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Bioelectronics: Revolutionizing the Research Landscape of Modern Medicine, Security & Environmental Applications

Krishna Sundari Sattiraju[1] and Harshith S Potapragada[2]

[1]JIIT, NOIDA, 201307, Uttar Pradesh
[2]GVPCE, JNTU (K), Andhra Pradesh
E-mail: [1]krishna.sundari@jiit.ac.in, [2]harshith.potapragada@gmail.com

Abstract—*Bioelectronics – A convergence of Electronics & Biological sciences, is emerging as a fast paced research intensive field furthering the reach of modern medicine, security and environmental applications. Bioelectronics finds their place wherever there is a requirement for functional integration of biological phenomena with physical, chemical, electrical, electrochemical environments. The paper presents a review on different biomaterials that are used in fabricating bioelectronic devices and implants. These devices incorporate transient, nature derived, biocompatible substances that could function as:organic conductors, transistors, dielectrisc, resistors, inductors, capacitors, etc.. The study also provides a detailed insight into the improved properties of bioelectronic devices and how they have rewritten the successful inventions in the fields of modern regenerative medicine, surveillance and smart environmentally safe solutions for consumer goods.*

1. INTRODUCTION

Advances in Biotechnology, Nano technology, Biophysics & Material sciences have greatly contributed to the inter disciplinary field of bioelectronics research with real time applications. Though the field of bioelectronics is fairly recent (evolved in the past two decades), research efforts are aggressive, meeting the challenges presented by complex systems that demand functional integration of live/biotic systems with physical/non-living matter. Programmable, degradable, organic biomaterials are increasingly used in bioelectronics, finding strong application in various areas of medicine (tissue engineering, medical implants, resorbable medical devices); security (surveillance, brain mapping, material sensing & forewarning systems, drones etc); and environmental research [1-2].

2. PROPERTIES DESIROUS OF BIOELECTRONICS

While there are as many numbers of chemical, physical, biological, mechanical and electrical parameters that require optimization and specific consideration in designing Bioelectronics, it suffices to say that it is the end application of the device which determines the properties desirous for a given bioelectronic device. Nonetheless, certain factors like biocompatibility, biodegradability, flexibility, conductivity and programmability top the list of the desirable features and are detailed in ensuing paragraphs.

2.1 Biocompatibility

Biocompatibility is of foremost concern in any of the implantable bioelectronic devices. Before any biomaterial is considered for fabricating implantable bioelectronic device, it is mandatory that these materials be tested *in vitro* at levels (I & II) as recommended by NIH guidelines for blood-materials interactions. Tests of significance include: study of physical properties (electrical charge, surface texture, charge conducting ability, elastic modulus, porosity), chemical composition, reactivity of functional groups on surface, solubility, evaluation of cytotoxicity to cells, clotting time and haemolysis testing, study of biomaterial surface properties like contact angle characterization, protein adsorption, etc.. At times the biocompatibility of materials is improved through surface modification techniques like surface coating (to minimize non-specific protein adsorption and protein fouling) or surface patterning (imprint arrays of hydrophobic nanostructures on surface to reduce adsorption of proteins) [3].

2.2 Transient nature

Electronic devices and platforms with a programmable dissolution or degradation property have great significance in bioelectronics used for military, surveillance, intelligence, security and biomedical applications. In biocompatible, bioelectronic devices, transiency can be achieved either through corrosion (erosion), reactive hydrolysis, enzymatic breakdown (of ester bonds by esterases) leading to depolymerization, or simple absorption. The property of transiency can be programmed real-time by manipulating physical (light, pressure, temperature), chemical (ionic balance, ph), biochemical (concentration of metabolites) changes in the microenvironment. It is preferred that the degradation of biomaterials used in bioelectronic devices release non toxic breakdown products. Moreover, for many applications, the rate of biodegradation also plays a significant role. The first generation organic semiconductors and PVA based gate dielectrics took two-and-a-half months to degrade at low environmental pH. These were fast replaced by biodegradable transistors, fabricated on peptide based substrates with properties of instant degradation (in phosphate buffered saline – PBS). While bio-resorability is most desirable incase of medical implants, eco-resorbability enables usage of bioelectronics in communication systems that escape unwarranted detection upon exposure to specific environment (reactive dissolution though hydrolysis) [2, 4].

2.3 Flexibility

Mechanical properties receive considerable emphasis in fabricating bioelectronics. Flexibility of the materials would ensure that they can be efficiently used in implants where it is required that the bioelectronic device should confer with the three dimensional structure of the organ/tissue. Techniques like photolithography and surface modification are used to fabricate the components on biocompatible & flexible platforms that can operate at living tissue interfaces. Researchers' demonstrated use of bacterial cellulose membranes (BCM), and silk based composites with remarkable flexibility and mechanical stability for fabricating transient bioelectronics [2]. Flexible electronic circuits also found their place in designing functional fabrics and development of e-textiles. Recent innovations have gone a step further in designing flexible bioelectronics that are even foldable (paper airplane circuits). Foldable paper based electronic circuits with advantages of fragility, combustibility, disposability and biodegradability are finding increasing acceptance in stealth and security applications. Their small bending radii and roll-to-roll processivity enable use of simple techniques of paper craft like Origami to interface circuit layout and design generating circuits of distinct topology [5].

2.4 Conductivity

Fabrication of electronic circuits initially used either magnesium or other magnesium based materials such as magnesium oxide to draw conductive paths connecting resistors, inductors and so on. Magnesium was the chosen material due to its solubility in water and compatibility with biological systems. However recent advancements in bioelectronics are increasingly employing silicon nano-membranes, polymers, peptide based templates for developing semi-conductors. Use of biopolymer protonic field transistors that work on proton-conduction and use of natural dyes (indigo, tyrian purple) and pigments (melanin) for demonstrated ionic and semi-conducting applications is finding increasing prominence in recent literature [6-7]

2.5 Programmability

Transiency of biomaterials can be exploited to its maximum only when the transiency can be programmed or regulated. Researchers have suggested that the composite nature of the bioelectronic materials themselves can be used as a means to control the rate at which the respective material dissolves. For instance, in order to alter the transiency rate of PVA (polyvinyl alcohol) polymer matrix, biomaterials like gelatin and sucrose can be applied [2].

2.6 Other features of interest

To find place in bioelectronic devices and implants, the materials are expected to possess selective permeability, adequate porosity, and strength to serve as mechanical support for cell growth, proliferation [8]

3. BIOMATERIALS FOR BIOELECTRONICS

Research on transient biomaterials suitable for fabricating bioelectronic devices is quite young and dynamic (currently in its 20s). The field is making its mark, scoring with most vital and path breaking discoveries revolutionizing the applicability of scientific principles that are of inter disciplinary nature.

Silk

Silk or silk-fibrions occupy a prominent position as the most preferred choice for fabricating implants that are to serve as bio-integrated electronic implants. Not only do they exhibit fast and programmable degradation kinetics, but they also offer ample flexibility coupled with mechanical stability and high optical transparency which makes them more amenable for fabricating circuits on to their surfaces using photolithographic techniques. Silk fibrions are water soluble and are enzymatically degradable. Between sericin and fibrion, the two principle silk proteins, fibrion with its mechanical strength attributing property is mostly used in fabricating flexible bioelectronic surfaces. They find utility as mechanical support / substrate / material for packaging bioelectronics. Several workers proposed the use of silk fibrion in drug delivery, disease prognosis/diagnostics, disease monitoring etc. Incorporating specific antibodies or enzymes in silk fibrions can make them sense disease biomarkers (*viz.*, monitoring insulin levels in blood and triggering controlled drug release), helping in diagnostics, and therapy. In thermal therapy mediated through silk fibrions, localized heating occurs at the site of implants, alleviating pain and bacterial infection. Silk has also been approved by FDA to be used in tissue engineering and wound closure. [4].

3.1 Carotenoids

Carotenoids with high hole mobility (10^6 to 10^7 cm^2/V/sec) are emerging as a good option for OTFTs. Completely biodegradable OTFTs are constructed using PLGA (poly lactide co glycolide) and PVA (poly vinyl alohol) as substrate and gate dielectric respectively where gld and silver nano materials are used as source-drain and gate contacts. Biodegradability of these devices relies on oxidative degradation of small organic molecules in cellular organelles like peroxisomes [5].

3.2 Silicon

Transient silicon nano-membranes (TSNM) were studied for their ability to provide thermal therapy through strategically placed implants in animal models. These TSNMs can even be integrated in living/non-living and indoor/outdoor environments. The fact that TSNM are biocompatible and show very high transience rate is an additional advantage for their application as bioelectronic material.

TSNMs can also be developed as transistors which upon integration into circuits would either disappear or undergo transformation. Other applications of TSNMs include utility as photovoltaic, inductive devices, high performance transistors, solar cells, detectors of physical stimuli(light, temperature) [4].

3.3 Melanin

The ubiquitous mammalian pigment Melanin is one of the first popular naturally available semiconducting biomolecule. It was lauded for its properties of conduction, ohmicity and processive nature. However, overlapping electronic structures in melanin presented complications for its potential to be used as organic transistors [5].

3.4 Organic Conducting polymers

Role of conducting polymers (CP) was extensively studied by many scholars in biological systems that respond to electrical stimulus including fibroblasts, stem cells (mesenchymatic), cardiac, muscle and bone cells. However conventional CP when used *in vivo* could lead to undesirable inflammatory response and have associated drawbacks like hydrophobicity, poor cell interaction capability and unreliable structural issues. The new age biodegradable CP of natural origin includes chitosan, poly urethane, collagen, gelatin, heparin etc. Similarly polyurethane with its better mechanical and process parameters is being increasingly used for biomedical applications. Not only does these CPs have adequate porosity but even the structure of fabricated scaffold and its pore size can be biochemically regulated.

The most recent advancement in conductive polymer research is the development of electrically conducting hydrogels that are biodegradable. These materials are synthesized from natural polymers like chitosan and gelatin with aniline oligomers. They are of rubbery nature, regulate exchange of nutrients, oxygen small molecules and are sensitive to ph while being biocompatible. These new age polymers come with a regulatable self assembly that can be controlled through electrical / redox response. This property was reported to have far reaching applications in vascular reconstruction, regeneration of soft tissue and constructing biomimatic systems [8].

3.4 Paper

Paper is derived from natural polymer (plant sourced) cellulose. Relative low cost, complete biodegradability, large surface area, ease of printing/ fabricating small foldable with very small bending radii, desirable surface, mechanical & insulating properties make paper an excellent option for organic field effect transistors. Paper has been used to fabricate active low voltage circuits, flexible electro- wetting display and paper photovoltaics [1, 6].

3.5 Natural dyes & Resins

Plant derived natural dyes such as indigo and tyrian purple can form thin crystalline films with considerable charge transport abilities. They can also serve as good semiconductor materials due to intermolecular hydrogen bonding. Blue dyes like Indigo & Tyrian purple have long since been used as organic counterparts to design radio frequency identification (RF-ID) tags in smart electronics. New discoveries in the field are assigning more challenging functions to these natural materials. Organic FETs (Field effect transistors) constructed using tyrian purple were found to exhibit high electron and hole mobilities. Shellac, a natural polymeric resin was also explored to make organic FETs [9, 10].

More and more smart biomaterials are being added to this impressive list of support materials for bioelectronic. Ecoflex, a completely biodegradable plastic produced from potato and corn starch in combination with polylactic acid and caramelized glucose is a very recent addition to this list [9].

4. APPLICATIONS OF BIOELECTRONICS

4.1 Medical applications

Stimulus responsive transient electronic devices have vastly improved disease, diagnosis, monitoring therapy while adding a whole new dimension to regenerative medicine, programmable drug release, *in-vivo* imaging &thermal therapy for post operative care. Biomaterials as nano-antibiotics can be applied for restricting post surgical sepsis and controlled wound healing (thermal therapy). Transient intra-vascular stems, programmed bone growth & resorbable plate- screw systems are all the result of modern bioelectronics research that have considerably decreased multiple surgical interventions [11].

4.1.1 Resorbable implants. Under circumstances where there is an absence of physiologically controlled electrical stimulus, MEMS (microelectromechanical systems) come to the rescue. Thus MEMS can function as implantable electronic devices either as neural implants, pacemakers, retinal implants etc. [12]. Natural polymer chitosan with its wound healing, antimicrobial and immunological properties is being used in fabricating bioelectronic implants intended for tissue engineering and targeted drug delivery applications [8]. Prosthesis for neural stimulations were developed by University of Michigan as MEMS devices that not only facilitate stimulation & recording from neurons but also serve as delivery ports for drugs at cellular levels. They can even transmit current stimuli and bring about activation of nerve impulses. Stimulating deep brain regions can help in parkinsons disease and can also prevent atrophy of paralyzed muscles. MEMS based retinal implants are also prevalent. Retinal implants are applied to rectify vision related problems occurring in bilateral corneal opaqueness, retinitis pigmentosa [12].

4.1.2 **Regenerative medicine.**

Several biological processes such as cell adhesion, proliferation, migration, differentiation, synthesis of DNA etc are all regulated through exchange of electrical signals. Conductive biopolymers with optimal biodegradability and biocompatibility are the materials of choice to fabricate bioelectronic devices in regenerative medicine [13]. Biocompatible, transient, photo reactive molecules like carbonates, carbamates etc are being used with increased efficiency in constructing scaffolds. Microstereolithography involving laser driven photopolymerization is the technique of choice for fabricating 3-D scaffolds in tissue engineering [14, 15]. Stimulus responsive biomaterials were found to effectively repair peripheral nerve damage and even close the spasm between severed nerve endings. This approach was reported to completely obviate the need for nerve grafting that not only requires multiple surgical procedures but can even result in loss of function at donor site. [14]. A copolymer of PLA (Poly (1-Lactide) and anniline pentamor was reported to improve the processiility and solubility of biocompatible and transient PLA enabling it to be employed as a conductive polymer scaffolding in cardiovascular and neuronal tissue engineering [14].

4.1.3 In vivo imaging

In order to successfully map progression of tumors *in vivo*, fluorescent imaging studies are well prevalent where quantum dots (qds) are used for the purpose. However, cadmium could result in cytotoxicity and was of concern in cancer diagnostics, therapy. The new age biomaterial discoveries have created encapsulated biocompatible silicon quantum dots that are completely free of heavy metal cadmium. They paved way to many *in vivo* cancer related applications including multichannel imaging in live animal models [10].

4.2 Intelligence / Military applications

Use of flexible, dissolvable bioelectronic materials in monitoring abnormal brain activities and mapping function was reported by multiple authors [2, 6, 14]. Such transient devices, comprising arrays of micro-fabricated electrodes, can be used for intelligence purposes where strategically located implants can decipher and record the electric signals from brain activity, transmit the data to a monitoring device where it can be appropriately analyzed and interpretations drawn. Security envelope was one of the most quoted applications of paper based foldable electronic circuits which upon breach of code would disintegrate completely. Paper based bioelectronic systems have presented an interesting anti-counterfeiting solution where active low voltage circuits were fabricated on bank notes [13].

The 'Georgia Tech Wearable Motherboard (GTWM)'was one of the first generation smart shirts developed using optical fibres. It was primarily designed for military, to detect bullet wounds and was also provided with sensors to monitor vital signs of personnel during combat conditions. However advancements in biocompatible e-textiles have furthered the research to offer smart fabrics for medical (geriatric, psychiatric) care, evaluate performance of sports personnel, space experiments (during manned aerospace missions), public safety (fire fighting, bomb diffusal), so on and so forth. Augmenting the smart fabrics with sensors, microchips and GPS was also explored for assisting researchers working in arctic environments [16].

4.3 Environmental applications

Based on a 2010 statistic, global consumption of plastic is 83 million metric tonnes and is said to triple by the end of this decade. Plastic being non-biodegradable, presents a issue of gigantic proportions with respect to environmental toxic waste management [6].Though a conscious effort to ease this burden on environment has been initiated more than two decades ago significant advancements in this direction are surfacing only recently with discovery of organic photovoltaics (OPV) organic light emitting diodes (OLEDS) and organic Field Effect Transistors(OFETS). These materials can lead to the development of environmentally safe, human friendly electronics in the near future. The dual ability of these materials to behave both as electronic and ionic conductors facilitates their use at interfaces where either ionic or protonic gradients drive the reaction mechanisms. The fact that these materials are flexible, non toxic and non inflammatory would only add to their tremendous applicative potential.

Detection of vaporous chemicals in the environment and specific analytes in aqueous systems was achieved using organic thin film transistors (OTFTs). These are basically comprised of an organic semi-conductor spread as a thin layer along with three conductive terminals (source, drain, gate) on organic, polymeric substrate and a dielectric layer of insulation. Organic field effect transistors (FETs) were successfully employed in detecting odorant molecules using antibodies of human olfactory receptor (hOR) as recognition probe in specially crafted nano-biosensors [1]. The sensitivity of bioelectronic nose (containing hOR conjugated nanotubes) was so high that they were demonstrated to detect specific odorants at femtomole concentrations. Silk optical fibres can receive light signals from LED array implants and could in turn transmit the signal to a recording / communication device (say a mobile phone), providing significant medical, security and surveillance applications [17].

4.4 Smart Electronics

TSNM based ultrathin solar cells were developed that show high power conversion efficiencies and unlike conventional solar cells do not require anti reflection coatings, light trapping structures or side reflectors. Another prominent discovery in synthesis of smart solar cells was with paper based organic photovoltaics, involving roll-to-roll flexographic printing techniques [13]. Silk based bioelectronic circuits were even integrated into edible foodstuffs, successfully, with a purpose to sense the food quality [6]. E-textiles or electronics embedded textiles are one more contribution of bioelectronics to modern advancements of science. These e-textiles also called the ‘smart fabrics’, are not only wearable but also contain embedded electronic devices that help in sensing, monitoring, computing, recording and wireless communication abilities [16].

5. FUTURE SCOPE

The greatest virtue of Bioelectronics that enables their application in hugely unrelated fields such as medicine, military and environment is due to their non continuous programmable discrete functionalities that closely resemble the meta stable behavior of natural (living) systems. Optimizng the conductivity of biocomaptible conducting polymers still presents a challenge to researchers. Design of hydrophilic and soluble DECPs(degradable and electrically conductive polymers) is the new direction being explored where researchers are experimenting with options to optimize their conductivity and study interactions of DECPs under *in-vitro/ in-vivo* conditions. The ph sensitive conducting hydrogels are adding a whole new pwerspective for biomedical applications. New advances in transient CP that are enriched with properties of auto assembly and have great potential in fabricating new vesicular systems for applications in biomedical/ microfluidic devices. Bioelectronic devices are bringing to reality targeted drug delivery coupled with tissue monitoring and regeneration under *in-vivo* conditions. This may culminate the dream of modern medicine 'pharamacy- on-a- chip'. Transient digital imaging devices and silicon solar cells are the future of military and civilian applications.

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