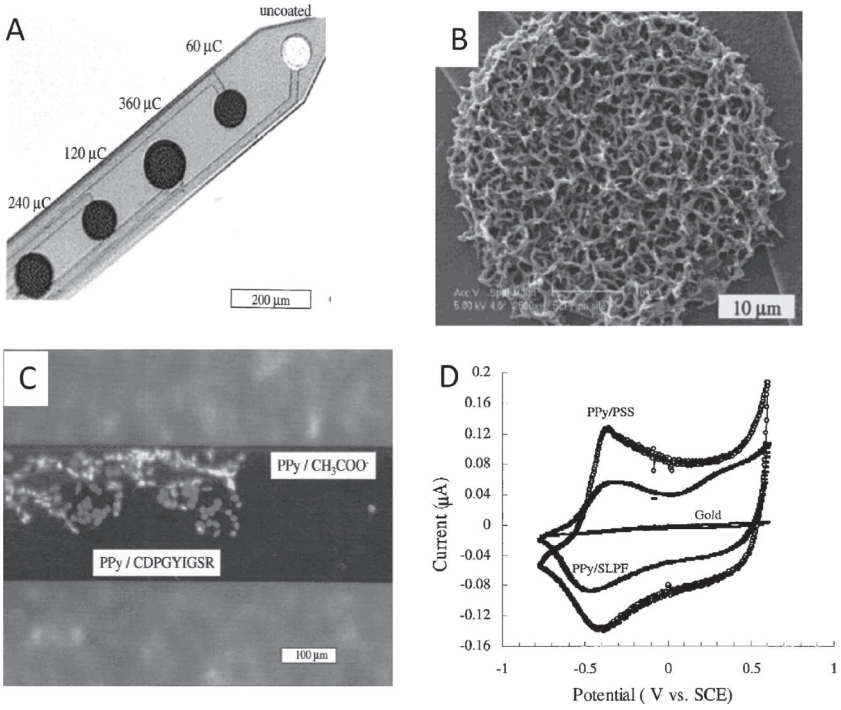

Figure 3. A) Optical microscopy image of polypyrrole/PSS-coated five-channel neural probe. B) Scanning electron microscopy (SEM) images of PPy/SLPP-coated electrode sites (total charged passed, 4 μC). C) Coated neural probe cultured with human neuroblastoma cells. D) Cyclic voltammetry of PPy/SLPP-coated electrode in comparison with bare gold and PPy/PSS.[62] Reproduced with permission.[62]

vitro.[56] Their approach was the first to show the cytocompatibility of in situ polymerization of a conducting polymer with living cells to form a neuroelectrode interface. In addition they showed that the electrical properties (impedance) of these electrodes were 1–1.5 orders of magnitude lower than PEDOT films prepared ex vitro.

The electronic conductivity of these organic materials and a composition that is biological in nature provide a somewhat unique platform for bionic applications. This is a significant step forward; however, organic conducting polymers such as polypyrrole provide further dimensions in endeavours to create more effective electrode/cellular interfaces.

The dual properties of conducting electricity and being able to be rapidly and reversibly switched between different oxidation states bring a new dimension to medical bionics. This switching results in dramatic changes in polymer properties such as surface energy, morphology and even the modulus of the material, imparting physical properties that may be employed to modulate biological behavior(s) in cells. ICP switching also allows uptake and release of dopant ions, which includes bioactive small molecules, protein and/or nucleic acid species, thus providing an avenue for controlled release of bioactive factors.[57]

2.1. ICP Neural Applications

ICP electrodes have been used both to record neuronal signals and/or to stimulate neural events. In terms of stimulating neuronal events the use of a conducting polymer platform provides a synergistic effect in that the same electrical impulses can provide direct electrical stimulation to the nerve cells as well as providing a means of controlled, triggered localized release of bioactive molecules.[58–61]

Using a micromachined silicon-based neural recording probe, a synthetic protein polymer, (silk-like protein polymer, SLPP) or the laminin fragment, CDPGYIGSR, were incorporated through electrodeposition of PPy onto gold electrode substrates (**Figure 3**A,B).[62] The use of SLPP that has multiple cell binding RGD (arginine-glycine-aspartic acid)sequence sites, or laminin fragments, is expected to promote cell growth and adhesion on the electrodes. When the neural probes were seeded with rat glial or neuroblastoma cells, the cells preferentially attached to the PPy/SLPP and PPy/CDPGYIGSR electrode coatings (Figure 3C). The PPy/SLPP coatings showed a lower charge capacity compared to PPy/polystyrene sulfonate (PSS) coatings (Figure 3D) but were still capable of recording good quality voltage signals from single neurons in the cerebellum of guinea pigs. In a different study,[63] the same researchers entrapped an additional laminin fragment, RNIAEIIKDI, into PPy, which had a lower impedance and higher charge capacity compared to the CDPGYIGSR fragment mentioned above. Importantly, the PPy/peptide composites showed less astrocyte adhesion compared to bare gold electrodes, which is a promising characteristic for controlling the foreign body response elicited by an electrode implanted into tissue.

A potential ICP-based component, albeit in much earlier stages of development for devices aimed at nerve regeneration applications, was recently devised.[61] A hybrid platform consisting of aligned biodegrable poly(lactic-*co*-glycolic acid) (PLGA) wetspun fibers on a PPy conducting layer was assessed as a scaffold to simultaneously augment growth and promote axial alignment of nerve axons. In this system, electrical stimulation via the PPy layer increased the axonal growth front of dorsal root ganglia nerve explants, while the PLA:PLGA fibers promoted axonal alignment. Importantly, schwann cell migration was guided along the axis of the axonal growth, giving rise to the potential that electrical stimulation via this system could modulate proper nerve regrowth.

These examples highlight the breadth of role diversity that ICPs can play as electrode components in bionics devices that are envisaged to span areas such as stimulation (electrical and chemical), recording, and tissue engineering.

More recently, PEDOT was grown around living neuronal cells.[64] The cells remained intact nor were lytic or necrotic after the first 24 h following polymerization. However, the detection of activated caspase-3 after 72 h following polymerization indicated induction of the apoptosis in some of the cells in the PEDOT matrix. The lower impedance in

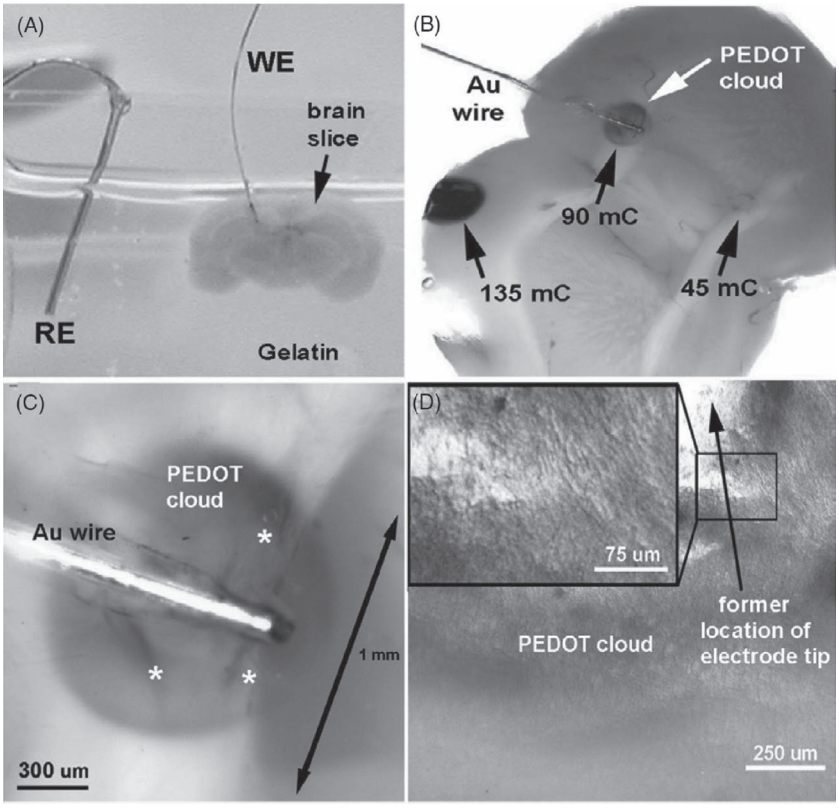

Figure 4. A network of conducting polymer PEDOT filaments polymerized directly within brain tissue from an implanted electrode. Reproduced with permission.[65] Copyright 2007, IOP Publishing Ltd.

these composites (1.3 kΩ at 1 Hz), compared to bare gold electrodes, was suggested to arise from the electrical activity of the embedded cells that may interfere with the signal transduction between the PEDOT and electrode. By going one step further to embed living cells into the conducting polymer matrix, Richardson-Burns et al. introduced a new paradigm for implantable electrodes based on conducting polymers when they polymerized a PEDOT network in situ throughout living brain tissue[65] (**Figure 4**). In this case, the biological constituent of the composite was the living tissue. The PEDOT networks were produced by firstly delivering monomer solutions to electrode sites (Teflon-coated gold wire) implanted into brain slices. During polymerization, the polymer deposited onto the electrode and then grew out into the tissue forming a diffuse cloud of PEDOT. A network of PEDOT interwoven with cells and their extracellular interstices and components, effectively innervating the PEDOT, had impedances <10 kΩ at 1 Hz when operated as the working electrode. From a bionic standpoint, while this is an important aspect of cell/polymer interaction that may find relevance in sensing applications, it must be noted that the integration of the cells within the polymer matrix has the potential to interfere with normal CNS function due to the isolation of neurons within the polymer from supportive cell types. In addition, such integration into CNS tissue does not readily facilitate removal of the polymer mass if or when the embedded cells die, giving rise to the possibility that dead tissue would need to be left behind or that any such removal would damage remaining living tissue and render the sensor inactive.

In previous work, we have shown that neurotrophin 3 (NT3) and brain-derived neurotrophic factor (BDNF) can be simultaneously incorporated into polypyrrole[66] and released using mild electrical stimulation. The delivery of two neurotrophins was shown to greatly increase the proliferation of primary spiral ganglion neuron (**Figure 5**) through the synergistic actions of BDNF that preferentially binds to the TrkB receptor and NT3 that binds to the TrkC receptor of the neuron. Such effects are deemed critical for the survival of auditory neurons in close proximity to an electrode implant.

Similar studies with NGF incorporated, but not released from a PEDOT matrix, has shown to improve the neurite outgrowth of PC12 cells, with impedance values of 15 KΩ (at 1 Hz) recorded for the composites.[67]

Electrical stimulation by ICPs has been shown to promote nerve cell growth, leading to the development of ICPs for a range of implant applications. Our own studies with primary sensory neuronal explants[61] and those of Langer's group[68] have shown that neurite outgrowth on polypyrrole is facilitated by passage of current through the structure. We have also shown that the electrochemical effects on cell growth to be fibronectin dependent,[69] a finding substantiated by Schmidt.[70]

3. Parallel Advances in Fabrication Relevant to Bionic Applications

As with other studies into the tissue engineering of 3D structures, the appropriate spatiotemporal resolution of mechanical, chemical, and biological properties is required in bionics. For nerve or muscle regeneration, a 3D conduit capable of facilitating cell differentiation and proliferation is typically desired. However, bionic technologies entail an added dimension in the form of electrical stimulation capabilities, a feature that amplifies the challenge but is not outside the realms of possibility. For example, advances in a number of processing and fabrication strategies that enable the production of micro- to nanodimensional fibers are showing promise in this area of research. Variation of these fabrication processes engenders new synergies between the materials used for the construction of devices that give rise to biomimetic effects not evident as the sum of the components' individual effects on cells or tissues that they come into contact with. One example of this in our work is the increase in numbers of nuclei per 100 μm of myotube when PLGA microstrucuture was added to PPy doped with PMAS compared to PPy

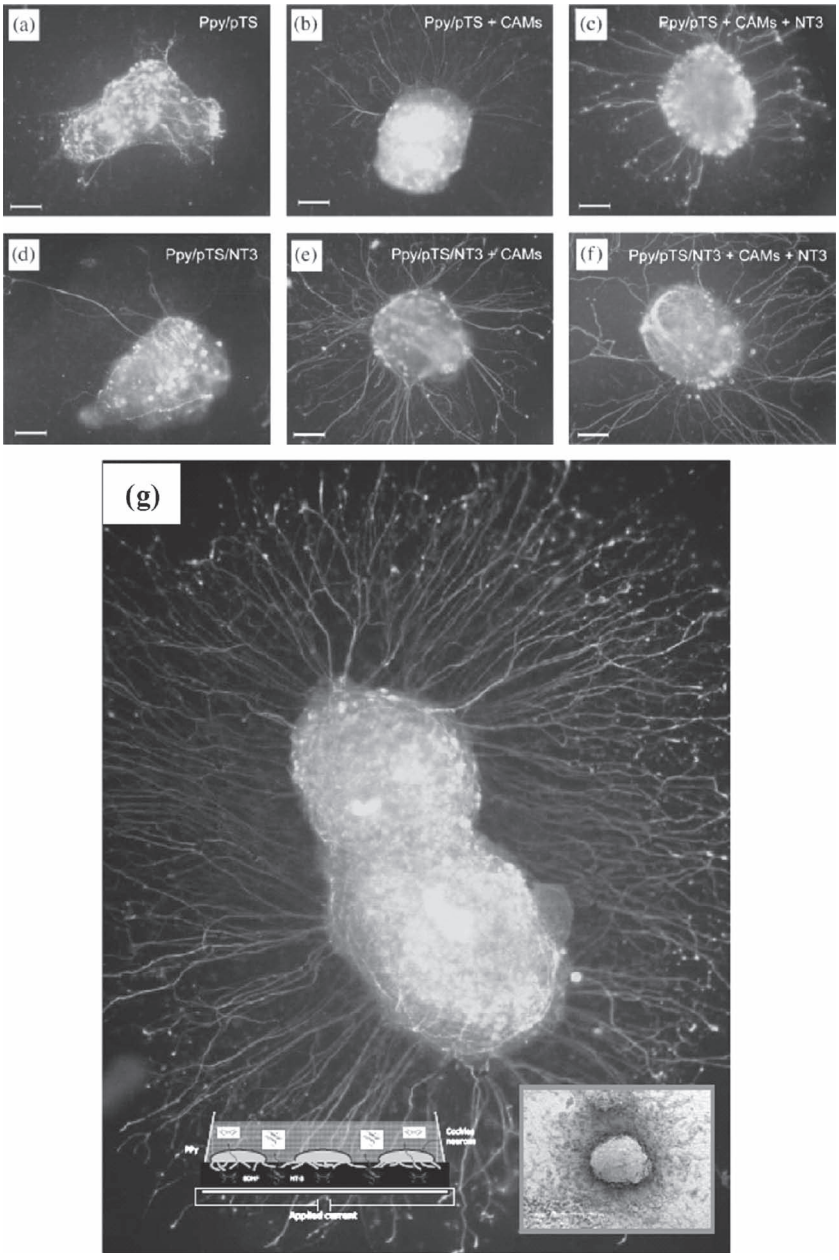

Figure 5. Neurite outgrowth is affected by surface chemistry. Spiral ganglion neurons (SGN) explants were grown on PPy/pTS or PPy/pTS/NT_3, with or without a coating of cell adhesion molecules (CAMs) and in media containing 0 or 40 ng mL^{-1} NT_3. a) Explants grown on uncoated PPy/pTS exhibited poor neurite outgrowth. b) The addition of a CAM coating to PPy/pTS enhanced neurite outgrowth, as did the inclusion of NT_3 in the culture media (c). Compared to PPy/pTS, neurite outgrowth was also improved by incorporating NT_3 into the PPy, exemplified by this explant, grown on PPy/pTS/NT_3 (d). The addition of a CAM coating to PPy/pTS/NT_3 (e) and NT_3 to the media (f) made further dramatic differences to neurite outgrowth. Scale bars are 100 mm. Explant (g) shows significantly increased neural outgrowth when two neurotrophins (NT_3 and BDNF) are delivered in vitro under electrical stimulation. Insets in (g) show a schematic of the electrical stimulation setup (left) and an SEM image of the explant tissue sitting on the drug loaded conducting polymer (right). Reproduced with permission.[59] Copyright 2007, Elsevier.

doped with chondroitin sulfate (CS) or para-toluene sulfonate (pTS) (**Figure 6**).[71]

4. Wet Spinning Microdimensional Fibers of Conducting Polymers

Wet spinning has been used to produce long lengths of micrometer sized polythiophene fibers. For example, PEDOT fibers have been produced by wet spinning[72,73] an aqueous solution of PEDOT/PSS into an acetone containing coagulation bath.[74] The wet spun fibers resulted in good conductivities of ≈1.0 S cm^{-1}. Smooth and straight 5 μm diameter PEDOT/PSS fibers with higher conductivities of 11–74 S cm^{-1} have been fabricated from commercial-based solutions. In this work, the researchers attempted to enhance conductivity by wet spinning the microfibers from PEDOT/PSS dispersions containing ethylene glycol (EG), however this failed due to the EG dissolving in the acetone coagulation bath. However, remarkably, subsequent dip-coating of the PEDOT/PSS fibers in EG increased the conductivities up to 195–467 S cm^{-1}.[75]

Recently, PPy has been rendered soluble through the use of di-(2-ethylhexyl sulfosuccinate) (DEHS) as the dopant (**6**).[76] The viscosity and surface tension of solutions containing PPy/DEHS are such that they are amenable to wet spinning. PPy fibers with good mechanical (ultimate tensile strength = 25 MPa, elastic modulus 1.5 GPa) and electronic (3 S cm^{-1}) properties can be produced. An alternative approach to spinning PPy fibers is the use of a reactive wet spinning protocol.[77,78] This involves formation of the polypyrrole during the wet spinning process. While the latter approach is more generically applicable it is inherently more difficult to optimize and implement. The biocompatibility of the electrically conducting, robust fibers comprising of both an alginate (Alg) biopolymer and a PPy component produced using reactive wet-spinning[78] was demonstrated using PC12 cell culture.[79]

5. Electrospinning Nanofibers of Conducting Polymers

There has also been much interest in the formation of nanofibers using the electrospinning technique,[80–84] which is a straightforward approach for making long polymer fibers with diameters ranging from 100 nm to 2 μm. The method involves dissolving the polymer in a suitable solvent and then applying a large voltage difference between a metal capillary containing the solution (e.g., a syringe) and a target. The target may be a metal foil upon which the nanofibers

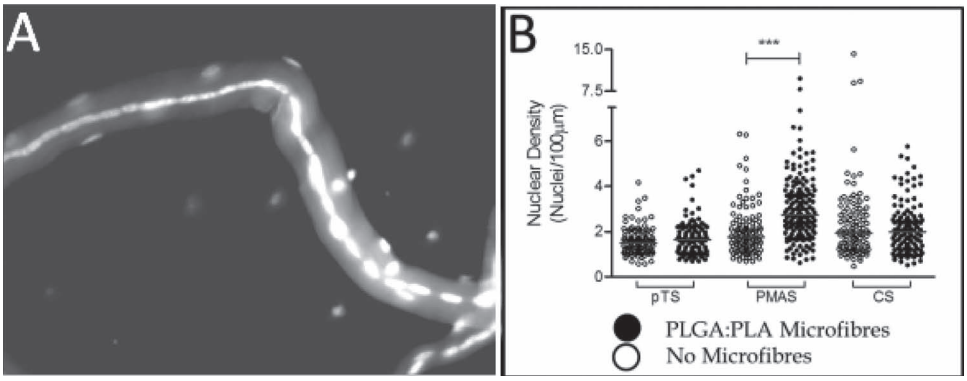

Figure 6. Synergistic pro-myoregenerative effect of PLGA microstructure and PPy-PMAS. A teased regenerating muscle fiber (grey) contains centrally aligned myonuclei (white) immediately juxtapose to each other (A). Plot of nuclear density as a function of ICP composition (B).

deposit. Modifications to the electrospinning method have also been developed in order to align the fibers during the electrospinning process,[81] including studies involving the fabrication of conducting polymer fibers.[84] Considering the dimensions of the electrospun fibers and the types of available topographies, they are well-suited to presenting topographical cues for directional growth in a bionic scaffold.[85]

It is possible to electrospin from soluble PPy solutions. For example, electrospinning has been used to produce 3 μm diameter PPy/dodecylbenzene sulfonic acid (DBSA) fibers in the form of a nonwoven mat and following compression gave conductivities of ≈0.5 S cm^{-1} (e.g., slightly higher than those of powder or cast films).[86] An alternative is to first electrospin the fibers from a chemical oxidant/polymer mixed solution followed by exposure of the fibers to pyrrole vapor.[87] This approach has been used to produce PPy/poly(styrene-beta-isobutylene-beta-styrene) (SIBS) composites as platforms for culturing cells[88,89] (**Figure 7**) with the aligned electrospun fibers providing nanotopographical cues to control the direction of cell growth.

Electrospinning has been employed to fabricate drug delivery systems using conducting polymer elements. Abidian and Martin[90] developed a fabrication process utilizing electrospinning of anti-inflammatory drug-incorporated biodegradable (PLGA) nanofibers followed by the encapsulation of these nanofibers by an alginate hydrogel layer. Polypyrrole was subsequently electrochemically polymerized around the electrospun drug-loaded nanofibers to form nanotubes and within the alginate hydrogel scaffold to form cloud-like nanostructures. Dexamethasone release profiles show that the alginate hydrogel coating slows down the release of the drug, significantly reducing the burst effect.

Nanofibers have also been produced from ester-functionalized organic soluble polythiophenes (poly-octanoic acid 2-thiophen-3-yl-ethyl ester). The electrospun fibers can be subsequently converted to the alcohol form by simple chemistries. Such versatility in the functionality can be built on to improve the compatibility of the fibers with the biological tissue of interest. Electrospun pre- and post-functionalized polythiophene fibers in the form of nonwoven mats or aligned mats, facilitated by a rotating collector drum, were shown to support the aligned growth and differentiation of muscle cells[91] (**Figure 8**A,B).

6. Printing Conducting Polymer Structures

An alternative route to bionic electrode structures involves the formulation of solution-processable ICPs into inks that are amenable to printing. This has attracted significant attention from those currently outside the bionics field but interested in high speed fabrication of printed flexible electronics based on organic conducting polymers.[92–94] It would appear the manufacturing protocol set up for printed organic electronics provides a flexible platform to develop manufacturing protocols for printed bionic devices.

Of the printing strategies currently available, it appears that inkjet printing and extrusion printing provide the resolution and flexibility required to print bionic devices. Inkjet printing technology provides tens of micrometer resolution and the ability to readily produce complex patterns in two dimensions. The applicability of inkjet printing to conducting polymer formulations was reviewed recently.[95]

Inkjet printed films of the conductive polymer PPy have been used for vapor sensing at room temperature by Mabrook.[96]

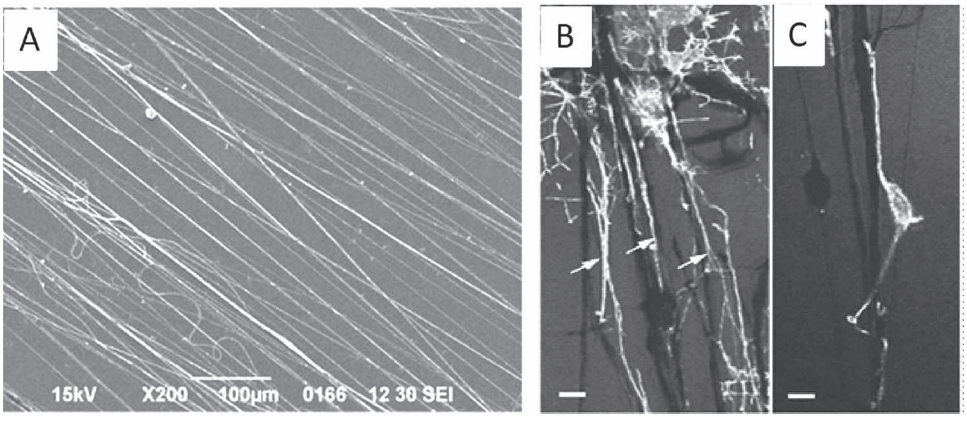

Figure 7. SEM images of aligned PPy/SIBS composite fibers (A). Fluorescence microscopy image showing aligned neurites of nerve cells (B and C arrows) on the fibers (dark lines).[89] Scale bars in B and C represent 10 μm. Reproduced with permission.[89] Copyright 2010.

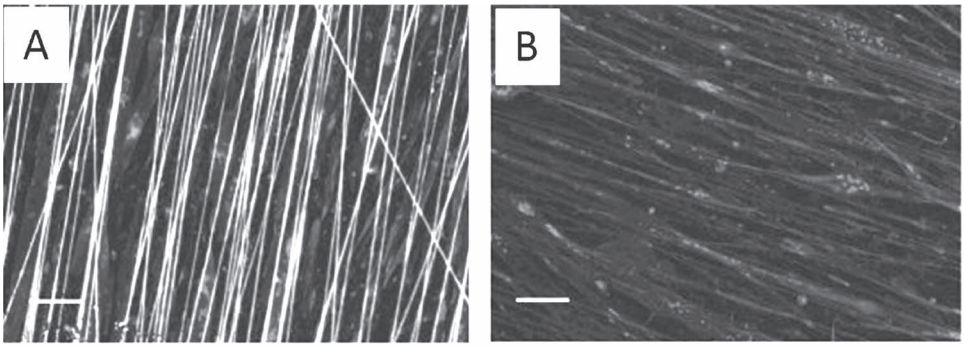

Figure 8. Fluorescence images of differentiated primary myotubes, aligned along medium density aligned fibers of poly(OTE) (A) or poly(HET) (B). Reproduced with permission.[91] Copyright 2010.

A commercial PPy dispersion from Sigma Aldrich (product number 482552) was printed using an HP thermal printer with a resolution of 600 × 600 dots per inch. We have developed cytocompatible polypyrrole based nanoformulations that are amenable to inkjet printing.[97] Inkjet printed tracks have been shown to be effective in guiding the direction of neural cell growth[98] and providing an electrical stimulation platform (**Figure 9**).

7. Inkjet Printing of Polythiophene

Printed structures based on polythiophenes such as PEDOT:PSS have also been produced and used as chemical sensors.[99–101] Polythiophene biosensors have also been fabricated by thermal inkjet printing of PEDOT:PSS and glucose oxidase (GOx) in sequence onto indium tin oxide (ITO) glass.[102] The use of these polythiophene printed structures for cellular interaction studies is yet to be reported.

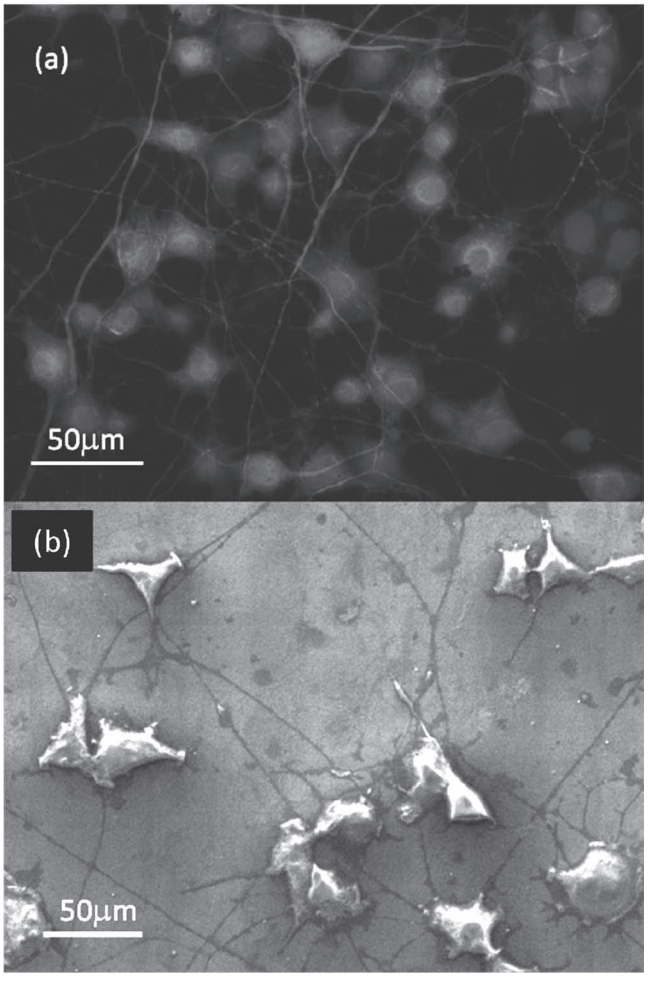

Figure 9. a) Fluorescent images of PC-12 cells on printed PPy film. Scale bar: 50 μm. b) SEM image of PC-12 cells on printed 30 layers film. Scale bar: 50 μm. Reproduced with permission.[98]

8. Printing in the Nanodomain

Dip pen nanolithography (DPN) also deserves mention as a printing technology of the future that is capable of providing nanometer resolution. DPN is a nanofabrication technique[103] that enables patterning of complex biocomposite materials and devices in the nanodomain. Patterning of micro- and nanocircuits based on the deposition of conducting nanomaterials is envisaged as a means to "write" nanocircuitry onto materials and other bionics devices requiring in-house electronics. The possibility of precisely placing biomolecules and chemical gradients onto existing polymers, fiber materials, and printed structures to control cellular interactions at the electrode is also exciting.

DPN operates by using existing atomic force microscopy (AFM) technology to deposit a wide variety of chemicals and materials onto a surface via a sharp probe tip. The probe tip acts as an "ink pen" by transferring molecules to the surface through a water meniscus that forms in ambient conditions as the tip nears the surface. Dot and line patterns with sizes down to 50 nm can be achieved. Alternatively, the liquid deposition method uses a carrier solvent to assist transport of conducting nanoparticles or proteins and together they deposit onto the substrate via physioadsorption processes.

Lu and co-workers have used DPN to pattern conducting polymer by "writing" lines of a commercial PEDOT/PSS ink and demonstrated their use as nitric oxide gas sensors.[104] DPN has also been used in a manner where the ink is composed of monomer/oxidant constituents and the conducting polymer is written as chemical polymerization occurs in situ beneath the probe tip.[105] Electrochemical-DPN is another interesting approach that relies on applying a voltage to the probe tip to electrochemically polymerize the polymer during the patterning process. This has been demonstrated for polythiophene materials on insulating and semiconducting substrates.[106]

Our laboratories have recently explored the development of commercial and "homemade" PEDOT:PSS inks

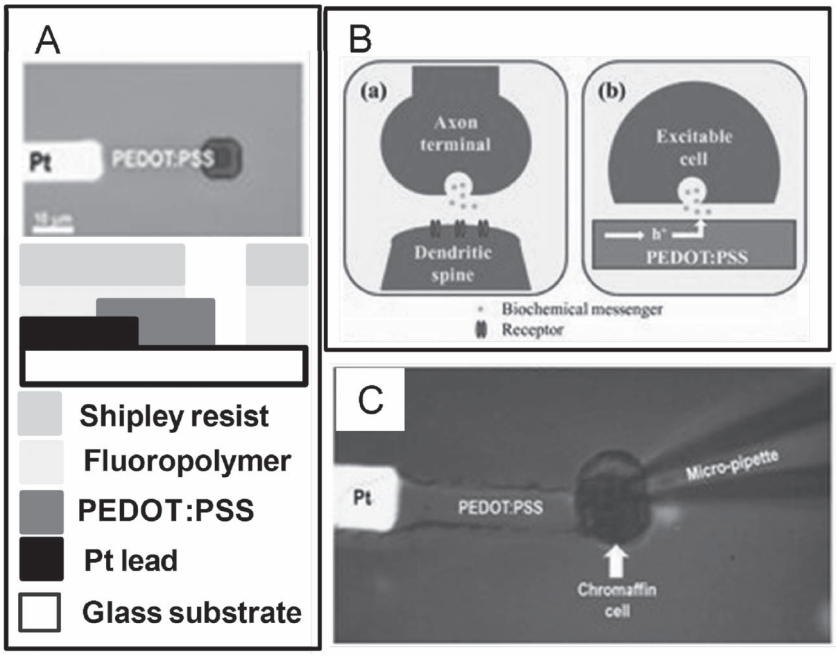

Figure 10. A) Optical microscopy image and schematic side-view of PEDOT:PSS microelectrodes. B) Analogy between a synapse in neurons (a) and a semiartificial synapse at a cell/PEDOT:PSS interface in which transmitter release from the cell results in the flow of a hole (h^+) current in the PEDOT:PSS film (b). C) Optical microscopy image of the test configuration with a single chromaffin cell placed on a PEDOT:PSS microelectrode. The micropipette was used to mechanically stimulate the exocytotic process by gently pressing on the cell. Reproduced with permission.[109]

biosensors, and functional interfaces. At present, other printing technologies such as inkjet printing, extrusion printing, and microcontact printing are the mainstay for producing larger, micrometer-sized conducting polymer patterns on hard and flexible substrates for device fabrication. A better understanding and further development of DPN approaches will enable this technique to be added to the nanofabrication toolkit required to progress a number of important areas of science and technology by filling the void in the sub-micrometer to nanodomain.

9. What the Future May Hold

The future of ICP medical bionics research is full of challenges that will rely upon multidisciplinary research teams to tackle such issues as polymer composition, formulation, and fabrication road blocks. Undoubtedly as we forge ahead in applying these unique ICPs in medical bionics, a wide range of applications and devices will evolve. For example, Malliaras and co-workers[109] have recently used a configuration of PEDOT:PSS and other

optimized for DPN and their printing onto a variety of substrates, including gold/silicon and flexible substrates such as polyethylene terephthalate and silicone gum.[107,108] The development of PEDOT:PSS inks specifically tailored for the operating conditions of DPN (e.g., nanometer scale confinement of the ink) has enabled structures as small as 150 nm to be patterned (**Figure 10**).[108] The feasibility of patterning chemical oxidants for subsequent vapor phase polymerization has also been assessed and has shown promise, with dot diameters and line widths as small as 150 nm being achieved (**Figure 11**).[108]

This work will be of significant interest to electronics research, particularly as recent DPN technological advances, including massively parallel, high-throughput, and large-area capabilities, have the potential to contribute to the areas of printable electronics,

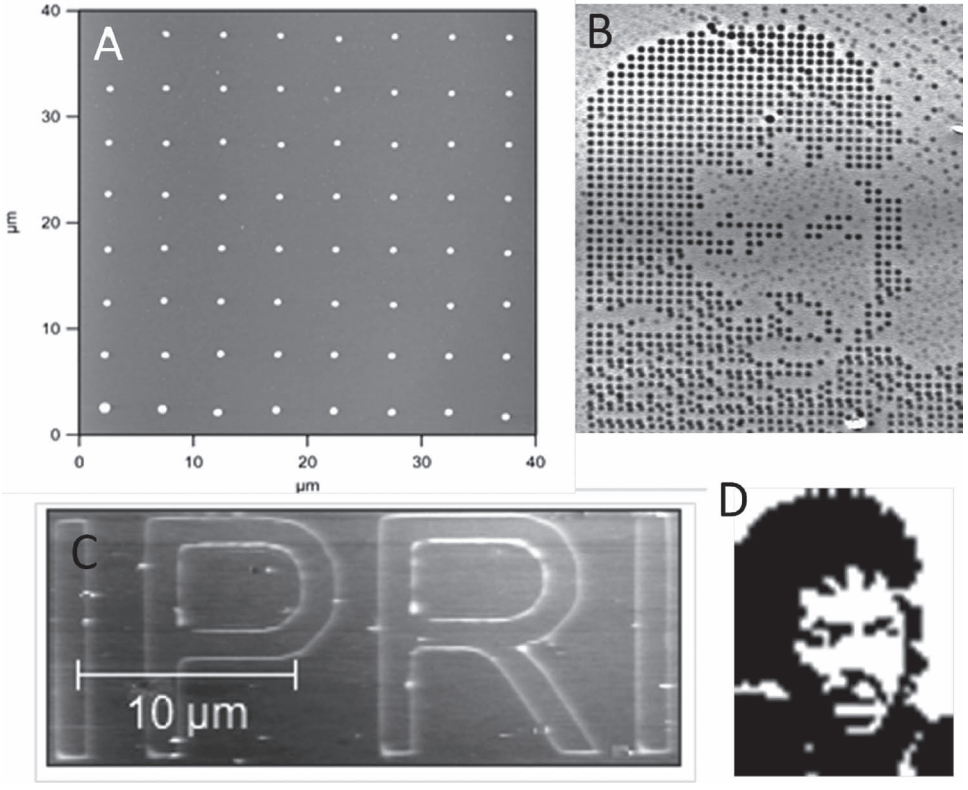

Figure 11. Sub-micrometer patterning of a homemade (A) and modified commercial PEDOT/PSS ink using DPN (B) of a scanned image of Jimmy Hendricks (D). DPN "writing" of the IPRI (Intelligent Polymer Research Institute) (C) using a chemical oxidant ink. Line widths ≈ 100–200 nm.

composite layers to develop a microelectrode sensing device for detecting the release of chemical neurotransmitters from single living cells (Figure 10). PEDOT:PSS films were firstly spin-coated and then covered with an insulating layer, except for a small window exposed by lithography to enable contact with the electrolyte harboring a living cell. The microelectrode area of the PEDOT:PSS ranged from 30–100 μm^2 and was used to amperometrically detect current spikes >100 pA related to catecholamine release when the cell positioned on the electrode was subjected to mechanical stimulation. Interestingly, the device architecture had a significant influence on the background electrode current noise during the measurements. In addition to decreasing the electrode's geometric area, introducing a fluoropolymer interlayer between the conducting polymer layer and insulating layer (i.e., a positive-tone photoresist) as part of the photoresist patterning process reduced the current noise by 60%. The success of the fluoropolymer interlayer lay in the fact that its use avoided direct exposure of the PEDOT:PSS to basic developer solution commonly used in the patterning process and prevented any damage at the PEDOT:PSS/insulator interface.

These conducting polymer based cell devices and others developed by the Malliaras group,[110,111] and other leading groups in the field[112] represent exciting developments that have potential to shape the future of organic bionics.

10. Conclusions

All of the bionic devices discussed above are composed of a stimulating electrode controlled by appropriate electronics that are wired to the electrode within appropriate insulating materials, thus completing the connection to the electrode/cellular interface. While advances in each of these components are critical, here we focused on the electrode/cellular interface and the use of organic conductors as alternatives or complementary materials to metals. We highlighted that the organic conducting materials to be used to provide effective cellular communications must first have appropriate electronic properties, provide high conductivity and low impedance in order to minimize the energy drain required to power the system. In addition low impedance is particularly important for increasing charge-injection capacity so as to avoid potentially toxic, non-faradaic reactions at the electrode/cellular interface. The materials must also have appropriate mechanical properties and as such the future lies with the continued development of flexible electrodes where the conductor itself is flexible or can easily be fabricated into a flexible device.

It is critical that the chemical properties, including hydrophobicity and hydrophilicity, of the conductor should be biocompatible, non-cytotoxic, and sufficiently stable to undergo sterilization without deterioration of the above properties. Long-term material stability (e.g., years) in vivo may also be a requirement. For regeneration bionics, the stability demands are more complex in that the implantable elements of the device should preferably be biodegradable, with no side effects, over an appropriate time frame for the application. Finally and critically, the electrode materials to be used should be processable in such a way that they lend themselves to fabrication into practically useful devices.

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