

Organic bionics: molecules, materials and medical devices

The use of organic conductors in bionic devices is an exciting field of research. Gordon Wallace and Simon Moulton discuss the applications of organic bionics.

Can you imagine the personal impact that the restoration of sound or sight brought about by the bionic ear or the bionic eye would have on those dependent on such devices to regain these critical senses? Or imagine the vast improvements in the quality of life brought about by a neuroprosthetic device that replaces a lost limb?

Such ambitions are no longer in the realm of science fiction.

A number of bionic devices are already available, the most famous being the cochlear bionic ear implant pioneered by Professor Graeme Clark.¹ The bionic ear consists of a number of critical components: a microphone that picks up the sound, a speech processor that translates this into a series of electrical impulses and electrodes that transmit this impulse to the spiral ganglion cells in the cochlea. The effectiveness of medical implants such as the bionic ear and others mentioned above is critically dependent on this electrode-cellular interface and so the design, discovery and development of new electromaterials are critical to the enhancement of existing, and the development of new, bionic devices.

These electromaterials provide the conduit for electrical stimulation to be delivered to the biological environment.

So what is bionics?

The effective integration of a **biological** entity and **electronic** devices to create **bionic** structures is critical to create the required seamless bridge between these two worlds. Another challenge upon implantations of a bionic device is the electronic chasm created at the electrode-cellular interface, as the immune response results in encapsulation of the foreign body by fibrous tissue.

The first and perhaps most defining role the implant plays is in determining the nature (composition and structure) of this electrode-cellular interface. The composition of the bionic device assembly must be such that it is not cytotoxic and may, in fact, encourage the growth of certain cells over others in the vicinity of the implant. The composition and structure must also be such that appropriate mechanical

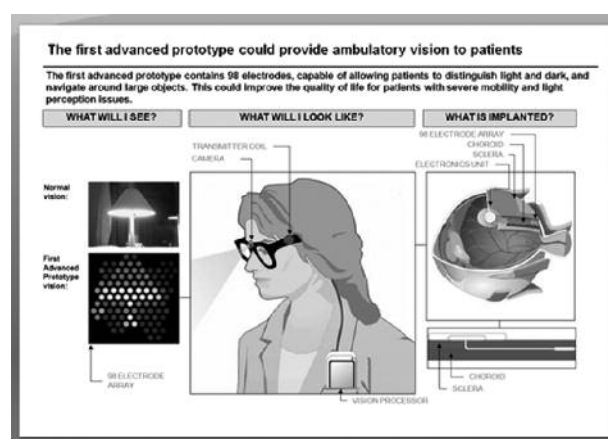


Figure 1. Bionic eye approach. (We gratefully acknowledge the permission of Bionic Vision Australia to use this image: www.bionicvision.org.au.)

properties are available during the implant's operational lifetime. The composition and structure of the device also determine its electronic properties, in particular conductivity (the ability to transport charge) and capacitance (the ability to store charge). After implantation, the composition and structure of the electrode-cellular interface dictate the ability to inject/transfer charge into the biological system. This will be determined by factors such as the cell types present and this is dependent on the nature of the electrical stimulation parameters used.²

Since the famous frog legs experiments conducted by Luigi Galvani in 1783, the electrodes of choice for bionic applications have been based on inert metals. These include platinum, as employed in the cochlear implant as well as in most bionic eye studies, and iridium oxide.³ Alloys of Pt and Ir have been utilised in deep brain simulator (DBS) electrodes.⁴ Pt was first used as a recording electrode for the cochlea in 1936⁵ and in 1975 as a stimulating electrode by Clark et al.⁶ for the cochlear implant. It was chosen because it is inert and has low impedance and low cytotoxicity. Pt has also been the material of choice for the development of the bionic eye^{7,8} (Fig. 1), in which the Pt electrodes are used to stimulate nerves in the retina. Iridium oxides have also been shown to be suitable electrodes for retinal stimulation for

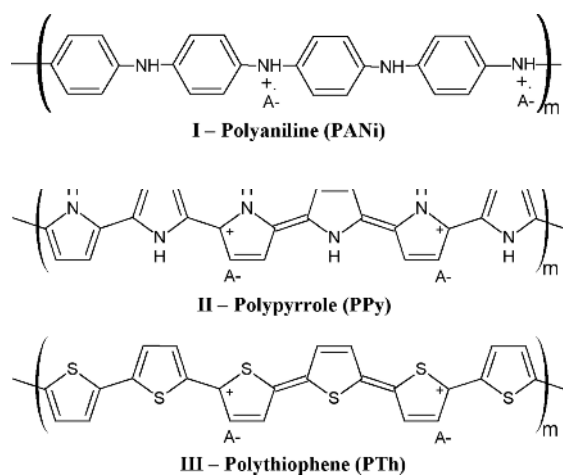


Figure 2. Some commonly used p-type organic conducting polymers. A⁻ represents anions, m determines molecular weight.

bionic eye applications.⁹ While Pt is a desirable metal for implantable electrodes due to its low impedance properties *in vivo*, its soft nature has its drawbacks. In order to improve its strength without compromising impedance properties, Ir-Pt alloys have been used. These alloys are frequently used in neuro-stimulation and recording applications such as direct neural sensory feedback and control of prosthetic limbs.¹⁰ Recently, nanostructuring of such electrodes has been shown to improve performance by reducing impedance and influencing cell compatibility.¹¹

Since the discovery of organic conducting polymers just on thirty years ago, researchers have devised a number of approaches to control the chemical/biological, electronic/electrochemical and mechanical properties. Control of each of these is critical for the optimisation of the electrode-cellular interface.

Given the degree of control thereby possible (see below), it is hardly surprising that there is now a rapidly increasing interest in the use of these organic conducting polymers to help bridge the electronic chasm often faced by bionic implants.

Organic bionics

Before discussing emerging applications for organic conductors in medical bionics, we will take a brief look at the control of implant properties through manipulation of the molecules and materials used to produce these devices. Finally, we will present some potential application areas for bionic structures based on conducting polymers.

Molecules: chemical/biological properties

The chemistry of organic conducting polymers is primarily dictated by the composition of the polymer backbone. There

are constraints in modifying this, in that to be electronically conductive the polymer must have a conjugated backbone and be amenable to doping (usually via oxidation to render p-doping) at relatively low electrochemical potentials.

Some of the more commonly used p-doped organic conducting polymers are shown in Figure 2, where A⁻ is a so-called 'dopant' anion incorporated to balance overall charge, and m determines molecular weight.

N-doped materials do exist, but they usually require application of a significant negative potential and such materials are famously unstable.

The polyanilines are not usually considered for bionic applications since the aniline monomer from which they are synthesised is only soluble at low pH and the polymer is usually only conductive at low pH - both factors limit the possibilities with respect to incorporation or attachment of biomolecules.

The pyrrole monomer is water soluble and hence polymer assembly can be initiated in biologically friendly media. This enables the incorporation/integration of biological entities such as antibodies, enzymes or biological polyelectrolytes, or other living cells at the time of polymerisation. Such an approach enables the matching of the polymer with the biological environment of interest. Some of the biological entities incorporated into polypyrrole (PPy) are summarised in Table 1. We have recently developed protocols that enable integration of nerve growth factors during the electrodeposition of PPy. These neurotrophin-loaded materials have then been used to facilitate interactions with nerve cells and promote neurite outgrowth using electrical stimulation that provides a direct effect as well as a means to control localised release of the growth factor exactly where the nerve cells are located. Electrical stimulation of PPy containing a nerve growth factor has been shown to be highly beneficial in promoting neurite outgrowth from cochlea explants (Fig. 3).

It is fortunate that facile routes to adjust the conducting polymer composition are at hand. The more obvious route is covalent attachment of groups to the polymer backbone. However, this is not straightforward. In the case of pyrrole or polypyrrole, this usually involves protecting and deprotecting the -NH group on the pyrrole ring to direct substitution to the 2- or 3-position. A number of bioactive functional groups have been covalently attached to polypyrroles, usually after polymerisation, to influence bioactivity. However, attachment to the pyrrole ring can cause a marked decrease in the electrical conductivity of the polymer. For example, covalent attachment work²²⁻²⁴ compromises electronic properties -

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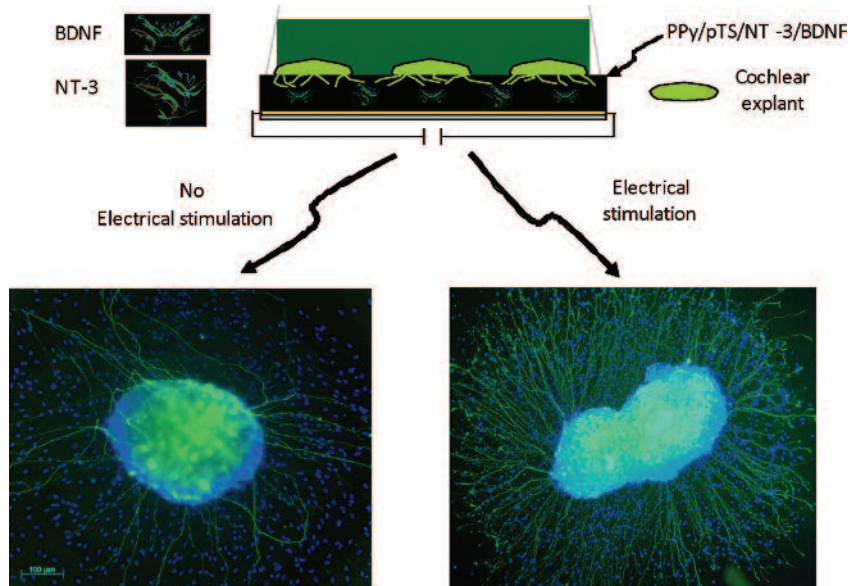


Figure 3. Experimental set-up for stimulating cochlea neurons in vitro (top). The chamber schematic shows the explants sitting on the polypyrrole polymer doped with neurotrophins (Neurotrophin 3, NT-3 and brain-derived neurotrophic factor, BDNF). Cochlea neuron explants cultured on PPy/pTS/NT-3/BDNF polymers (bottom left and right) show growing neurites extending from the explant cell body. Electrical stimulation increases the rate at which neurotrophins are released from the polymer structure. The increased concentration of neurotrophins causes the explant to differentiate to a greater extent. (Fluorescent images courtesy of Miss Brianna Thompson, ARC Centre of Excellence for Electromaterials Science, University of Wollongong.)

Table 1 Biological entities incorporated into PPy

Bioentity	Purpose	Reference
Enzymes:		
Horseradish peroxidase	Amperometric detection of rifampicin	12
Glucose oxidase	Amperometric detection of glucose	13, 14
Antibodies:		
Anti-isoproturon	Detection of the isoproturon pesticide in solution	15
Anti-human fibronectin	Electrically controllable sensing platform	16
Biological polyelectrolytes:		
Hyaluronic acid	Support and stimulate cell growth	17
Chondroitin sulfate	Support and stimulate cell growth	18
Neurotrophins	Enhance neural differentiation	19–21

Table 2 Functional groups covalently attached to polythiophenes for improved biomedical applications

Functionalisation entity	Purpose	Reference
Oligonucleotide	Genosensor	27
Biotin	Transducer for detection of avidin	28
Alkyl chains	Change hydrophobicity of polymer for cellular interaction	29
Glucose oxidase	Fabrication of electrodes for a glucose fuel cell	30, 31

compromising ability to transducer biomolecular binding events.

For polythiophenes, the thiophene monomers (thiophene, bithiophene or terthiophene) are not water soluble, so organic solvents are generally used for polymerisation. On the other hand, polythiophenes are more easily functionalised than polypyrroles.^{25,26} Table

2 shows some examples of functional groups covalently attached to polythiophenes to render them more bio-compatible.

Materials: physical and mechanical properties

The above conducting polymer materials have been used in various forms for bionic applications. The most

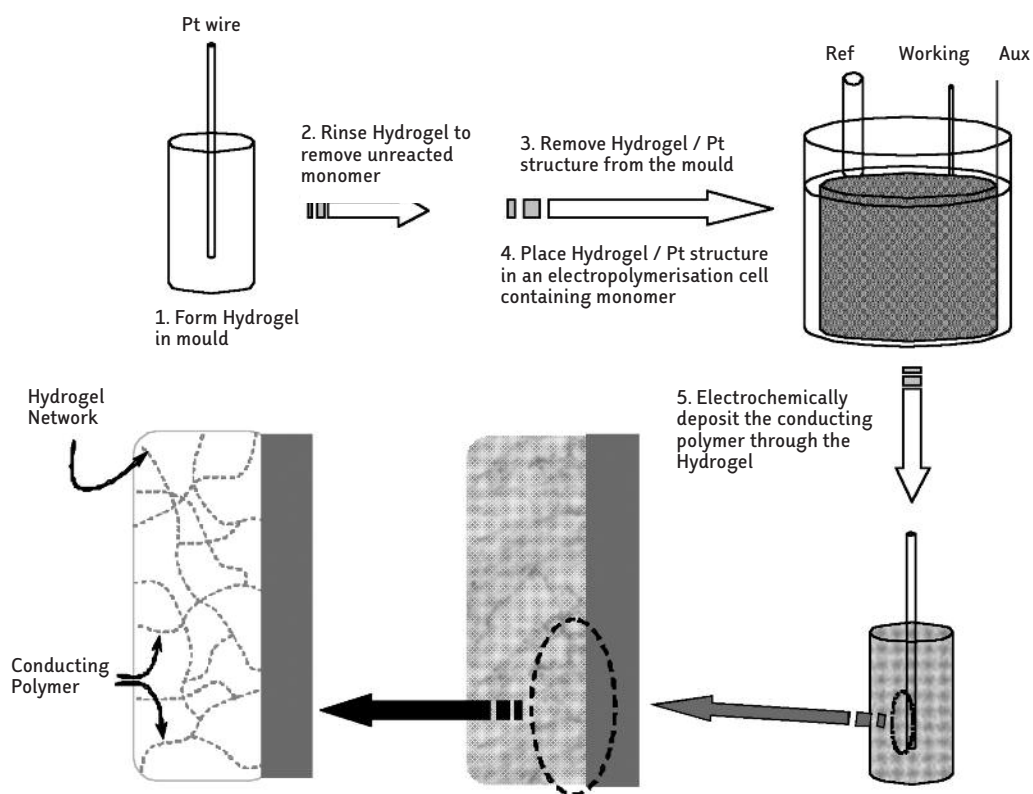


Figure 4. Process for fabricating conducting polymers-hydrogel composite.

common form is as a film produced via electrodeposition in which biomolecules are incorporated/attached using one of the strategies described above. A more detailed discussion of the protocols used for electrodeposition of each of these monomers is available elsewhere.³²

Electrodeposited films

Electrochemical formation of conducting polymers generally results in the formation of an insoluble deposit on the electrode. The composition of the material is dependent on the electrolyte solution used in the polymerisation. For bionic applications, an adherent film with good mechanical properties and high conductivity is desirable. While polymer composition (polymer backbone and the dopant, A^-) obviously will influence the resultant material properties, the electrochemical conditions (e.g. current density, applied potential) and the substrate employed also have a great influence.³² Varying the dopant has been shown to greatly effect the tensile strength of conducting polymers.³³ Their mechanical properties also vary with the concentration of dopant used in the polymerisation solution. For example, Kaynak et al.³⁴ demonstrated that the tensile strength of polypyrrole films highly doped with *p*-toluenesulfonate were lower than that of lightly doped ones. In addition, they showed that regardless of doping level, the polymer breaking strain decreased upon

ageing, while the breaking stress, Young's modulus and toughness increased. The use of biological polyelectrolytes such as dextran sulfate as the dopant is beneficial due to the biological character imparted at the molecular level, and also because of the formation of an electronically conducting hydrogel with high water content.³⁵

Electrically conducting hydrogels can also be formed by electropolymerising within a preformed gel (Fig. 4³⁶). The support structure of the original gel is retained with water content changing by only a few per cent after incorporation of the conducting polymer.³⁷ Processable (ethanol soluble) hydrogels based on block copolymers of poly(ethylene oxide) and poly(ϵ -caprolactone), or heat-extrudable gels based on cross-linked poly(acrylic acid) have also been used as the host matrix for conducting polymers.³⁸

Martin and co-workers recently reported an ingenious protocol that allows formation of a conducting polymer in the presence of living cells (neuroblastoma-derived cells) *in vitro*,³⁹ they further demonstrated the ability to polymerise a conducting polymer in living neural tissue *in vitro*.⁴⁰ This opens up the intriguing possibility of electropolymerisation of conducting polymers *in vivo*. These novel approaches enable, for the first time, the seamless integration of an

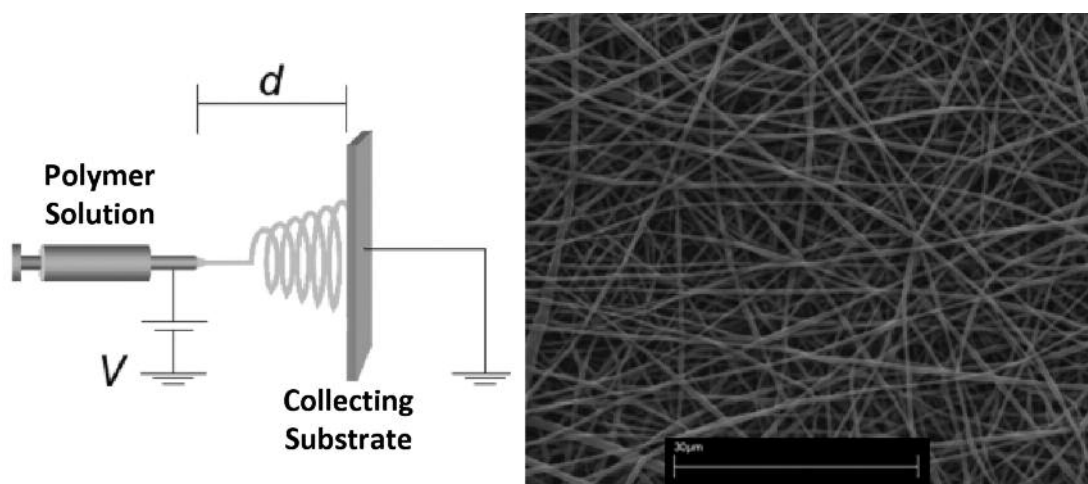


Figure 5. Electrospinning set-up (left) showing the resulting porous mat (right). The polymer in the syringe is dispensed at a set flow rate and a voltage (V) is applied between the syringe needle and the metal collecting substrate which is kept at a constant separation distance (d).

electrode with living cells. Conducting polymers, PEDOT and polypyrrole have also been evaluated *in vivo* with promising results indicating good biocompatibility⁴¹ with the ability to measure clinically relevant levels of chemical species in real time in such organs as the brain.⁴²

Spinning fibres

For some bionic applications, alternative material forms are required. Another attractive option therefore involves the use of more soluble, processable conducting polymers. The use of nano- or micro-dimensional fibres is of particular interest when directional cues for cell growth are required.

Electrospinning nanofibres

The use of electrospinning (Fig. 5) to produce nanofibres has been explored for biomaterials used in vascular grafts, wound dressings and tissue engineering scaffolds.⁴³ Electrospinning has been widely used for making non-woven, small-diameter, fibro-porous materials. It involves injecting charge into a polymer solution (typically 5–40 kV) contained in a syringe. Pressure is slowly applied to the syringe, forcing the polymer solution to the tip of the syringe needle. The charged polymer solution, at the needle tip, is separated from a second electrode (collecting substrate) of opposite polarity to generate an electric field. The charged polymer solution forms a Taylor cone due to competing forces generated in the static electric field and the polymer solution's surface tension. These forces cause charged fibres to disperse from the Taylor cone towards the collecting plate. Electrospun fibres have been prepared from biocompatible non-conducting polymers such as poly(lactic acid)/poly(lactic-co-glycolic acid) (PLA/PLGA)⁴⁴ and polyurethane.⁴⁵ The desire to impart additional functionality into electrospun fibres has recently resulted in the fabrication of conducting polymer fibres.⁴⁶ Significantly, nanofibres containing the conducting

polymer polypyrrole were fabricated into mats that successfully supported the growth of PC12 cells *in vitro*.⁴⁷

Wet spinning fibres

The technique of wet spinning has been used for many years to produce fibres for the textile industry. In more recent times, researchers have used this technique to produce fibres from a variety of polymers^{48,49} and polysaccharides⁵⁰ for use in a range of biomedical applications. These fibres have also been made electrically conducting by the incorporation of carbon nanotubes⁵¹⁻⁵³ and conducting polymers.⁵⁴⁻⁵⁶ Wet spinning offers the attractive feature of producing long lengths of fibres with uniform properties (conductivity and strength) along their length in one experimental run. These novel conducting fibres are now being investigated as suitable materials to be interfaced with cells to form components of bionic applications, such as stimulated drug delivery as well as neural growth and differentiation.

Medical devices

Extraordinary advances have already been made with medical devices using more conventional electrode materials. Piersma and Greatbatch⁵⁷ performed a comprehensive study of over thirty metals, alloys and other materials in simulated physiological conditions using galvanostatic pulses typically employed by cardiac pacemakers. They classified pacemaker electrode materials into five groups representing different electrochemical processes:⁵⁷

- 1 platinum group metals and alloys that exhibit no measurable dissolution and couple at the electrode-tissue interface by means of oxygen adsorption
- 2 valve metals like titanium and tantalum that undergo corrosion of the bare metal but are protected by an irre-

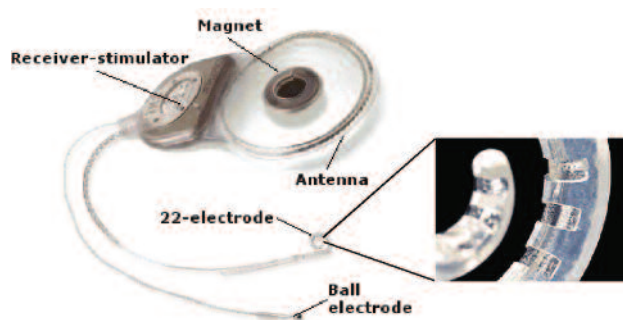


Figure 6. Internal components of the cochlear implant showing a close-up of some of the twenty-two Pt bands in the stimulating electrode array. Image courtesy of Cochlear Ltd 2009.

versibly formed oxide which cannot be electrochemically reduced

- 3 silver and similar materials that react with chloride ion, resulting in a metal chloride-metal ion equilibrium and an almost ideally non-polarisable electrode system
- 4 alloys of iron or cobalt that can experience significant dissolution under certain conditions and apparently do not couple by a reversible oxygen mechanism
- 5 carbon, which has current-voltage behaviour very similar to the platinum metals but which may have a different coupling mechanisms.

This comprehensive study enables researchers to choose the correct electrode material to match the bionic application and environment in which the electrode will be used.

For the cochlear implant (bionic ear) and bionic eye devices the metal of choice is platinum. The cochlear implant utilises twenty-two banded Pt electrodes (Fig. 6) while the most advanced bionic eye prototype utilises an electrode array comprising 60-micron-sized Pt pad electrodes. The Pt band electrode of the cochlear implant shows remarkable stimulating properties over years of operation with negligible increase in impedance. While the bionic eye is yet to undergo large-scale trials, the early indications suggest that the Pt pad electrodes perform as well in vivo as the cochlear implant electrodes.

The use of stimulating electrodes implanted into a patient's muscle to operate prosthetic limbs enables the user to manoeuvre the prosthetic via natural muscle contraction and relaxation triggered through normal neural pathways. In order for a robotic prosthetic limb to work, it must have several components to integrate it into the body's function. The electrodes (biosensors) detect signals from the user's nervous or muscular systems and relay this information to a controller located inside the device. They also process feedback from the limb and actuator (e.g. position, force) and send it to the controller. Electrode examples include wires

that detect electrical activity on the skin, needle electrodes implanted in muscle, and solid-state arrays with nerves growing through them. One type of electrode is the electromyographic electrode (Epimysial), which consists of a platinum-iridium disk mounted in a silicone backing reinforced with Dacron.⁵⁸

A bionic device has the capability to stimulate cells/tissue to initiate a response, such as contraction in muscle tissue or acceleration of cellular proliferation. These applications of bionic devices have been utilised for muscle and bone regeneration. Electrical stimulation of muscle cells and muscle tissue has been investigated in in vivo and in vitro environments, respectively. A range of electrode materials have been employed, such as carbon rods,⁵⁹ Pt-Ir⁶⁰ and a bilayer of Ti and Au.⁶¹

To initiate bone growth, there are two types of bone growth stimulators: one that sits on the outside of the skin and utilises electromagnetic fields, and an implantable (in vivo) system that utilises direct bone-pulsed current stimulation. The material of choice for the in vivo electrodes include titanium⁶² and stainless steel.⁶³ In vivo bone growth stimulation has been shown to produce new bone growth twice as fast as untreated fractures. Much research has been undertaken to accurately map the electric fields generated in bone.⁶⁴ As a result, the effects of electrode shape, size and material of the stimulating electrode on bone regrowth are well characterised.

Conclusions and future developments

The world of bionics should be revolutionised in the next few decades. Astounding advances in electronics and materials science will undoubtedly impact on our ability to influence the **biological world using electronics**. The development of highly effective devices such as the bionic eye⁹ and the bionic ear,^{1,2} as well as the ability to integrate prosthetic devices with neural control⁵⁸ or to use bionic devices in regenerative medicine will have tremendous implications for individuals and the society in which they live.

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