Guest Lecture Series (2 of 2)

Tailoring Cell-Biomaterial Interfaces: Organic Bioelectronics

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Purpose of these lectures

The aim of these two guest lectures is to introduce you to state-of-the-art ongoing research in the area of cell-biomaterial interactions. These are techniques that broadly still laboratory-based but are slowly being translated into clinical environments. Trying to understand their underlying mechanisms helps us design better biomaterials.

The two lectures are distinct, the common link is that they present different ways of modifying the cell-biomaterial interface. The first lecture considers how the topography of a material can be modified to create an extreme nanostructured environment for interfacing with cells and tissue. The second lecture considers how using a class of polymeric materials that have unusual electronic and ionic properties can be used to modulate a bioelectronic interface with cells and tissue.

As both topics are under active research, these lectures are based on the best available information at the time of writing. Where there is academic debate, I will try to highlight that. With time the understanding and knowledge in this area will improve, and some of the unknowns presented here may be resolved (possibly by you, if you continue in research).

Further reading

For your interest, a further reading list is provided below to give you direct links to the underlying academic literature supporting these lectures. There is no textbook, because we don't know enough yet to write one.

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Executive summary

- Organic Bioelectronics is a roughly decade-old research field that uses conjugated polymers to create biological interfaces

- Conjugated polymers are plastics that can be made to conduct electricity

- The mixture of electronic and ionic conduction in conjugated polymers makes them inherently useful transducers of bioelectricity (ionic currents) and the electronic currents of measurement and stimulating devices

- Both the synthesis and processing of conjugated polymers can be tuned to give a wide range of electrical and mechanical properties, including creating conductive, stretchable hydrogels

- These materials have been used in neuroscience, drug delivery, peripheral nerve stimulation and as electrically-active tissue scaffolds

- Much research is ongoing into both fundamental interaction mechanisms and applications across multiple bioengineering domains

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Glossary

- Bioelectricity
    - The presence of electrical fields inside living systems, and their subsequent influence of electrical fields upon the behaviour and development of cells and tissue

- Endogeneous electric field
    - Electric fields found within tissues as a result of the separation of different concentrations and charges of ions by membranes (such as cell membranes or epithelial layers)

- Galvanotaxis/electrotaxis
    - The directed motion of cells in response to an electric field

- Bioelectronics
    - The integration of electronic devices with living systems in order to both sense and stimulate biological behaviour

- Organic electronics
    - Research field that uses conjugated polymers and small organic molecules to create electronic devices

- Conjugated polymer
    - A polymer that contains carbon-carbon bonds that have hybridised to form overlapping π-π bonds. These bonds give the polymer interesting electrical properties

- Conductive polymer

    - A conjugated polymer that has been processed in such a way that the resulting material has high conductivities, comparable to those found in metals

- Organic bioelectronics
    - A recent offshoot of organic electronics, which aims to use conjugated polymers and molecules to build bioelectronic interfaces

- Bioelectronic/bioelectric medicine
    - The use of bioelectronic devices to stimulate cells, nerves or tissue in order to induce a desirable physiological responses and/or treatment of diseases or disorders, as an alternative to drug-based pharmacology

- Electroceutical
    - A device that delivers electrical stimulation in order to achieve a desirable physiological response, e.g. a pacemaker, a deep brain stimulator

- PEDOT:PSS
    - A composite made of the conjugated polymer poly(3,4-ethylenedioxythiophene) (PEDOT) and the polymer polystyrene sulfonate (PSS). Under specific processing conditions, the PSS acts to make the PEDOT conductive. By far the most commonly used material system in organic bioelectronics, thanks in part to the perceived biocompatibility and ability to form a dispersion in water that can be readily processed

Lecture notes

1. Bioelectricity is the presence of electrical currents and fields within living organisms [1–3]
    a. Bioelectricity originates from the presence of different ion concentrations separated by membranes
        i. Electrical fields (endogenous fields) exist at different levels of hierarchy within living systems
        ii. Fundamentally emerge where different concentrations of ions are separated by a barrier (nuclear membrane, cellular membrane, epithelial layer)

            e.g. characterised by a cell membrane potential V_{mem}

            e.g. characterised by a transepithelial potential V_{TEP}

        iii. Movement of ions across membranes and around biological systems is mediated by both passive and active mechanisms

            e.g. disruption of a barrier by a wound/injury – resulting in the passive diffusion of ions

            e.g. passively passing through voltage-mediated ion channels

            e.g. active transport via ion transporters/pumps

        iv. Electrically-excitable cells use a continuous wave of ion movements that result in a continuous wave of membrane depolarisation and hence the transmission of signals through the organism

            e.g. in cardiac or neural tissue

    b. Interaction mechanisms between endogeneous electric fields and other biological mechanisms are complex and non-linear
        i. Behaviours are complex and linked to feedback mechanisms

            e.g. voltage-gated ion channels open in response to a given membrane potential resulting in the movement of ions and hence a change in membrane potential

        ii. Other interaction mechanisms present, and how they act is open area of research
    c. Bioelectricity in plays a role in wound healing and regeneration
        i. Where an epithelial layer in damaged, this can result in the diffusion of ions and hence a change in electric field strength and alignment

            e.g. keratinocytes (skin cells) can migrate towards a wound site following an electric field, suggesting endogenous fields play a large role in wound healing

        ii. In bone repair, both direct injection of electrical current and/or exposure to an external electric field aligned with a fracture region can result in improved bone regeneration
    d. Bioelectronic medicine attempts to deliberately manipulate bioelectricity within the body to create a desirable response
        i. The vagus nerve is a peripheral nerve that emerges from the brain and interfaces with the heart, lungs and digestive tract

ii. Vagus nerve stimulation (from an implanted electrode in the chest) has been used as a treatment for seizure control in patients with drug resistant epilepsy

iii. More recently, vagus nerve activity has been linked to asthma, diabetes and other diseases and conditions, motivating many researchers to find potentially electroceutical treatments

iv. Electroceutical treatments would allow localised treatments without the reliance of drugs, and readily tailorable to patients by varying the stimulation behaviour

v. Much remains unknown about the underlying mechanisms

2. Organic Bioelectronics is an offshoot from the field of Organic Electronics, which uses electrical devices made from conjugated polymers and molecules to build a wide range of biological interfaces [4–7]
    a. The field of Organic Electronics originated in the late 1970s
        i. Researchers working with the polymer polyactylene found that when processed under appropriate conditions the material could be made conductive. This was revolutionary because it had always been assumed that plastics can only be electrically insulating
        ii. The research led to the award of the Nobel Prize in Chemistry in 2000 "for the discovery and development of conductive polymers" to Alan J. Heeger, Alan G. MacDiarmid and Hideki Shirawaka
    b. Much has happened in the past 40+ years
        i. By modifying the polymer sidechains, chemists could give conjugated polymers desirable processing characteristics, such as making them soluble in a wide range of organic solvents
        ii. Researchers started to substitute these new 'plastic' semiconducting, conducting and light-emitting materials into electronic devices that, up until that point, had typically been manufactured from inorganic materials such as silicon or gold
        iii. This most successful translation of the field to date has been the emergence of the multi-billion dollar industry of organic light emitting diode (OLED) televisions, and more recently to the development of flexible displays for smartphones
        iv. These materials have also been used to make flexible solar cells, photodetectors, and chemical sensors
    c. In the last ~10 years the focus has turned to biological applications
        i. Initial experiments found that conjugated polymers were biocompatible (in the sense that cells could be successfully cultured on their surface)
        ii. Conjugated polymers have been used to modify the surface of metal electrodes, to lower their impedance (resistance to charge) to build better sensors of bioelectricity
        iii. Conjugated polymers can be manufactured into freeze-dried scaffolds for tissue engineering applications, such as bone repair

    iv. More recently, there has been a focus on creating deformable conducting hydrogels from conjugated polymers to create soft bioelectronic interfaces that minimise immune response

3. The motivation for developing organic bioelectronic interfaces comes from the ability to readily change the properties of the material using organic chemistry and material science to create soft, biologically compatible systems [8]
    a. Existing materials and devices used to sense and stimulate biological systems have limitations
        i. There is a strong mechanical mismatch between metals and inorganic semiconductors and biological tissue. Tissue has a Young's modulus typically in the kilopascal range, metals and inorganic semiconductors are much stiffer, with moduli in the gigapascal range
        ii. This mismatch can result in increased interfacial stress and disruption of devices as the body moves
        iii. Implanted metal electrode can trigger a foreign body reaction, which results in the build-up of protein that decreases the efficiency of implanted electrodes, ultimately leading to device failure
        iv. Planar metal electrodes in an ionic environment form a high-capacitance ionic double layer, which increases the impedance, and noise, resulting in worse sensing performance
    b. Organic chemistry can be used to modify the side chains of conjugated polymer to change the biological and material properties
        i. Biologically relevant groups (such as RGD peptide mimics) can be incorporated in the polymer sidechains to promote cell adhesion
        ii. Conjugated polymers can be engineered into natively stretchable composites and devices, accommodating bodily motion
        iii. Polymer films can be engineered to allow the percolation of ions, effectively exposing a large volume of the polymer for electrical sensing, lowering the effective impedance
    c. High-throughput manufacturing techniques can be used for the mass production of electronic devices from conjugated polymers
        i. Devices can be manufactured using printing presses and inkjet printers onto flexible plastic or paper substrates
        ii. Costs can be kept low – a desirable regime for practical biomedical devices

4. There are a number of state-of-the-art organic bioelectronic devices
    a. 'Neurogrid' is a modified micro-electrode array for sensing neuronal activity in the brain [9,10]
        i. A flexible array conforms directly to the surface of the brain and can be used to monitor local field potentials (small spikes of electrical activity created by the action potentials of multiple neurons firing together)
        ii. The system uses the conducting polymer PEDOT:PSS to reduce the impedance mismatch between the electrode and tissue, improving the signal to noise ratio

        iii. The device has been tested in epilepsy patients, and also used to study electrical oscillations in different regions of the brain as part of a neuroscience study exploring the link between long term memory storage and sleep

    b. An ‘Organic Electronic Ion Pump (OEIP)’ is a device used for drug delivery [11,12]

        i. An OEIP uses two regions of a conductive polymer, separated by a cation exchange membrane (a polymeric film that only allows the flow of cations, positively charged ions, through it)

        ii. Applying a voltage across the device causes the flow of cations from a source reservoir, through that cation exchange medium and into a region of media where cells or tissue exist

        iii. This principle has been used to create an implantable soft probe that can simultaneously detect neural activity and deliver a neurotransmitter (gamma-aminobutyric acid, GABA)

        iv. In a mice model, the probe could detect the onset of a chemically-induced seizure, and immediately suppress it by delivering GABA

    c. Stretchable conductive hydrogels have been developed for peripheral nerve stimulation [13,14]

        i. Researchers created a conductive hydrogel by combining a conductive polymer (PEDOT:PSS) and an ionic liquid

        ii. This material was patterned into a soft neural cuff for peripheral nerve interfacing

        iii. The soft hydrogel cuff resulted in significant reduction in immune response compared to a hard plastic/metal coated neural cuff

        iv. In a mouse model, researchers could stimulate the sciatic nerve with enough precision that they could trigger different toe and leg movements depending on the stimulation pattern, and at much lower voltages than traditional platinum-coated cuffs

    d. Tissue scaffolds fabricated from conjugated polymers [15,16]

        i. Conjugated polymers can also be processed into three-dimensional scaffolds using techniques such as ice-templating

        ii. In one example, osteogenic precursor cells successfully cultured on the scaffolds, resulting in increase in extracellular matrix mineralisation and osteocalcin deposition

        iii. In another example, the conductive scaffold was incorporated into an electronic device. Researchers could electrically monitor cell adhesion to the scaffold, creating a 3D model system with quantifiable electrical output

5. Conjugated polymers are an area of intense research effort in multiple fields

    a. Bioengineering/bioelectronics

        i. Efforts are focusing on developing better understanding of how devices interact with cells and tissues

    ii. Similar there is a focus on the development of more advanced 3D scaffolds that allow greater resolution of sensing and stimulation and reconciling this with desirable tissue engineering behaviours

b. Bioelectronic medicine
    i. Focus on using soft materials made of conjugated polymers to create neural interfaces that reduce the chronic inflammation seen with the current generation of hard plastic/metal cuffs

c. Neuroscience
    i. Efforts to downscale electrode systems and add in-situ electrical amplification of signals to improve the spatial and electrical resolution of measurements

d. Organic chemistry
    i. Focus on synthesising new conjugated polymers with different backbones and sidechains to give a wider palette of materials to work with (e.g. electron-transporting, stable conjugated polymers)

e. Material science
    i. Developing improved processing methods that retain electrical transport properties while enabling desirable stretchy mechanical properties

f. Physics
    i. Focus on understanding underlying mechanisms, for example understanding why recently developed amorphous, disordered polymer systems still seem to show relatively high charge transport properties (where the traditional paradigm is that crystalline/semicrystalline materials are more conductive than amorphous ones)

Further reading

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