University of Wollongong

Research Online

Australian Institute for Innovative Materials -
Papers

Australian Institute for Innovative Materials

1-1-2013

Controlled delivery for neuro-bionic devices

Zhilian Yue

University of Wollongong, zyue@uow.edu.au

Simon E. Moulton

University of Wollongong, smoulton@uow.edu.au

Mark Cook

University of Wollongong

Stephen O'Leary

University of Melbourne

Gordon G. Wallace

University of Wollongong, gwallace@uow.edu.au

Follow this and additional works at: <https://ro.uow.edu.au/aiimpapers>

Part of the [Engineering Commons](#), and the [Physical Sciences and Mathematics Commons](#)

Research Online is the open access institutional repository for the University of Wollongong. For further information contact the UOW Library: research-pubs@uow.edu.au

Controlled delivery for neuro-bionic devices

Abstract

Implantable electrodes interface with the human body for a range of therapeutic as well as diagnostic applications. Here we provide an overview of controlled delivery strategies used in neuro-bionics. Controlled delivery of bioactive molecules has been used to minimise reactive cellular and tissue responses and/or promote nerve preservation and neurite outgrowth toward the implanted electrode. These effects are integral to establishing a chronically stable and effective electrode-neural communication. Drug-eluting bioactive coatings, organic conductive polymers, or integrated microfabricated drug delivery channels are strategies commonly used.

Keywords

delivery, neuro, controlled, bionic, devices

Disciplines

Engineering | Physical Sciences and Mathematics

Publication Details

Yue, Z., Moulton, S. E., Cook, M., O'Leary, S. & Wallace, G. G. (2013). Controlled delivery for neuro-bionic devices. *Advanced Drug Delivery Reviews*, 65 (4), 559-569.

Controlled Delivery for Neuro-Bionic Devices

Zhilian Yue^{a,b}, Simon E. Moulton^a, Mark Cook^{c,d}, Stephen O'Leary^e, Gordon G. Wallace^{a*}

^aARC Centre of Excellence for Electromaterials Science (ACES), Intelligent Polymer Research Institute, AIIM Facility, Innovation Campus, University of Wollongong, NSW 2522, Australia.

^bThe HEARing CRC, 550 Swanston Street, Melbourne, VIC 3010, Australia

^cClinical Neurosciences, 5th Floor, Daly Wing, St. Vincent's Hospital, 35 Victoria Parade, Fitzroy, Victoria 3065, Australia

^dDepartment of Medicine, University of Melbourne, St. Vincent's Hospital, 35 Victoria Parade, Fitzroy, Victoria 3065, Australia

^eBionics Institute, University of Melbourne, 384–388 Albert St, East Melbourne, VIC 3002, Australia

***Corresponding Author:**

Prof. Gordon G. Wallace

Email: gwallace@uow.edu.au

Tel: +61-2-4221-3127

Fax: +61-2-4221-3114

Abstract

Implantable electrodes interface with the human body for a range of therapeutic as well as diagnostic applications. Here we provide an overview of controlled delivery strategies used in neuro-bionics. Controlled delivery of bioactive molecules has been used to minimise reactive cellular and tissue responses and/or promote nerve preservation and neurite outgrowth toward the implanted electrode. These effects are integral to establishing a chronically stable and effective electrode-neural communication. Drug-eluting bioactive coatings, organic conductive polymers, or integrated microfabricated drug delivery channels are strategies commonly used.

Keywords: Neuro-bionics, controlled release, organic conductive polymers, drug-eluting coatings, nerve preservation, electrode-neural interfacing, foreign body response

Graphical abstract

Content

1. Introduction	5
1.1. Neuro-bionic devices	5
1.2. Electrode-neural interfacing	6
2. Controlled delivery systems based on conventional polymers	8
2.1. Bioactive coatings	8
2.2. Integrated microfabricated systems	13
3. Electrically on-demand delivery systems based on OCPs	16
3.1. OCP coatings for delivery of anti-inflammatory drugs	18
3.2. OCP coatings for delivery of neuroactive molecules	21
4. Conclusions	26
Acknowledgements	27
References	28

1. Introduction

Medical bionic systems provide a link between electronic devices and the human body in order to restore or enhance sensory and/or motor function lost through disease or injury. A great deal of attention has been paid to the development of neuro-bionics for monitoring, stimulatory and recording applications.

1.1. Neuro-bionic devices

A number of implantable bionic devices aim to improve human performance by monitoring some aspect of our biological system. The placement of an electrode grid consisting of four platinum-iridium electrodes into the brain enables pre-emptive detection of epileptic seizures [1]. Electric impulses emanating from the brain are recorded in order to give warning of an impending seizure. Such a device has significant benefits for the treatment of epilepsy through the management of medication, or potentially other therapeutic options such as neurostimulation.

Systems have been developed to apply a predetermined electrical stimulation for the treatment of neurological disorders. Examples of routine clinical use include deep brain stimulators to relieve symptoms of Parkinson's disease, spinal cord stimulators to alleviate chronic neuropathic pain [2,3], and vagal nerve stimulators to treat intractable epilepsy and treatment-resistant depression [4]. In cancer treatment, deep brain and spinal cord stimulation using implanted electrodes have long been used for modulation of chronic pain [5,6]. In addition, implantable electrodes can also be applied to enhance the tumoricidal effect of hyperthermia via elevating the lethal temperature levels in the tumors [7], and to improve the efficacy of radiation therapy via *in situ* tumor oxygenation [8].

The bionic ear (cochlear implant) electrically provides sound to the profoundly deaf through stimulating the auditory nerve [9]. It comprises a microphone to collect sound, a speech processor to transcode the sound to electronic impulses, a transmission coil, an array of electrodes that stimulate targeted areas of the auditory nerve, and a power supply (Fig. 1). More recently, the development of the bionic eye has been actively pursued. Two main types of visual prostheses, retinal and cortical implants, are currently under investigation. For retinal implants, imaging data is processed for electrical stimulation of the optical nerve via electrode arrays implanted on the retina [10], whereas for cortical implants, microelectrode arrays are implanted in the visual cortices [11].

Fig. 1. Cochlear implant (Bionic Ear). (A) Schematic of the components of a cochlear implant, image courtesy of Cochlear Ltd, Australia. (a) The microphone to capture sound. (b) The external transmitter to convert the sound into radio-frequency signal. (c) The implantable portion of the cochlear implant consisting of a receiver/stimulator to convert the radio-frequency signal to electrical impulses and send them along the electrode array positioned in the cochlea. – (d) The implant's electrodes to stimulate the cochlea's auditory nerve and send the impulses to the brain for sound perception. (B) Nucleus[®] 5 cochlear implant (CI512) showing the internal components of the system. (1) Receiver stimulator in titanium casing. (2) Implant coil enabling telemetry. (3) Two extracochlear electrodes for different stimulation modes. (4) 22 half-banded platinum electrode contacts providing focused stimulation to the spiral ganglion cell region of the cochlea, the part mostly needing drug delivery for better electro-neural interfacing. (5) Removable magnets for MRI safety. (6) Symmetrical exit leads from main casing. Reproduced with permission from www.bionicsinstitute.org.

Apart from the above monitoring and stimulating implants, an emerging field is brain-computer and peripheral nerve interfacing systems that utilise recording electrodes to decode signals from the brain for direct control of motor prosthesis or body muscles to restore movement [12]. These systems will ultimately allow patients with severe movement limitations, such as paralysis, to perform many activities of daily living now requiring caretakers, such as dexterous hand and finger movements, standing, walking and gait. The proof of concept of such neurotechnologies has been demonstrated in a number of studies conducted in non-human primates or paralyzed patients [13,14,15]. For example, with intracortical microelectrode arrays implanted in the primary motor cortices, *Macaca mulatta* monkeys demonstrate the ability to control a robotic arm for self-feeding [13]. In a recent pilot clinical trial, patients with tetraplegia have shown to be able to control a computer's cursor and rudimentarily operate a multi-jointed robotic arm using the motor cortical signals recorded through an implanted 96-microelectrode array [15].

1.2. Electrode-neural interfacing

The Achilles heel of all bionic devices is the electrode-cellular/tissue interface [16]. Bioelectronic communication between the implanted electrode and the neural targets is compromised over extended periods [17], primarily due to encapsulation of the electrode with connective tissue. For example, the host responses to the cochlear implant are characterised by fibrosis and new bone formation, which increases electrical impedance and power consumption, limiting the efficacy of safe stimulation at the auditory nerve [9]. For brain implants, such as intracortical probes, the host body response takes the form of reactive gliosis, involving with the formation of an astroglial scar that electronically insulates the electrode from nearby neurons [18].

A degradation in performance with time may also be attributed to neuronal loss arising from acute and chronic inflammatory responses associated with implantation, and also from further degeneration of neurons as a result of central or peripheral nerve pathologies [19]. The long-term performance of the bionic ear directly correlates to the survival rate of the remanent spiral ganglion cells following sensorineural hearing loss, while the bionic eye relies critically on retinal ganglion cell survival [20].

The ideal electrode-neural interface requires both a minimal foreign body response and intimate communication between electrodes and a sufficient amount of neuron targets to permit efficient stimulation and recording. Numerous studies have been undertaken with a view to controlling the nature of this electrode interface through the delivery of bioactive molecules during or subsequent to implantation. These studies have primarily focused on local delivery of neurotrophic factors (to facilitate neurite outgrowth and neural preservation) and/or anti-inflammatory drugs in the vicinity of the implanted device.

A variety of bioactive coatings have been developed for bionic devices. Three approaches are reviewed here. The first involves drug-eluting structures formulated with anti-inflammatory drugs [21,22,23,24,25] and neurotrophin-eluting hydrogels [26,27,28,29,30,31]. The second approach involves integration of microfluidic channels into neural prostheses for *in situ* delivery of bioactive molecules with high temporal and spatial resolution [32,33,34,35,36,37,38,39]. Finally the use of organic conductive polymer (OCP) coatings, a novel class of materials that significantly decrease the impedance of electrodes, and also can provide controlled delivery of bioactive molecules at the electrode-neural interface [40,41,42,43,44,45,46,47,48,49,50].

2. Controlled delivery systems based on conventional polymers

Numerous sustained delivery systems for use in tandem with bionic devices have been developed. They involve the use of either bioactive coatings or modified electrode housing structures that act as reservoirs for the delivery of neurotrophins and/or anti-inflammatory drugs.

Microfabricated systems integrated with neurobionic devices are also included, as they reflect the increasing need for greater spatial/temporal control over the delivery of complex biological cues as required for optimising neuro-electrode interfaces.

2.1. Bioactive coatings

Nitrocellulose coatings have been developed for sustained delivery of anti-inflammatory agents, such as α -melanocyte stimulating hormone (α -MSH) and dexamethasone (DEX), from silicon recording electrode arrays [21,22,23]. These coatings comprise a drug-embedded matrix of nitrocellulose surrounded by layers of pure nitrocellulose (Fig. 2) [21]. The level of control in drug release can be modulated by varying the number of layers of nitrocellulose as well as the porosity of the coatings. *In vitro* testing of the MSH-nitrocellulose coatings showed sustained release of the drug over 21 days, with the anti-inflammatory activity against lipopolysaccharide-stimulated microglia retained over this period. Silicon neural probes coated with DEX-nitrocellulose were tested *in vivo* to assess the influence of coating on brain tissue response [23]. The coatings reduced the astroglial scar formation and the level of neuronal loss at the electrode-brain interface, as a result of the localised release of the DEX. These anti-inflammatory effects were achieved without affecting the electrical performance of the electrodes.

Fig. 2. Schematic illustration of nitrocellulose-based drug-eluting coatings for Si-multi-electrode arrays. Adapted with permission from [21].

To improve the quality of chronic neural recording, nanotechnology has been exploited to control the release of DEX around implanted electrode arrays [24,25]. DEX-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) were prepared using an oil-in-water technique, and those embedded into an alginate hydrogel coating deposited on the neural electrodes [24]. The NP-loaded coatings exhibited a sustained DEX release profile for up to 3 weeks, a process that is governed by a combination of retarded degradation of NPs due to entrapment in the hydrogel matrix. Unlike the uncoated electrodes, DEX-loaded electrodes were able to maintain the initially low *in-vivo* impedance over a period of 3 weeks after implantation (Fig. 3). In addition to the local administration of DEX, the presence of the hydrogel coating itself is advantageous in reducing the inflammatory reaction to the implanted electrodes by providing mechanical buffering between the stiff electrodes and soft brain tissue.

Fig. 3. Optical images of hydrogel-coated neural microelectrode arrays: (a) without DEX-loaded nanoparticles, (b) with DEX-loaded nanoparticles in the hydrogel coating. (c) *In vivo* impedance at 1 kHz of DEX-loaded electrode chronically implanted in the auditory cortex in the guinea pig as a function of time. Adapted with permission from [24].

A similar approach was taken by Mercanzini et al. [25] in the preparation of drug-eluting coatings for microfabricated cortical neuroprostheses. The coatings were formulated with poly(ethylene oxide) (PEO) and DEX-loaded NPs of poly(propylene sulphide). DEX loading was achieved using a co-solvent-evaporation procedure [51]. The release profile was determined by both the oxidation of poly(propylene sulphide) and diffusion. The effectiveness of these NP-embedded coatings in managing the local tissue reaction to implanted devices was demonstrated by histological and *in vivo* impedance experiments. In comparison to uncoated devices, a substantial reduction (25%) in the impedance at the Peak Resistance Frequency was noted at the end of the 46 day experiment.

Hydrogels are highly hydrated polymeric networks with structural and mechanical properties mimicking soft tissue. Their capability to provide sustained delivery of bioactive molecules, such as proteins, has been intensively exploited in a broad range of biomedical applications. Their mechanical properties make them attractive coating materials in controlled delivery for both stimulation and recording devices, in order to improve neural survival and neuron-electrode proximity. Research in this area is still at an early stage, but will greatly benefit from the enriched knowledge and experience accrued in the field of hydrogel, especially for the applications in protein delivery/therapy and tissue engineering.

Several photo-crosslinkable gel systems have been investigated *in vitro* [26,27,28,29,30,31]. For example, biodegradable neurotrophin-eluting hydrogel coatings, based on poly(ethylene glycol)-poly(lactic acid) (PEGPLA), were developed for multi-electrode arrays with sputtered iridium oxide charge-injection sites [26,27]. This was achieved by applying the aqueous solution of PEGPLA precursor and neural growth factor (NGF)/brain-derived neurotrophic factor (BDNF) to the electrode array surface and inducing crosslinking via UV irradiation.

The coatings were shown to adhere well to the electrode array surface, and were able to elute neurotrophin at biologically significant concentrations for at least one week. Importantly, the coatings had little impact on the iridium oxide electrochemical properties, including charge storage capacity, impedance, and voltage transition during current pulsing.

A number of parameters can be employed to regulate the release profile of neurotrophin-eluting hydrogel coatings. Reducing the biodegradability of coating materials can significantly prolong the duration of sustained release as achieved by introducing a poly(ϵ -caprolactone) (PCL) component into the PEGPCL hydrogel coating [28]. Similarly introduction of the PCL component via electrospinning extends the duration of sustained release [29]. Other approaches used to control the delivery of neurotrophin involve chemical modification to promote protein-matrix interactions, and varying the porosity of hydrogel coatings. For example, modification of poly(2-hydroxyethyl methacrylate) (pHEMA) hydrogel coatings with lysine resulted in more extended release of NGF, while introducing macroporosity into the pHEMA hydrogel coatings shortened the release of NGF [31].

Controlling the biodegradability of the hydrogel has been shown to be a viable approach in improving the coating-electrode adhesion [28]. When tested using an agarose tissue phantom, PEGPCL hydrogels were able to adhere to the electrode devices for at least 4 weeks, which was attributable to a slower degradation rate of the PCL component, and a significant improvement than PEGPLA coatings that adhered up to 11 days [28]. Another approach to improving the stability of hydrogel coatings involves surface treatment of electrode substrate to permit the chemical bonding with the coating [30,31].

2.2. Integrated microfabricated systems

Silicon intracortical probes with integrated microfluidic channels have been fabricated to enable controlled localised delivery [32,33,52,53,54]. *In vivo* experiments have demonstrated the feasibility of delivering chemicals into relevant volumes of reactive tissue [32,33,53]. Drug release in these fluidic channels can be mediated by diffusive or convective transport. The latter offers a significant degree of versatility, and precise control of the biochemical environment of tissue up to a millimetre away from the inserted site [33,52]. However, it requires additional parts such as integrated pumps, valves, or connections to an outside device for control of the release, which raises concerns over added complexity of device fabrication, higher failure rate, and increased size of devices that may cause more insertion injury and consequently increased tissue reactions and risk of infection.

Microfluidic channels have also been built into parylene flexible neural recording probes [34]. Compared to rigid silicon probes, these flexible neural probes are of increasing interest as they conform to the shape and deformation of soft tissue. In addition to providing a means for *in vivo* drug delivery, the fluidic channel also provides transient and yet sufficient mechanical stiffness for insertion, through filling the channel with a biocompatible, solid poly(ethylene glycol) (PEG). After the insertion, the probe regained its original flexibility following the dissolution of PEG. *In vivo* experiments showed ease of insertion of the probe, and that inclusion of the drug release channel did not affect the quality of neural recording, as compared with conventional rigid probes. Future work should evaluate the long-term performance of the probe with and without the aid of drug delivery. The knowledge gained will provide insights into future development of neural probes with chronic recording functionality.

Post-operative degeneration of spiral ganglion neurons is best prevented in order to achieve optimal performance of cochlear implants. To promote preservation of the auditory nerve, a number of studies have focused on modification of cochlear implants with an integrated drug delivery channel for intracochlear pharmaceutical intervention [36,37,38,39]. The channel is linked to a micro-osmotic pump or an infusion pump to control the flow rate. The feasibility of concurrently delivering drugs and stimulating the auditory nerve has been demonstrated in animal models [36,39]. An example of a cochlear drug delivery device, based on a Nucleus Contour electrode, is described here. The electrode has an inbuilt lumen for a stylet that straightens the electrode array for insertion. The stylet is then removed, leaving the lumen to be connected to an Alzet pump mini-osmotic pump. The applicability of this device to the human cochlea was evaluated *in vitro* using samples of human temporal bone [37]. Passche et al. [55] compared dye delivery in three different electrode prototypes with openings at various position along the electrode array using an *in vitro* plastic cochlear model, i.e. release of dye at the tip; release of the dye at the tip and the side of the electrode; and release of the dye only at the side of the electrode (Fig. 4). Dye concentration in apical, middle, and basal regions at different times was shown to be influenced by pump rate, numbers and location of outlets. The results indicated that the best distribution of dye within the cochlea was reached when using multiple outlets with an opening at the tip being mandatory. To facilitate manufacturing multiple outlets at desired locations and sizes, a technology has been developed using femtosecond laser [56].

Fig. 4. Dye is delivered from three different prototypes at a pump rate of 100 $\mu\text{l/h}$. (A) Opening at the tip; (B) release at the tip and the side; (C) release only at the side of the array. The openings for fluid delivery are indicated by arrows. Reproduced with permission from [55].

Using an alternative approach Williams et al. developed Micro-MEMS (electro-mechanical systems)-based neural probes with built-in micromachined wells within micrometers of individual electrodes [57]. These wells extended through the device's thickness, and thus permitted the deposition of hydrogels infused with bioactive molecules without increasing the footprint of the device. The release profile in the wells was mediated by diffusion, and can be manipulated by controlling well geometry and hydrogel materials to effect both the duration and rate of drug release. *In vivo* testing verified the integration of the bioactive molecules with intended neural targets and concurrent extracellular recoding using nearby electrodes. Perhaps, the most significant benefit of this technology, yet to be demonstrated, is spatial and temporal control over the presentation of different drugs, multiple biological cues, or gradients of growth factors at selected sites; to both effectively direct neurite growth toward the electrodes and alleviate the reactive cell and tissue responses. This could be achieved by loading each well individually with a different and appropriately formulated bioactive molecule. The importance of complex biological cues in addressing electrode-neural interfacing has been increasingly recognised, and is also supported by recent studies that implied the short-lived effect of neurotrophins eluted from hydrogel coatings of neuroprosthetic devices, and the necessity of presenting other biological mechanisms in order to sustain the effect of eluted neurotrophins [27,28].

3. Electrically on-demand delivery systems based on OCPs

The most commonly studied OCPs for biomedical applications are polypyrrole (PPy) and the functionalised thiophene, Poly(3,4-ethylenedioxythiophene) (PEDOT) [58]. These OCPs have been studied in a wide range of cell types and are considered to be chemically stable and non-cytotoxic. Therefore their potential clinical application predominantly lies in the area of excitable cell interactions, namely nerve repair. The biggest limitation of conductive

polymers for *in vivo* applications is their inherent inability to degrade, which may induce chronic inflammation and require surgical removal [59]. To address the drawbacks of existing conductive polymers, attempts to blend them with suitable biodegradable polymers have been carried out [59,60,61].

OCPs are unique amongst bionic electromaterials in that they provide a conduit for direct electrical stimulation and a concomitant means of controlled, triggered bioactive molecule delivery within the same platform. OCPs, in their oxidised (conducting) form require counter ions to be incorporated into the polymer backbone to achieve charge neutrality. This provides a mechanism for the incorporation and release of bioactive anions via electrically triggered redox cycling (Fig. 5A and B). To broaden the scope of molecules suitable for OCP mediated delivery to include neutral and cationic therapeutic agents, a biotin-doped platform has been developed based on polypyrrole (PPy) [62]. Biotinylated drugs can be attached onto the polymer surface through biotin-streptavidin binding, and released upon electrical stimulation (Fig. 5C).

Fig. 5. (A) Synthesis of an OCP showing the incorporation of dopant A^- . (B) Release of the dopant A^- during redox cycling of the OCP. Reproduced with permission from [40]. (C) Electrically triggered release of biotinylated NGF from biotin-doped PPy. Reproduced with permission from [62].

PPy and poly(3,4-ethylenedioxythiophene) (PEDOT) are the most intensively investigated OCPs for neural interfacing applications. Coating of the electrode with PPy or PEDOT is

generally achieved by electrodeposition, a simple procedure that, when coupled with the controlled release capability of OCPs, can permit convenient and precise engineering of individual electrode sites for simultaneous optimisation of both the biochemical environment around and electrical performance of the electrode. Importantly, PPy and PEDOT have demonstrated compatibility with numerous cell types including neurons, neuronal-like cells and neural stem cells [63,64,65]. *In vivo* evaluation in rodent cortex has shown a positive biocompatibility profile with the central nervous system parenchyma that is comparable to Teflon or platinum control [66,67]. The tissue biocompatibility of PPy and PEDOT is further supported by their extensive applications in neural tissue engineering (as scaffolding materials) and regenerative bionics (as accessory electrode array systems) toward the regeneration of damaged nerve [68,69,70,71]. Together, it is these features that make PPy and PEDOT superior coating materials for the development of advanced neuro-bionics aimed at both high spatial selectivity and high signal fidelity over the long term.

3.1. OCP coatings for delivery of anti-inflammatory drugs

Precisely controlled local release of anti-inflammatory drugs at desired points in time is important for treating the inflammatory response of neural prosthetic devices in the central and peripheral nervous systems. Wadhwa et al. [45] reported on PPy coating doped with an anionic prodrug form of dexamethasone (PPy-Dex), dexamethasone 21-phosphate disodium, for chronic recording electrode arrays. The PPy-Dex coating has a thickness of 50 nm, and is capable of on-demand, dose-controlled release of the drug upon cyclic potential stimulation. The amount of drug released is directly proportional to the numbers of CV stimulus in the given CV cycle range (Fig. 6), and is sufficient to markedly reduce the number of reactive astrocytes and microglial, while provoking no toxic effect on healthy primary neurons *in vitro*.

Fig. 6. Release profile of dexamethasone 21-phosphate disodium (Dex) from the polymer-drug coated electrodes. For PPy–Dex, the x-axis represents number of CV cycles. A control was set up to study the release from the film in the absence of any electrical stimulation. In this case the x-axis represents the number of minutes (at 100 mV/s scan rate, 1 CV cycle between -0.8 to 1.4 V takes approximately 1 min). Reproduced with permission from [45].

Abidian et al. [46] reported a method to fabricate OCP nanotubes onto a neural prosthetic electrode that could be used for precisely controlled drug release. Their fabrication process involved electrospinning of biodegradable poly(lactic-*co*-glycolic acid) (PLGA), into which dexamethasone was incorporated, followed by electrochemical deposition of PEDOT around the drug-loaded, electrospun PLGA fibers (Fig. 7). The PEDOT nanotubes significantly decreased the impedance (by ~2 orders of magnitude at 1 kHz, the characteristic frequency of neuronal-action potential), and increased the charge capacity (by ~3 orders of magnitude) of the recording electrode sites on microfabricated neural prosthetic devices. Dexamethasone could be released from the PEDOT nanotubes in a desired fashion by electrical stimulation of the nanotubes. The authors suggested that this drug release process presumably proceeds by a local dilation of the tube that then promotes mass transport.

Fig. 7. (A)-(C) Schematic diagrams illustrating the surface modification of neural microelectrodes to create nanotubular PEDOT and controlled release of Dex: (A) electrospinning of PLGA fibers with well-defined surface texture (1) on the probe tip; (B) electrochemical polymerization of PEDOT (2) around the electrospun fibers; and (C) dissolving the electrospun core fibers to create nanotubular conducting polymers (3). (D) Scanning electron micrographs of electropolymerized PEDOT nanotubes on the electrode site of an acute neural probe tip after removing the PLGA core fibers. (E) Cumulative mass release of dexamethasone from: PLGA nanoscale fibers (black squares), PEDOT-coated PLGA nanoscale fibers (red circles) without electrical stimulation, and PEDOT-coated PLGA nanoscale fibers with electrical stimulation of 1 V applied at the five specific times indicated by the circled data points (blue triangles). Adapted with permission from [46].

Whilst drug release systems based on OCPs have been extensively studied, the application of such systems has been limited due to some intrinsic technical barriers. For instance, the drug loading capacity of a conventional OCP film is limited, and the amount of drug released per stimulation is not sustainable over long periods [48]. In order to increase drug loading of PPy coatings, Luo et al. [48] incorporated carbon nanotubes (CNTs) into the PPy coatings to act as drug reservoirs (Fig. 8). Dexamethasone 21-phosphate disodium was loaded to the inner cavity of the CNTs and sealed with PPy via electropolymerization (Fig. 8). It was shown that the coatings not only significantly increased the amounts of electrically loaded and releasable drug, but also enabled a more linear and sustainable drug release profile, attributable to the incorporation of CNTs. Incorporation of CNTs into OCPs is also a viable approach to

improving the electrode performance, especially for the application in high density chronic neural stimulation [72,73,74]. Pt microelectrodes coated with CNT-doped PPy or PEDOT exhibit remarkably lower impedance and higher safe charge injection limit, both by 1-2 orders of magnitude in comparison to those coated with conventional OCPs. More importantly, these microelectrodes exhibit much improved mechanical and electrochemical stability during prolonged and intensive electrical stimulation, without any cracking or delamination of the coating materials. Formation of macroscopic cracks and/or delamination under stimulation has been reported in a number of studies for conventional OCP coatings [45,75,76], and is regarded as a critical barrier limiting the application of OCPs in neural interfacing.

Fig. 8. Schematic of the drug loading and release process of CNT nanoreservoirs. (A) Drug solution is filled into the interior of acid treated CNTs through sonication. (B) Pyrrole is added to the suspension containing CNTs and the drug, and electropolymerization is carried out. (C) Drug is released from CNT nanoreservoirs to surroundings through diffusion or electrical stimulation. Reproduced with permission from [48].

3.2. OCP coatings for delivery of neuroactive molecules

We have shown that neurotrophin-3 (NT3) and brain-derived neurotrophic factor (BDNF) can be incorporated into PPy [40,44] coatings and then released using a clinically relevant biphasic electrical stimulation (Fig. 9). The drug loading capacity and electrically controlled drug release efficacies are subject to parameters such as polymerisation time [40] and dopant structure *etc* [44]. These coatings have been shown to promote a significant increase in

neurite extension from spiral ganglion neuron explants *in vitro* [41], and some level of preservation of cochlea nerves *in vivo* [43]. Recently we reported on co-delivery of NT3 and BDNF to synergistically encourage neurite outgrowth from cochlea explants [77]. Last but not the least, concurrent electrical stimulation may work in concert with the released neurotrophins to promote neuron rescue [78,79]. All these capabilities are highly desirable for promoting the survival of auditory neurons and neurite outgrowth toward the electrode implant, especially the cochlear implant.

Fig. 9. ^{125}I NT3 release kinetics from stimulated and non-stimulated PPy/pTS/ ^{125}I NT3-coated electrodes. Cumulative release of ^{125}I NT3 was 3.5-fold greater from stimulated 1.0 cm^2 PPy/pTS/ ^{125}I NT3-coated electrodes compared to non-stimulated PPy/pTS/ ^{125}I NT3-coated electrodes over 7 days. Error bars indicate the standard error of the mean. Reproduced with permission from [43].

Our study [41], as well as others [27], has revealed that the environmental cue via cell adhesion molecules is essential for achieving optimal effect of neurotrophin on neurite extension. Indeed, controlling the presentation of cell adhesion molecules has been seen as an important strategy to improve neural-implant interfaces [80,81,82,83,84]. For instance, a synthetic protein bearing fibronectin fragments, SLPF, or a laminin fragment, CDPGYIGSR, was incorporated through the electrochemical deposition of PPy onto micro-machined silicon recording probes (Fig. 10A and B) [85]. Rat glial or neuroblastoma cells, were shown to preferentially attach to the neural probes coated with PPy/SLPF and PPy/CDPGYIGSR

composite, respectively (Fig. 10C). The PPy/SLPF coatings showed a lower charge capacity compared to control PPy/poly(styrene sulphonate) (PPy/PSS) coatings (Fig. 10D), but were still capable of recording good quality voltage signals from single neurons in the cerebellum of guinea pigs. In a different study [86], 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 surrounding an electrode.

Fig. 10. (A) Optical micrograph of PPy/PSS coated 5-channel neural probe. (B) SEM images of PPy/SLPF SFP coated electrode sites (total charged passed, 4 μC). (C) Coated neural probe cultured with human neuroblastoma cells. (D) Cyclic voltammetry of PPy/SLPF coated electrode in comparison with bare gold and PPy/PSS. Adapted with permission from [85].

To address the growing need for both biocompatibility and bioactivity in advanced neural interfacing, coating structures for stimulation and recording electrodes are becoming increasingly sophisticated. Significant efforts are being put into hybrid coatings of OCP and

hydrogel to combine the advantages of the two types of materials, in particular low impedance, controlled release of bioactive molecules and biomechanical integrity with soft tissue [49,50,87,88]. This strategy is of particular interest in brain implants; the inclusion of an appropriately engineered hydrogel component in the coating is expected to minimise the mechanical mismatch between hard electrode and soft brain tissue, thereby reducing micromotion, and consequently micromotion associated inflammatory response and tissue damage.

A number of methods have been developed for the preparation of hybrid OCP-hydrogel coatings [89]. A simple and popular approach is direct electrodeposition of OCPs in the hydrogel coating of an electrode [87,90]. With the hydrogel networks acting as a 3D template, cloud-like OCPs are produced vertically around the electrode site, with enormously larger effective surface area and consequently much lower *in vitro* impedance characteristics compared to those grown on flat electrode substrates (Fig. 11) [87]. Some level of improvement in device performance has recently been demonstrated *in vivo*. For example, deposition of PEDOT on the electrode sites has been shown to improve the acute neural recoding functionality of alginate hydrogel-coated neural probes implanted in the auditory cortex of guinea pigs [49]. Cochlear implants with multifunctional coatings comprised of PEDOT, arginine-glycine-aspartic acid (RGD)-functionalized alginate hydrogel and BDNF, were shown to improve the stability of *in vivo* impedance during 6 months implantation [50]. However, the presence of RGD and BDNF seemed to have no effect on the survival of spiral ganglion neuron. Further improvement in both material design and fabrication is required, in order to achieve the optimal effect of hybrid OCP-hydrogel coatings on the performance of implanted electrodes.

(A)

(B)

(C)

Fig. 11. Schematic of conventional OCP coating on the gold electrode (A) and cloud-like conducting polymer on the gold electrode polymerized through the hydrogel matrix (B). Optical microscope images of top view of the conducting polymer in the hydrogel coating (C). Adapted with permission from [87].

4. Conclusions

Neuro-bionics provides new dimensions in both therapeutics and diagnostics. The biological processes at implanted electrode interfaces, in particular cellular reactions and subsequent tissue remodelling, determine the safety, function and longevity of neuro-bionic implants. The past few decades have seen significant progress in improving the electrode performance through optimising the properties of electromaterials including composition, surface roughness, porosity, nanofeatures and modulus. Whilst significant progress has been made *in vitro*, the improvement in *in-vivo* is limited, and often transient. Thus there is a high demand for bionic devices with *in situ* drug delivery capacity to assist in controlling the cellular and tissue processes at the electrode interface.

The general considerations for a drug delivery system, such as biocompatibility, drug loading capacity, release efficiency and a desired dosage profile, are important. In addition, the introduction of the delivery system should not result in any adverse effects on the electrical properties of electrodes, they should be mechanically stable to endure the implantation process and prolonged use, and not cause additional inflammatory response. Furthermore, such systems should not significantly increase the footprint of the implanted device.

Here we review a number of controlled delivery systems that have been developed in tandem with neuro-bionic devices. The majority of such systems are based on bioactive coatings that serve as reservoirs of bioactive molecules for local intervention to improve the biocompatibility (via minimising reactive cellular and tissue responses), and/or the neuroactivity (via promoting neural preservation and outgrowth) of the implanted electrodes. Both biocompatibility and neuroactivity are integral to the engineering of a chronically stable interface enabling efficient signal transmission from the device to the neuronal targets.

Integrating microfabricated channels into neural prostheses is discussed as an alternative approach, with the advantage of high temporal and volumetric resolution in delivering molecules.

OCP based delivery systems have attracted increasing attention. This may be attributed to their unique capacity to simultaneously improve the electrical properties of the electrode, and to control the local biochemical environment at the electrode interface via electrically on-demand delivery of bioactive molecules.

Acknowledgements

The authors are grateful for financial support provided by the Australian Research Council, and National Health, Medical Research Council, and the HEARing CRC established and supported under the Australian Government's Cooperative Research Centres Program. The authors also gratefully acknowledge Dr Chee Too and Dr Brianna Thompson for their comments and advice during the preparation of the manuscript.

References

- [1] K.A. Davis, B.K. Sturges, C.H. Vite, V. Ruedebusch, G. Worrell, A.B. Gardner, K. Leyde, W.D. Sheffield, B. Litt, A novel implanted device to wirelessly record and analyze continuous intracranial canine EEG, *Epilepsy Res.* 96 (2011) 116-122.
- [2] J.A. Boockvar, A. Telfeian, G.H. Baltuch, B. Skolnick, T. Simuni, M. Stern, M.L. Schmidt, J.Q. Trojanowski, Long-term deep brain stimulation in a patient with essential tremor: clinical response and postmortem correlation with stimulator termination sites in ventral thalamus, *J. Neurosurg.* 93 (2000) 140-144.
- [3] K.D. Wise, *Silicon Microsystems for Neuroscience and Neural Prostheses: Interfacing with the Central Nervous System at the Cellular Level*, *IEEE Eng. Med. Bio. Mag.* 24 (2005) 22-29
- [4] B.M. Uthman, B.J. Wilder, E.J. Hammond, S.A. Reid, Efficacy and safety of vagus nerve stimulation in patients with complex partial seizures, *Epilepsia* 31(Suppl 2) (1990) 44-50
- [5] P.L. Gildenberg, History of electrical neuromodulation for chronic pain, *Pain Medicine* 7 (2006) S7-S13.
- [6] A.E. Yakovlev, B.E. Resch, S.A. Karasev, Treatment of cancer-related chest wall pain using spinal cord stimulation, *Am J Hosp Palliat Care* 27 (2010) 552-556.
- [7] O.H. Frazier, P.M. Corry, Induction of hyperthermia using implanted electrodes, *Cancer Res. (Suppl.)* 44 (1984) 4864s-4866s.
- [8] T. Maleki, N. Cao, S.H. Song, C. Kao, S.-C. Ko, B. Ziaie, An ultrasonically powered implantable micro-oxygen generator (IMOG), *IEEE Tran. Biomed. Eng.* 58 (2011) 3104-3111.
- [9] G.M. Clark, *Cochlear Implants: Fundamentals and Applications*, Springer-Verlag, New York, 2003.
- [10] M.S. Humayun, J.D. Weiland, G.Y. Fujii, R. Greenberg, R. Williamson, J. Little, B. Mech, V. Cimarusti, G. Van Boemel, G. Dagnelie, E.J. de Juan, Visual perception in a blind subject with a chronic microelectronic retinal prosthesis, *Vision Res.* 43 (2003) 2573-2581.
- [11] W.H. Dobelle, M.G. Mladejovsky, J.P. Girvin, Artificial vision for the blind: Electrical stimulation of visual cortex offers hope for a functional prosthesis, *Science* 183 (1974) 440-444.
- [12] J.E. O'Doherty, A.M. Lebedev, P.J. Ifft, K.Z. Zhuang, S. Shokur, H. Bleuler, M.A.L. Nicolelis, Active tactile exploration using a brain-machine-brain interface, *Nature* 476 (2001) 228-231.
- [13] S. Perel, A.B. Schwartz, M.C. Spalding, M. Velliste, A.S. Whitford, Cortical control of a prosthetic arm for self-feeding, *Nature* 453 (2008) 1098-1101.
- [14] E.E. Fetz, C.T. Moritz, S.I. Perlmuter, Direct control of paralysed muscles by cortical neurons, *Nature* 456 (2008) 639-643.
- [15] L.R. Hochberg, M.D. Serruya, G.M. Fiehs, J.A. Mukand, M. Saleh, A.H. Caplan, A. Branner, D. Chen, R.D. Penn, J.P. Donoghue, Neuronal ensemble control of prosthetic devices by a human with tetraplegia, *Nature* 442 (2006) 164-171.
- [16] G.G. Wallace, S.E. Moulton, G.M. Clark, Electrode-Cellular Interface, *Science* 324 (2009) 185-186.
- [17] S.A. Norman, Technology insight: Future neuroprosthetic therapies for disorders of the nervous system, *Nat. Clin. Pract. Neurol.* 3 (2007) 444-452.
- [18] V.S. Polikov, P.A. Tresco, W.M. Reichert, Response of brain tissue to chronically implanted neural electrodes, *J. Neurosci. Methods* 148 (2005) 1-18.

-
- [19] R.K. Shepherd, Special issues on medical bionics, *J. Neural Eng.* 6 (2009) 060201.
 - [20] C. Veraart, F. Duret, M. Brelen, M. Oozeer, J. Delbeke, Vision rehabilitation in the case of blindness, *Expert Rev. Med. Devices* 1 (2004) 139-153.
 - [21] Y. Zhong, R.V. Bellamkonda, Controlled release of anti-inflammatory agent α -MSH from neural implants, *J. Control. Release* 106 (2005) 309-318.
 - [22] Y. Zhong, G.C. McConnell, J.D. Ross, S.P. DeWeerth, R.V. Bellamkonda, A novel dexamethasone-releasing, anti-inflammatory coating for neural implants, *Proceeding of the 2nd International IEEE EMBS Conference on Neural Engineering*, Arlington, USA, 522-525.
 - [23] Y. Zhong, R.V. Bellamkonda, Dexamethasone-coated neural probes elicit attenuated inflammatory response and neuronal loss compared to uncoated neural probes, *Brain Res.* 1148 (2007) 15-27.
 - [24] D.H. Kim, D.C. Martin, Sustained release of dexamethasone from hydrophilic matrices using PLGA nanoparticles for neural drug delivery, *Biomaterials* 27 (2006) 3031-3037.
 - [25] A. Mercanzini, S.T. Reddy, D. Velluto, P. Colin, A. Maillard, J.-C. Bensadoun, J.A. Hubbell, P. Renaud, Controlled release nanoparticle-embedded coatings reduce the tissue reaction to neuroprostheses, *J. Control. Release* 145 (2010) 196-202.
 - [26] J.O. Winter, S.F. Cogan, J.F. Rizzo III, Neurotrophin-eluting hydrogel coatings for neural stimulating electrodes, *J. Biomed. Mater. Res. B Appl. Biomater.* 81 (2007) 551-563.
 - [27] J.O. Winter, M. Gokhale, R.J. Jensen, S.F. Cogan, J.F. Rizzo III, Tissue engineering applied to the retinal prosthesis: neurotrophin-eluting hydrogel coatings, *Mater. Sci. Eng. C Mater. Biol. Appl.* 28 (2008) 448-453.
 - [28] S.S. Rao, N. Han, J.O. Winter, Polylysine-modified PEG-based hydrogels to enhance the neuro-electrode interface, *J. Biomater. Sci.* 22 (2011) 611-625.
 - [29] N. Han, S.S. Rao, J. Johnson, K.S. Parikh, P.A. Bradly, J.J. Lannutti, J.O. Winter, Hydrogel-electrospun fiber mat composite coating for neural prostheses, *Front. Neuroeng.* 4 (2011) 2.
 - [30] S.B. Jun, M.R. Hynd, N.M. Dowell-Mefin, Y. Al-Kofahi, B. Roysam, W. Shain, S.J. Kim, Modulation of cultured neural networks using neurotrophin release from hydrogel coated microelectrode arrays, *J. Neural Eng.* 5 (2008) 203-213.
 - [31] S.J. Jhaveri, M.R. Hynd, N.M. Dowell-Mefin, J.N. Turner, W. Shain, C.K. Ober, Release of nerve growth factor from HEMA hydrogel-coated substrates and its effect on the differentiation of neural cells, *Biomacromolecules* 10 (2009) 174-183.
 - [32] J. Chen, K.D. Wise, J.F. Hetke, S.C. Bledsoe, A multichannel neural probe for selective chemical delivery at the cellular level, *IEEE Trans. Biomed. Eng.* 44 (1997) 760-769.
 - [33] S.T. Retterer, K.L. Smith, C.S. Bjornsson, K.B. Neeves, A.J.H. Spence, J.N. Turner, W. Shain, M.S. Isaacson, Model neural prostheses with integrated microfluidics: a potential intervention strategy for controlling reactive cell and tissue responses, *IEEE Trans. Biomed. Eng.* 51 (2004) 2063-2073.
 - [34] S. Takeuchi, D. Ziegler, Y. Yoshida, K. Mabuchi, T. Suzuki, Parylene flexible neural probes integrated with microfluidic channels, *Lab. Chip* 5 (2005) 519-523.
 - [35] D. Ziegler, T. Suzuki, S. Takeuchi, Fabrication of flexible neural probes with built-in microfluidic channels by thermal bonding of parylene, *J. Microelectromech. Syst.* 15 (2006) 1477-1482.
 - [36] R.K. Shepherd, J. Xu, A multichannel scala tympani electrode array incorporating a drug delivery system for chronic intracochlear infusion, *Hear. Res.* 172 (2002) 92-98.
-

-
- [37] G. Paasche, P. Gibson, T. Averbek, H. Becker, T. Lenarz, T. Stöver, Technical report: modification of a cochlear implant electrode for drug delivery to the inner ear, *Otol. Neurotol.* 24 (2003) 222-227.
 - [38] I. Hochmair, P. Nopp, C. Jolly, M. Schmidt, H. Schöber, C. Garnham, MED-EL cochlear implants: State of the art and a glimpse into the future, *Trends Amplif.* 10 (2006) 201-220.
 - [39] S.J. Rebscher, A.M. Hetherington, R.L. Snyder, P.A. Leake, B.H. Bonham, Design and fabrication of multichannel cochlear implants for animal research, *J. Neurosci. Methods* 166 (2007) 1-12.
 - [40] B.C. Thompson, S.E. Moulton, J. Ding, R. Richardson, A. Cameron, S. O'Leary, G.G. Wallace, G.M. Clark, Optimising the incorporation and release of a neurotrophic factor using conducting polymers, *J. Control. Release* 116 (2006) 285-294.
 - [41] R.T. Richardson, B. Thompson, S. Moulton, C. Newbold, M.G. Lum, A. Cameron, G. Wallace, R. Kapsa, G. Clark, S. O'Leary, The effect of polypyrrole with incorporated neurotrophin-3 on the promotion of neurite outgrowth from auditory neurons, *Biomaterials* 28 (2007) 513-523.
 - [42] A.J. Evans, B.C. Thompson, G.G. Wallace, R. Millard, S.J. O'Leary, G.M. Clark, R.K. Kapsa, R.T. Richardson, Promoting neurite outgrowth from spiral ganglion neuron explants using polypyrrole/BDNF-coated electrodes, *J. Biomed. Mater. Res. A* 91 (2009) 241-250.
 - [43] R.T. Richardson, A.K. Wise, B.C. Thompson, B.O. Flynn, P.J. Atkinson, N.J. Fretwell, J.B. Fallon, G.G. Wallace, R.K. Kapsa, G.M. Clark, S.J. O'Leary, Polypyrrole-coated electrode for the delivery of charge and neurotrophins to cochlea neurons, *Biomaterials* 30 (2009) 2614-2624.
 - [44] B.C. Thompson, S.E. Moulton, R.T. Richardson, G.G. Wallace, Effect of the dopant anion in polypyrrole on nerve growth and release of a neurotrophic protein, *Biomaterials* 32 (2011) 3822-3831.
 - [45] R. Wadhwa, C.F. Lagenaur, X.T. Cui, Electrochemically controlled release of dexamethasone from conducting polymer polypyrrole coated electrode, *J. Control. Release* 110 (2006) 531-541.
 - [46] M.R. Abidian, D.H. Kim, D.C. Martin, Conducting-polymer nanotubes for controlled drug release, *Adv. Mater.* 18 (2006) 405-409.
 - [47] M.R. Abidian, K.A. Ludwig, T.C. Marzullo, D.C. Martin, D.R. Kipke, Interfacing conducting polymer nanotubes with the central nervous system: chronic neural recording using poly(3,4-ethylenedioxythiophene) nanotubes, *Adv. Mater.* 21 (2009) 3764-3770.
 - [48] X. Luo, C. Matrangola, S. Tan, N. Alba, X.T. Cui, Carbon nanotube nanoreservoir for controlled release of anti-inflammatory dexamethasone, *Biomaterials* 32 (2011) 6316-6323.
 - [49] D.H. Kim, J.A. Wiler, D.J. Anderson, D.R. Kipke, D.C. Martin, Conducting polymers on hydrogel-coated neural electrode provide sensitive neural recording in auditory cortex, *Acta Biomater.* 6 (2010) 57-62.
 - [50] J.A. Chikar, J.L. Hendricks, S.M. Richardson-Burns, Y. Raphael, B.E. Pfingst, D.C. Martin, The use of a dual PEDOT and GRD-functionalized alginate hydrogel coating to provide sustained drug delivery and improved cochlear implant function, *Biomaterials* 33 (2012) 1982-1990.
 - [51] G. Kwon, M. Naito, M. Yokoyama, T. Okano, Y. Sakurai, K. Kataoka, Block copolymer micelles for drug delivery: loading and release of doxorubicin, *J. Control. Release* 48 (1997) 195-201.
-

-
- [52] S.T. Retterer, K.L. Smoth, C.S. Bjornsson, J.N. Turner, M.S. Isaacson, W. Shain, Constant pressure fluid infusion into rat neocortex from implantable microfluidic devices, *J. Neural Eng.* 5 (2008) 385-391.
 - [53] T. M. Pearce, J. J. Williams, S. P. Kruzel, M. J. Gidden, J. C. Williams, Dynamic control of extracellular environment in *in vitro* neural recording systems, *IEEE Trans. Neural Syst. Rehabil. Eng.* 13 (2005) 207-212.
 - [54] K.B. Neeves, C.T. Lo, C.P. Foley, W.M. Saltzman, W.L. Olbricht, Fabrication and characterisation of microfluidic probes for convection enhanced drug delivery, *J. Control. Release* 111 (2006) 252-262.
 - [55] G. Passche, L. Bögel, M. Leinung, T. Lenarz, T. Stöver, Substance distribution in a cochlear model using different pump rates for cochlear implant drug delivery electrode prototypes, *Hear. Res.* 212 (2006) 74-82.
 - [56] T. Stöver, G. Passche, T. Lenarz, Development of a drug delivery device: using the femtosecond laser to modify cochlear implant electrodes, *Cochlear Implant Int.* 8 (2007) 38-52.
 - [57] J.C. Williams, M.M. Holecko II, S.P. Massia, P. Rousche, D.R. Kipke, Multi-site incorporation of bioactive matrices into MEMS-based neural probes, *J. Neural Eng.* 2 (2005) L23-L278.
 - [58] L. Ghasemi-Mobarakeh, M.P. Prabhakaran, M. Morshed, M.H. Nasr-Esfahani, H. Baharvand, S. Kiani, S. Al-Deyab, S. Ramakrishna, Application of conductive polymers, scaffolds and electrical stimulation for nerve tissue engineering, *J. Tissue Eng. Regen. Med.* 5 (2011) e17-e35.
 - [59] L. Huang, J. Hu, L. Lang, X. Wang, P. Zhang, X. Jing, X. Wang, X. Chen, P.I. Lelkes, A.G. MacDiarmid, Y. Wei, Synthesis and characterization of electroactive and biodegradable ABA block copolymer of polylactide and aniline pentamer, *Biomaterials* 28 (2007) 1741-1751.
 - [60] T.J. Rivers, T.W. Hudson, C.W. Schmidt. Synthesis of a novel biodegradable electrically conducting polymer for biomedical applications, *Adv Funct Mater* 12 (2002) 33-37
 - [61] G. Shi, M. Rouabhia, S. Meng, *et al.* Electrical stimulation enhances viability of human cutaneous fibroblasts on conductive biodegradable substrates. *J Biomed Mater Res A* 84A (2007) 1026-1037.
 - [62] P.M. George, D.A. LaVan, J.A. Burdick, C-Y Chen, E. Liang, R. Langer, Electrically controlled drug delivery from biotin-doped conductive polypyrrole, *Adv. Mater.* 18 (2006) 577-581.
 - [63] C.E. Schmidt, V.R. Shastri, J.P. Vacanti, R. Langer, Stimulation of neurite outgrowth using an electrically conducting polymer, *Proc. Natl. Acad. Sci. USA* 94 (1997) 8948 - 8953.
 - [64] R.T. Richardson, B. Thompson, S. Moulton, C. Newbold, M.G. Lum, A. Cameron, The effect of polypyrrole with incorporated neurotrophin-3 on the promotion of neurite outgrowth from auditory neurons, *Biomaterials* 28 (2007) 513-523.
 - [65] L. Zhang, W.R. Stauffer, E.P. Jane, P.J. Sammak, X.T. Cui, Enhanced differentiation of embryonic and neural stem cells to neuronal fates on laminin peptides doped polypyrrole, *Macromol. Biosci.* 10 (2010) 1456-1464.
 - [66] P.M. George, A.W. Lyckman, D. A. LaVan, A. Hegde, Y. Leung, R. Avasare, C. Testa, P. M. Alexander, R. Langer, M. Sur, Fabrication and biocompatibility of polypyrrole implants suitable for neural prosthetics, *Biomaterials* 26 (2005) 3511-3519.
-

-
- [67] M. Asplund, E. Thaning, J. Lundberg, A.C. Sandberg-Nordqvist, B. Kostyszyn, O. Inganäs, H. Von Holst, Toxicity evaluation of PEDOT/biomolecular composites intended for neural communication electrodes, *Biomed. Mater.* 4 (2009) 045009.
 - [68] J.Y. Lee, C.A. Bashur, A.S. Goldstein, C.E. Schmidt, Polypyrrole-coated electrospun PLGA nanofibers for neural tissue applications, *Biomaterials* 30 (2009) 4325-4335.
 - [69] A.F. Quigley, J.M. Razal, B.C. Thompson, S.E. Moulton, M. Kita, E.L. Kennedy, G.M. Clark, G.G. Wallace, R.M.I. Kapsa, A conducting-polymer platform with biodegradable fibers for stimulation and guidance of axonal growth. *Adv. Mater.* 21 (2009) 4393-4397.
 - [70] J.Y. Lee, J.W. Lee, C.E. Schmidt, Neuroactive conducting scaffolds: nerve growth factor conjugation on active ester functionalized polypyrrole, *J. R. Soc. Interface.* 6 (2009) 801-810.
 - [71] G.-E. Anthony, Electroconductive hydrogels: synthesis, characterization and biomedical applications, *Biomaterials* 31(2010) 2701-2716.
 - [72] G.Z. Chen, M.S.P. Shaffer, D. Coleby, G. Dixon, W. Zhou, D.J. Fray, A.H. Windle, Carbon Nanotube and Polypyrrole Composites: Coating and Doping, *Adv. Mater.* 12 (2000) 522-526.
 - [73] Y. Lu, T. Li, X. Zhao, M. Li, Y. Cao, H. Yang, Y.Y. Duan, Electrodeposited polypyrrole/carbon nanotubes composite films electrodes for neural interfaces, *Biomaterials* 31 (2010) 5169-5181.
 - [74] X. Luo, C.L. Weaver, D.D. Zhou, R. Greenberg, X.T. Cui, Highly stable carbon nanotube doped poly(3,4-ethylenedioxythiophene) for chronic neural stimulation, *Biomaterials* 32 (2011) 5551-5557.
 - [75] X.T. Cui, D.D. Zhou, Poly(3,4-ethylenedioxythiophene) for chronic neural stimulation, *IEEE Trans. Neural Syst. Rehabil. Eng.* 15 (2007) 502-508.
 - [76] E. Jan, J.L. Hendricks, V. Husaini, S. M. Richardson-Burns, A. Sereno, D.C. Martin, N.A. Kotov, Layered carbon nanotube-polyelectrolyte electrodes outperform traditional neural interface materials, *Nano Lett.* 9 (2009) 4012-4018.
 - [77] B.C. Thompson, R.T. Richardson, S.E. Moulton, A.J. Evans, S. O'Leary, G.M. Clark, G.G. Wallace, Conducting polymers, dual neurotrophins and pulsed electrical stimulation – dramatic effects on neurite outgrowth, *J. Control. Release* 141 (2010) 161-167.
 - [78] R.K. Shepherd, A. Coco, S.B. Epp, Neurotrophins and electrical stimulation for protection and repair of spiral ganglion neurons following sensorineural hearing loss, *Hear. Res.* 242 (2008) 100-109.
 - [79] J.A. Chikar, D.J. Colesa, D.L. Swiderski, A.D. Polo, Y. Rapael, B.E. Pflingst, Over-expression of BDNF by adenovirus with concurrent electrical stimulation improves cochlear implant thresholds and survival of auditory neurons, *Hear. Res.* 245 (2008) 24-34.
 - [80] W. He, R.V. Bellamkonda, Nanoscale neuro-integrative coatings for neural implants, *Biomaterials* 26 (2005) 2983-2990.
 - [81] C. Marin, E. Fernández, Biocompatibility of intracortical microelectrodes: current status and future prospects, *Front. Neuroeng.* 3 (2010) 8.
 - [82] J.B. Leach, A.K.H. Achyuta, S.K. Murthy, Bridging the divide between neuroprosthetic design, tissue engineering and neurobiology, *Front. Neuroeng.* 2 (2010) 18.
 - [83] X. Liu, Z. Yue, M.J. Higgins, G.G. Wallace, Conducting polymers with immobilized fibrillar collagen for enhanced neural interfacing, *Biomaterials* 32 (2011) 7309-7317.
-

-
- [84] Z. Yue, X. Liu, P. Molino, G.G. Wallace, Bio-functionalization of polydimethylsiloxane with hyaluronic acid and hyaluronic acid-collagen conjugate for neural interfacing, *Biomaterials* 32 (2011) 4714-4724.
- [85] X. Cui, V.A. Lee, Y. Raphael, J.A. Wiler, J.F. Hetke, D.J. Anderson, D.C. Martin, Surface modification of neural recording electrodes with conducting polymer/biomolecule blends, *J. Biomed. Mater. Res.* 56 (2001).261-272.
- [86] W.R. Stauffer, X.T. Cui, Polypyrrole doped with 2 peptide sequences from laminin, *Biomaterials* 27 (2006) 2405-2413.
- [87] D.H. Kim, M. Abidian, D.C. Martin, Conducting polymers grown in hydrogel scaffolds coated on neural prosthetic devices, *J. Biomed. Mater. Res.* 71A (2004) 577-585.
- [88] M.R. Abidian, D.C. Martin, Multifunctional nanobiomaterials for neural interfaces, *Adv. Funct. Mater.* 19 (2009) 573-585.
- [89] R.A. Green, S. Baek, L.A. Poole-Warren, P.J. Martens, Conducting polymer-hydrogels for medical electrode application, *Sci. Technol. Adv. Mater.* 11 (2010) 014107.
- [90] B.C. Kim, G.M. Spinks, G.G. Wallace, Electroformation of conducting polymers in a hydrogel supported matrix, *Polymer* 41 (2000) 1783-1790.