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Bioelectronic properties of DNA, protein, cells and their applications for diagnostic medical devices

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ABSTRACT:

From a couple of centuries ago, understanding physical properties of biological material, their interference with their natural host and their potential manipulation for employment as a conductor in medical devices, has gathered substantial interest in the field of bioelectronics. With the fast-emerging technologies for fabrication of diagnostic modalities, wearable biosensors and implantable devices, which electrical components are of essential importance, a need for developing novel conductors within such devices has evolved over the past decades. As the possibility of electron transport within small biological molecules, such as DNA and proteins, as well as larger elements such as cells was established, several discoveries of the modern charge characterization technologies were evolved. Development of Electrochemical Scanning Tunneling Microscopy and Nuclear Magnetic Resonance among many other techniques were of vital importance, following the discoveries made in sub-micron scales of biological material. This review covers the most recent understandings of electronic properties within different scale of biological material starting from nanometer range to millimeter-sized organs. We also discuss the state-of-the-art technology that's been made taking advantage of electronic properties of biological material for addressing diseases like Parkinson's Disease and Epilepsy.

1. Introduction

The word bioelectronic is defined as devices and information systems that are derived from both biological material and biological-inspired architecture, with the former being the focus of our investigation in this review. With the advancement of knowledge in today's technology, an essential need of scaling down electronics to our demands has arisen. Today's fast expanding knowledge of sub-Nano scale world, has made it possible to employ intrinsic electronic properties of smaller molecules, such as DNA and proteins in fabrication of complex bioelectronics. With applications in advancing the sustainability of devices such as electrocardiographs, cardiac pacemakers, blood pressure and flow monitors, understanding the concepts of charge transfer within organic material is highly advantageous.

Majority of today's technology are either derived and charged by electrical energy or are producing it to be used elsewhere. Such technology ranges from medical diagnostic devices, implantable sensors, wearable therapeutics to state-of-the-art organ-on-chip models used for drug testing and physiological analysis of the target organ (e.g. automation and stimulation applications) (Choi and Park, 2017; Conant et al., 2017; Johnson et al., 2015; Lee et al., 2017; Nyein et al., 2018; van der Helm et al., 2016; Xuan et al., 2018). Every single of the above-mentioned technologies are challenged by providing fast and sensitive conductors for transferring data. Although most researchers have been taking advantage of already existing natural metallic elements (e.g. gold, platinum, silver, etc.) as conductors, with limitation of such resources and high expenses of their extraction and production into biological systems, others started thinking about exploiting the biological elements themselves as electrical conductors. Not only will the application be more biocompatible (in case of implantable with wireless sensing (Mostafalu et al., 2016)) but since it's coming from an embedded natural circuitry, it will be more efficient in the process of charge transfer. On the other hand, the process of manipulating metallic elements to fit smaller scales, such as applications in microfabricated devices, requires extensive clean room technology and cumbersome synthesis methodologies of Nanotechnology (Hafez et al., 2005; Legant et al., 2009; Ribet et al., 2017). Taking benefit of already existing electrical transport properties within biological molecules such as DNA (Carter and LaBean, 2011), proteins (Xu et al., 2014), peptides (Sek, 2013) and cells (Söhl et al., 2004), provides outstanding potential in

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fabrication of novel bioelectrical devices. DNA, for instance, being called the best Nanowire, is highly flexible and given its self-assembly features, can adopt to various conformations. It can act as an insulator, semiconductor or a metallic connection in lower scale electronics used in specific gene identifications and fundamental studies of small molecules' electronic behavior.

To fully exploit such potentials, an essential understanding of what they encompass, what are their potentials, which molecules are most successfully been used recently and which properties to approach, are of vital importance prior to experimental design and fabrication. In this review, we will start from the smallest attainable biological entity, the DNA and scale up to a systemic understanding of protein and cellular intrinsic electrical properties and how their modulation can correspond to development of state-of-the-art technology. We will then discuss their application in not only current medical devices and technology but also active animal and clinical trials. Finally, we will summarize with their drawbacks and a future perspective on most efficient output of electrical properties of biological entities.

2. DNA electronics

Deoxyribonucleic Acid (DNA), is a repository for genetic information in the cell. An individual strand of DNA consists of a phosphate-deoxyribose backbone connecting nitrogenous bases, either purines (adenine and guanine) or pyrimidines (cytosine and thymine). In addition, the bases of DNA are composed of aromatic rings with pairs spaced 3.4 Å (A) in the double helix; due to this double helix structure, the electron density, which is the relative probability of finding an electron in a specific point in space, overlaps on adjacent bases. The spacing between adjacent pairs in DNA is similar to graphite's Z-direction spacing, which is known to contribute to graphite's conductivity (Chaban et al., 2014). This gave a lead on possibility of DNA's capability of electron transfer. The conductivity properties of DNA which are associated with its structure, are a vital biological factor in formation of cellular and further organ electrical characteristics. Several studies have been done either with analysis of direct formation of DNA complexes or devices in better studying its helix changes in response to electrical stimuli (Alwarappan et al., 2012; Chen et al., 2010; Hondroulis et al., 2013; Hou et al., 2017; C. Z. Li et al., 2012; Li et al., 2005a, 2005b, 2004, 2003; Liu et al., 2005; Long et al., 2004, 2003b, 2003a; Prabhulkar and Li, 2010; Skourtis, 2013; Song et al., 2018; Sukumaran et al., 2017; Wettig et al., 2003; Xing and Cheng, 2006; Zhu et al., 2014, 2013b). Hence, researchers started to hypothesize that DNA could also be conductive through the overlap of adjacent π-orbitals. For example, research made by Grodick et al. (Michael A. Grodick, Natalie B. Muren, 2015) and Elias et al. (2008) established that DNA can conduct charge efficiently through the π-stack of the nitrogenous bases (Arnold et al., 2016). Grodick's group used an aqueous based chemical experiment, where the dynamics of the DNA bases is unrestricted, employing quenching effect and luminescence they were able to reach to their conclusion. Elias's group on the other hand, studied the DNA photoredox processes using a tethered iridium (Ir) intercalator that functions as a photooxidant and reductant. These photoredox processes were characterized using spectroscopic and photolysis measurements by cyclopropylamine-substituted bases as electron and hole traps.

Triberis & Dimakogianni (Triberis and Dimakogianni, 2009) along with others developed theoretical models and arguments for electric properties regarding DNA interactions with the external world. However, there are no experimental measurements of DNA electromagnetic properties. M.H Bukhari et al.(Bukhari et al., 2018) concluded in their research that if there was a bio-electromagnetism within the DNA, the amplitude would be extremely low and hard to measure with the sensitivity of the current technology. They used extremely sensitive ultra-low-noise trans-impedance amplifiers and a high-precision data acquisition system to record any possible electromagnetic signals from the DNA. A unique feature of small single stranded DNA (up to length of 1 nm) is its high flexibility, which allows for their conjugated assembly into rigid structures. In early studies, this led to the creation of geometric and small building blocks known as "DNA Tiles". These tiles were used to assemble sheets, ribbons, lattices and tubes that were used to bring together other functional molecules and diverse Nanomaterials (Joshua D. Carter§ and Thomas H. LaBean†, 2011; Xin and Woolley, 2003). There are many difficulties associated with this process, such as purifying the synthetic DNA and matching desired strand stoichiometry for each design. In order to handle such difficulties, DNA Origami technique was invented (Saaem and Labean, 2013). DNA origami, a programmed DNA assembly system based on the DNA nanotechnology, allows for design and creation of various 2D and 3D nanostructure with a wide variety of shapes and defined sizes (Douglas et al., 2009a; Rajendran et al., 2012; Rothemund, 2006). This method consists of mixing long single stranded DNA (ssDNA) and complementary DNA (Staple DNA) strands with designed sequences to the target structures, after which the mixture goes into an annealing process where it's heated and cooled slowly to form the predesigned structure via self-assembly (Dietz et al., 2009; Douglas et al., 2009b, 2009a). The annealing process decreases self-assembly hybridization error and helps build more complex nanostructure (Saaem and Labean, 2013). In another study, a three-dimensional DNA origami was developed which alters its structure in response to variations in salt concentration and temperature (Gerling et al., 2015). In their design, the X-Shaped structure (the open form) changed to the rod shape (closed form) by manipulating these two factors. In order to control the origami feature, this structure was modified with photo responsive molecules that react to photoirradiation. The origami was able to open and close more than 1000 times in response to temperature changes without breaking. In order to have a better understanding of this techniques and its application, Linko et al. measured the conductivity, and analyzed the mechanism of a single rectangular DNA origami structure (Linko et al., 2009). They immobilized it between nanoelectrodes by utilizing alternating-current impedance spectroscopy, where they quantitatively described the DC and AC conductivity of rectangular DNA origami. They concluded that the origami's conduction contained both electronic and ionic components, which suggests that the structure could have both solid and aqueous material behavior.

DNA Charge Transport (CT) potentially provides a means to communicate across the genome by activation of redox reactions over long molecular distances. This genomic communication will enable sensing of small perturbation to the DNA base pair stack with high sensitivity. According to Arnold et al.(Arnold et al., 2016), two of the most effective platforms to investigate DNA CT consists of photoinduced reactions using DNA assemblies in solution with tethered donors/acceptors and ground state electrochemistry on DNA monolayers. Using both techniques, two fundamental aspects of DNA CT chemistry can be proven; DNA CT can proceed over long molecular distances and it is sensitive to intervening perturbation in π-stacking DNA, which could be caused by dynamic motions in the base pairs of DNA, single base mismatches, base lesions/modifications or events like protein binding.

The first technique we mentioned for characterization of DNA CT is photoinduction with tethered intercalators, in which DNA is assembled with tethered photooxidants, through an intercalating ligand. Irradiation of this photooxidant withdraws an electron from DNA (Arnold et al., 2016). Olmon et al. established that this procedure damages the DNA due to the metallointercalators, which are positively charged aromatic compounds that separate the two strands of DNA helix and insert themselves within the base pairs of DNA (Olmon and Hill, 2011). The level of damage induced depends on the degree of electronic coupling to the DNA π-stack, the efficiency of back electron transfer processes and the thermodynamic driving force for charge transport.

Electrochemistry technique is one major platform for CT studies in DNA. DNA CT in ground state is done by assembling DNA monolayers onto gold electrodes through the formation of covalent gold-thiol bonds (Kelley et al., 1997), or for a wider potential window to be acquired, they are formed with pyrene (Gorodetsky and Barton, 2006). After

forming the DNA monolayer, the DNA CT on the surface is investigated using a DNA-bound redox probe. In this process, the charge can flow from the electrode to the redox probe. Otherwise it can be conducted in a DNA-mediated fashion, where the charge flows from the electrode to the alkane-thiol tether through DNA π-stack to reach the redox probe. According to Genereux and Barton (Joseph C. Genereux and Jacqueline K. Barton, 2011), the electrochemical charge transport could occur below the potential of individual DNA bases, which on average is about 5 eV. Due to such low voltage and high sensitivity of electrochemical method, the experiments using electrochemistry for charge transport studies do not damage the DNA. Slinker et al. (Jason D. Slinker, Natalie B. Muren, Sara E. Renfrew, 2011), demonstrated the shallow distance dependence of DNA CT which concluded that electrical charge can be transported efficiently through DNA in the ground state over up to 100 base pairs in molecular distance.

Generally speaking, in order to measure the electrical conductance of DNA it is required to wire it to two probing electrodes, from which several biosensors were designed for DNA conductance measurement and technologies such as Scanning Probe Microscopy (SPM), Scanning Tunneling Microscopy (STM) and Atomic Force Microscopy (AFM) were developed (Xing and Cheng, 2006). Xu and Tao (2003) demonstrated that STM Break junction (STM-BJ) was a technique that could repeat the formation of metal-molecule-metal junction, which is used to measure the conductance of a molecule. This method uses a metal STM tip, that moves by a piezoelectric transducer. The information of tip displacement helps creating a histogram, that would be used for identifying the conductance of the molecule. After this discovery, STM-BJ has been the most widely-used experimental platform to measure conductance for different molecules, including DNA (Wang, 2018). Similar to STM-BJ, the Conductive Probe AFM Break Junction (CPAFM-BJ) method is used for measuring conductance. In this method a metal coated AFM tip is used, and laser-reflection-controlled force signal detector is used that enables measurements of forces and conductance simultaneously (Engelkes et al., 2004; Kim et al., 2011; Seong Ho Choi, BongSoo Kim, 2008).

Wang et al. discussed several factors that affects electrical conductance of DNA such as environmental parameters, type of ssDNA, base pair mismatch and structure dependence (Wang, 2018). Focusing on environmental effects, Tran et al. using contactless AC conductance of λ-DNA in a buffer solution demonstrated that the conductance of DNA in a wet environment was an order of magnitude higher than in dry state (Tran et al., 2000). Regarding the DNA strand type, Guo et al. used STM-BJ to conclude that dsDNA was several orders of magnitude higher regarding conductance compared to ssDNA (Guo et al., 2016). It is also shown that alteration of a single base in the stack can increase or decrease the conductivity of the dsDNA helix (Hihath et al., 2005). From a structural perspective, Wang et al. explored the conductance change due to structural transition from B to Z form of an 8 base pair poly $(GC)_4$ DNA (Wang et al., 2014). By increasing magnesium (Mg) ion concentration, they found that the conductance of DNA is decreased by an order of two due to the abovementioned transition occurs, compared to no effect when three A-T base pairs were bridged in the middle of the sequence. Another study confirmed that the conductance increases by one order of magnitude when the structure changed from B to A, as a response of changing phosphate buffer to 80% ethanol.

Charge transport is one of our genetic storage properties that allows the communication between genome to define cellular functionalities. Several detection methods made it possible for scientists to explore its application, interference and manipulation for a variety of employment, in which DNA origami is known as the state of the art in the field. But the charge transport isn't limited to this unit and goes into larger scales which will be followed in the next section.

3. Protein and peptide electronics

Considering a scale up application from DNA-level electronic properties, proteins and other larger molecules will be the next biological target for such investigations. Proteins play a critical role as enzymes, antibodies, messenger proteins, structural components or transport/storage proteins depending on their specific function in the body. (Kaushik et al., 2018; Li et al., 2004; Prabhulkar et al., 2012b; Yang et al., 2013). Proteins are made of their building blocks of amino acids and are usually 3–4 nm (nm) in diameter. The building block sequence determines the unique 3D structure of the protein. Each protein has 4 different categories of its structure: primary structure refers to the unique sequence of amino acids by which the protein is made; secondary structure comes from the pattern of hydrogen bonds between the amino acids and the peptide backbone; the tertiary structure is the 3 dimensional folding of the abovementioned structures into a 3D format; finally the quaternary structure of the protein is the number of multiple folded protein subunits into a multi-unit complex. Fig. 1 shows the abovementioned structures of a protein. Proteins were known as biological factors and it wasn't until 1936 when Pauling et al. confirmed for the first time the magnetic properties of proteins like hemoglobin (Brück et al., 1936). It inspired scientists to explore further into other physical properties of proteins and coming up with several methodologies to investigate electrical fields, magnetic properties and thermal effects on desired proteins. In this section we will go over some of those investigations and their resultant applications into fabrication of bio-electronic devices like filed effect transistors, data storage elements, biomolecular circuits, biomolecular solar cells and bio-computers.

To understand protein electronics and other physical characteristics related to electrical behavior, we need to understand that there are two separate phenomena happening in electrically active proteins: 1. Electron transfer and 2. Electron Transport. Electron transfer indicates flow of electrons within a protein that is completely or partially in contact with an ionically conducting electrolyte, which facilitates redox reactions. In a process where the electrolyte is omitted, the flow of electrons within a protein in presence of non-ionically conducting electrodes is called electron transport. It is also worth mentioning that electron transport above the temperatures of 160–200 K is a thermally activated process and below that is independent of temperature. In such case the mechanism switches to a tunneling process, in which electrons tunnel through a barrier in the presence of high electric fields (Amdursky et al., 2014). A group of researchers investigated not only temperature-dependent but also force-dependent electron transport process with an Azurin protein using Conducting Probe Atomic Force Microscopy (CP-AFM) (W. Li et al., 2012). They concluded that with increased pressure, electron transport changes from temperature-independent to thermally activated at higher temperatures (>310 K), however its mechanism doesn't change as the activation energy stays the same. It has also been shown that presence of a cofactor (known as a small molecular moiety that is either within the protein structure or attached to it externally) will increase the efficiency while decreasing the activation energy for electron transport process.

Measuring differences in electrical potential between electron donor and acceptor can quantify both electron transport and electron transfer processes. Such measurements can be done using several techniques such as Nuclear Magnetic Resonance (NMR) or electrochemistry (Electrochemical Scanning Tunneling Microscopy), however the results of spectroscopy-based techniques are significantly higher in resolution and more sensitive compared to electrochemical methods, most likely as a result of higher number of electron transfer pathways in spectroscopy (Cahen et al., 2018). However, interpretation of such data is complex, as several different paths and a variety of charge transfer mechanism exist. A comprehensive study would include not only a computational model for understanding the variations between different paths, but also quantifying it using experimental techniques. Besides the methods mentioned above, there are also CP-AFM for nanometer scale measurements, Saturated Scanning Tunneling Microscopy (STM), Saturated Electromigration, conjugated CP-AFM and conjugated STM, which their working concepts is out of the scope of our article.

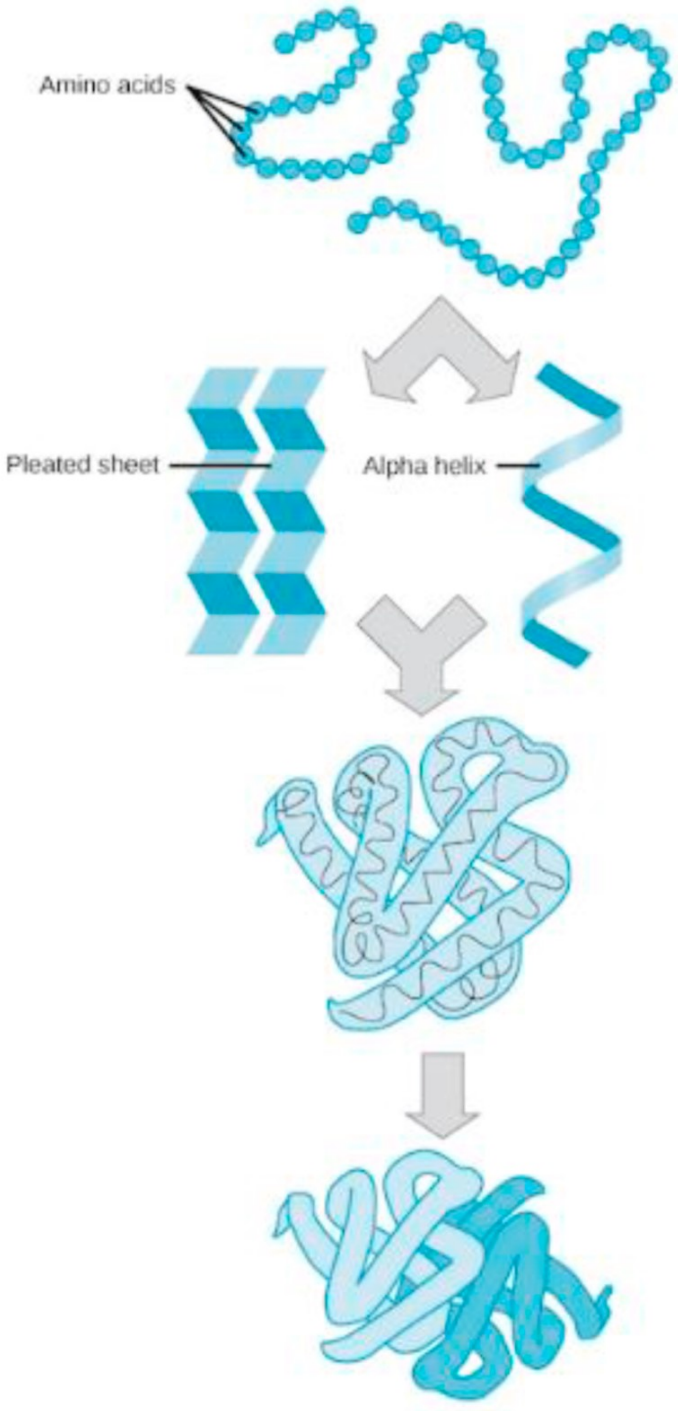

Fig. 1. Different subsections of a protein. From top to bottom: Primary, Secondary, Tertiary and Quaternary structures.

Conventional methods used to measure the conductivity and dielectric parameters for charge transport in proteins; Conductivity of Bovine Serum Albumin (BSA) and lysozyme were measured using quantifying their sodium chloride (NaCl) content and hydration of their freeze-dried powders (Stephen et al., 1981). However, since then, conductive electrodes either based on electrochemical measurements or direct electrical charge transfer became necessary to capture the charge and output a related signal, as was also mentioned in the previous section (Abe et al., 2015a; C.-Z. Li et al., 2009; Prabhulkar et al., 2012a; Xu et al., 2014). Protein immobilization on such electrodes can to a high extend affect the signal acquisition and should be monitored very closely. The immobilization technique controls the orientation, conformation and structure of the immobilized protein, which in turn should be characterized before signal acquisition using Atomic Force Microscopy (AFM), Scanning Tunneling Microscopy (STM), Surface Plasmon Resonance (SPR), etc. techniques. Immobilizations that have been done on long chained Self Assembled Monolayers (SAMs) will decrease the measured potential across the protein as a result of increasing the strength of electrical field (Kelly et al., 2005). Studies on electrical behavior of proteins have been cumbersome due to low sensitivity of detection device or inefficient conjugation of proteins to electrode surface. Ron et al. approached the aforementioned issues with possible electron carrier proteins, Azurin, bacteriorhodopsin and BSA (Ron et al., 2010). They exploited AFM and ellipsometry to characterize their SAM conjugation and used a hanging mercury drop (60 nm in diameter) on a gold pad on top of their SAM fabrication to have two electrodes for analyzing electron transport process. Their technique maintained proteins in their original conformational state and confirmed the electrical active behavior of all three subjects.

Microtubules are one of the most important proteins that have been studied widely for their electrical activities, potential in bio-electronic interfaces, quantum computing and even revealing information on higher brain functions such as “consciousness” and molecular aspects of anesthesia (Cantero et al., 2018). Microtubules are found in cellular cytoskeleton and besides supporting the structure of cytoplasm they have several other functions such as material transport, cell mobility, chromosome separation during mitosis, signal transduction in axons and communication between cell’s exterior and the nucleus . Investigations have been done on their charge distribution (Dwyer, 2001), dipole moments of tubulin in a microtubule (Tuszynski et al., 2006), their alignment and manipulation using alternative current electro-kinetics (Uppalapati et al., 2008) and are used for conductivity models (Friesen et al., 2015). Chiolerio et al. fabricated a microtubule (MT) droplet and inserted two electrodes within the droplet to measure its electrical features, showing that the droplet is acting as an electrical switch (Chiolerio et al., 2019). Other studies have shown the resistor activity of tubulin along with actinin in cytoskeletal network of cells and their application to cancer therapy (Gharooni et al., 2019). Priel et al. investigated the electrodynamic properties of microtubules (Priel et al., 2006). They showed that MTs are capable of amplifying electrical information using a patch clamp system to collect electrical data. They also investigated the surface charge (determined to be strongly negative) and charge distribution within MTs using a molecular dynamic simulation. Showing that positive charges are sandwiched between two strong layers of negative charge, they confirmed that microtubules can make an effective transistor. Such information sheds more lights on signal amplification through MTs in neural signal transduction. It is known that microtubules move along electric field lines, hence the power of electric field is used to align such molecules either in or out of lines with the rest of microtubules, in case of signal amplification or cancer treatment respectively. Stracke et al. using this fact and employing video contracts microscopy, showed that microtubule formation is accompanied by substantial changes in charge distribution within tubulin subunits (Stracke et al., 2002). Another group in 2018 in a fascinating experiment using AFM and Shock Pulse Method (SPM) confirmed that rat brain microtubule bundles are electrically active and can generate an electrical oscillation, which is dependent on magnitude and polarity of the electrical stimulus and in turn generates dynamic electric fields emitting from the full bundle (Cantero et al., 2018).

As mentioned earlier, proteins can be used as electrical elements to form a circuit or assemble a computer that operates in quantum levels. Several groups with the similar hope, have explored the use of proteins as electrical components. Alfinito et al. used both a computational model as well as experimental designs using electrochemical impedance spectroscopy (EIS) measurements to find that the electrical properties of a protein is very similar to a medium-gap semiconductor (Alfinito et al., 2015). They also showed that there is a sequential tunneling mechanism

of charge transfer between amino acids in a protein which is defined by a highly linear current-voltage graph. Conformational changes in protein due to its sensing behavior of targets will result in a variety of electrical changes. They have proven theoretically that this change is consistent with spatial location changes of its amino acids. Impedance Network Protein Analogue (INPA), a numerical code, is highly useful, given that the tertiary structure of the protein is known, for determination of electrical properties of proteins. Another group explored the transistor-like behavior of the protein Azurin (Artés et al., 2012). They used EC-STM bridge junctions with a 4-electrode electrochemical setup (platinum: Iridium counter electrodes, mini Ag/AgCl reference electrode and a gold working electrode) to avoid significant conformational changes of a protein from its original form due to sensing modalities. With exploring the current-time and current-voltage characteristics of the Azurin, they concluded that a biomolecular transistor can be built using single metalloproteins.

Another physical property of proteins is their magnetism. Michael Faraday in 1845 showed that proteins that are consisted of a ferrous atom like hemoglobin are not magnetic (Bren et al., 2015). He used a scale with a magnetic field within it, in which if the samples had a magnetic characteristic they would've been drawn to the field, increasing the weight showing on scale and vice versa (Fig. 2). However, his method wasn't sensitive enough. It wasn't until 1936 that Brück and Pauling groups used the same weighing method within an electromagnet for their target agents, which were several different types of heme groups (ex. ferroheme, ferriheme, oxyferroheme, carbon-monoxyferroheme) (Brück et al., 1936; Pauling and Coryell, 1936). They concluded that deoxyferroheme unlike the other groups showed magnetism behavior of its unpaired electrons to ferrous atom. The physiological output of such conclusion suggested that arterial and venous blood had different magnetic properties. As is known, heme-based proteins such as hemoglobin and myoglobin are very important in blood oxygenation and metabolite regulation in organ-level structures and have been used throughout research for several applications (Assan et al., 2015; Leung et al., 2014; C. Li et al., 2009; C. zhong Li et al., 2009; Li et al., 2000; Taniguchi et al., 1999). Hence understanding their intrinsic physical properties is highly important in fabricating manipulative devices and designs for therapeutic applications. Another interesting study with heme-based proteins, investigated the properties of myoglobin, its covalent bonds of Fe atoms to amino acids, energy levels of Fe atom and aqueous and dry state of its bonds to neighboring amino acids (D. Li et al., 2012). What was eye catching about their study was the design of their micro-fabricated device to capture and sense the electron transport within a single protein. Their design included fabrication of a break junction grown on silicon substrate, using electron-beam lithography and a lift-off technique along with sputtering machine for depositing platinum electrodes. They used an electromigration technique or an electrical pulse to break the junction, just enough to house a single protein. They placed the protein solution on the electrodes and tested with Raman Spectroscopy to check protein's activity before and after the cooling process, making sure no denaturing has occurred (Fig. 3). The conductance (dI/dV) as a function of bias voltage (V_B) and gate voltage (V_G) was acquired by numerically differentiating current-bias voltage (I-V) curves. Junctions were measured without any protein, with apomyoglobin, and with myoglobin. In the investigation of myoglobin, an earlier group focused on developing computer models and simulations for determining its electrical properties (Aschi et al., 2004). They used a long molecular dynamic (MD) simulation in combination with perturbed matrix method (PMM) calculations for their analysis. Their comparison of this model and previously published experimental methods confirmed that their simulations were highly reliable.

Peptides on the other hand, are shorter proteins, which consist of a smaller number of amino acids. As mentioned earlier, the transportation of electrons uses the pathways created by structural motifs of proteins where environment would play an important role on the efficiency of this process. For that reason, the peptides chains are investigated for their electron transfer properties. One of the most favored methods of ET measurement is tunneling. In this technique the charges move in a direct pathway between units of the peptides bridge due to superexchange charge-coupling. The conductance of this junction is exponentially related to the length of the bridge (tunneling) and the height of the barrier of the bridge, known as a decay constant.

Sek Slawomir et al. (Sek, 2013) presented a simple model where donor and acceptors of electrons are separated by a peptide linker and

Fig. 2. Faraday's Electromagnetic Scale (Reproduced with permission from J. PNAS. 112, 43 (2015). Copyright 2015 PNAS) (Bren et al., 2015).

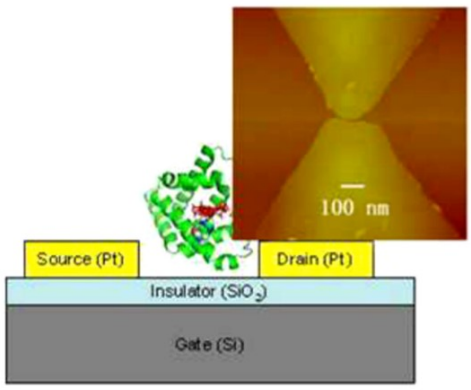

Fig. 3. Three-dimensional device schematic and AFM image of broken junctions, with 5 nm gap, using electromigration. (Reproduced with permission from J. Nanotechnology. 23, (2012). Copyright 2012 journal of Nanotechnology) (D. Li et al., 2012).

the electron transfer (ET) rate between them would be calculated using the length of the spacer and the chemical structure. They discuss in their paper that as the spacer becomes longer, the chemical structure plays a more important role than the length of the bridge, where then the decay constant would be considered as a measure of electronic coupling. Therefore, the decay constant would be proportional to the efficiency of the ET. However, in the case of peptides and proteins most of the times the distance would be longer than the upper limit distance suggested by Gray and Winkler for tunneling (Gray and Winkler, 2003). The limit distance suggested is 2 nm and usually, the distance present in peptides and proteins is 3.5 nm.

To address the shortcomings of the above mentioned, electron hopping is employed as the ET measurement mechanism later, where it's not as strongly distance-dependent like electron tunneling. According to Long et al. (2005) in the hopping mechanism, the electron that is being transferred resides on the bridge while it passes from one redox center to the other. Here, the conductance is proportional to the number of hopping sites (Fig. 4). Contrarily, in the superexchange concept, the electrons can only reside in either the donor or the acceptor and are limited by distance for transfer. Using the electron hopping model, sequential ET between adjacent units of the bridge (peptide) are involved. This site would act as a relay which is described as amide bonds' or carbonyl groups' role in the chain.

Petrov et al. in a detailed study proved that the electron transfer in peptides occurs through both superexchange and hopping mechanisms (Petrov et al., 2001). When the distance is long the mechanism for this phenomenon would be electron hopping and if the distance is short, electron tunneling would be the deriving model, which in certain lengths the mechanism will switch between the two.

Peptides' size and their electric properties has made them a favorable option in fabrication of several nanodevices with biomedical applications. One of the best qualities of these molecules is the opportunity to modulate their ET behavior by applying external factors such as changes in pH, external electric field or complexation, to alter the electron transfer efficiency. This valuable flexibility of the electrical properties would be useful for applications such as nanoscale logic gates, memory devices and constructions of sensing devices for metal ions (Sek, 2013). Nevertheless, there is a need for studying peptide properties in more depth in order to take advantage of their full potential for such device applications.

The long list of research and amount of work that researchers have put into understanding electronic properties of proteins, shows how essential their role is in operating electronic devices and interfering with smaller electronic structures in biological and environmental applications. However, the research doesn't stop there. As all the subunits in the human body are correlated and work in a cascade of events, there needs to be studies on how integration and manipulation of DNA and protein electronics can affect a cell behavior and what would the biological response be for it. In the next section we will expand our investigation into a larger scale conduction of electrons within organic matter, called the cells.

4. Cell electronics

Electrical signals are essential for human body's function, especially the nervous system. As it was mentioned before, the electrical conductance within the DNA and proteins is highly studied today to acquire better understanding of sub-cellular processes and their manipulation for several vital applications. In a higher scale, studying the electrical properties of cells as a whole, would help to determine how the electrical signals spread in an organ in terms of cellular communication and metabolism.

A good approach to better understand cell electrical properties is thinking about the cell membrane as an electrical capacitor (Fig. 5),

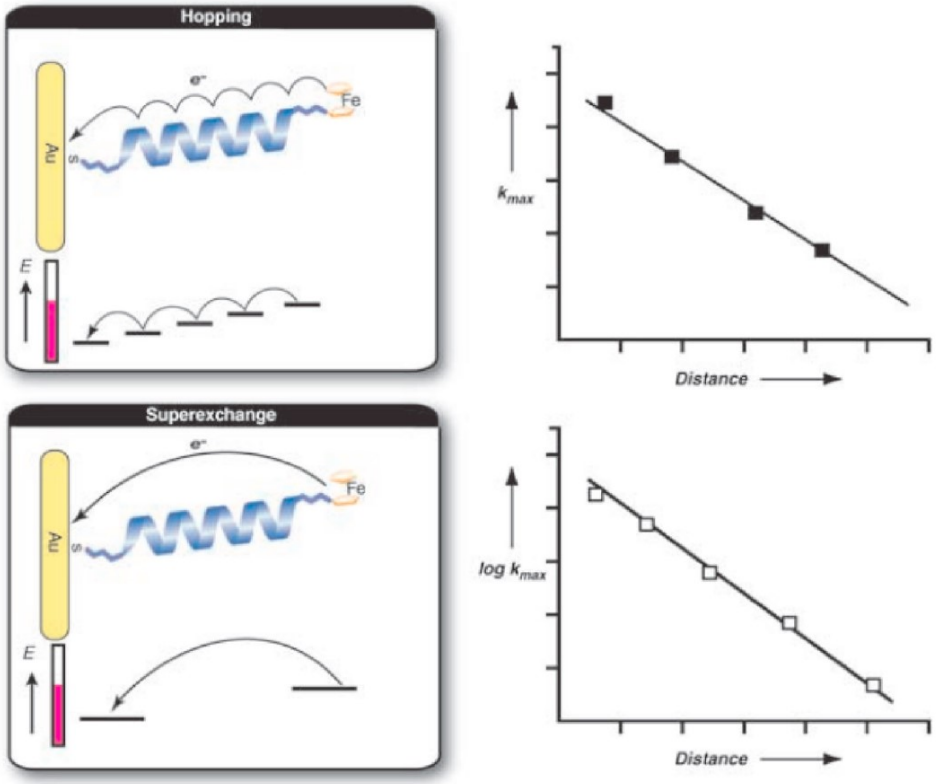

Fig. 4. Comparison between the hopping and tunneling (superexchange) mechanisms in peptide electron transfer. Showing the linear dependency of ET rate in the hopping method and the exponential dependency on the tunneling mechanism. (Reproduced with permission from Wiley Online Library 11, 18, (2005). Copyright 2005 Wiley Online Library) (Long et al., 2005).

where the lipid bilayer of the plasma membrane is the insulating barrier between the electrical conductivity of the intracellular fluid (ICF) and extracellular fluid (ECF). In a capacitor the voltage of the battery causes an electron to go from one plate and accumulate in the other, until the gradient is the same as the battery. In this case, the plates are ICF and ECF. The capacitance is directly proportional to the area of the plates and inversely proportional to the distance between the plates (Fig. 6) (Sabir and Usher-Smith, 2008). The potential difference in the membrane is referred to as the Nernst potential. All living cells have a membrane potential, which would depend on the ion concentration inside and outside of the cell. Depending on the type of cells, the membrane potential would be different. For example, fat cells and smooth muscle cells have a membrane potential between -50 and -60 mV, whereas for skeletal muscle cells it's -90 mV; Cancer cells and Stem cells have the same range between -10 mV (embryonic stem cells) and -30mV (adult stem cells) (Levin, 2012). Ion channels localized in the cell membrane are large transmembrane (TM) proteins that work as a pathway for ions to move across the membrane (Mirtaheri et al., 2019), based on the electrochemical potential. The process behind propagation of a nerve impulse is the response to changes in TM potential due to rapid opening and closing of sodium (Na^+) and potassium (K^+) selective channels (Hodgkin et al., 1952). These communications help with synchronization of different molecular processes. When a stimulus occurs, the membrane depolarizes because of the fast opening of voltage-activated Na^+ channels. During depolarization, the membrane Nernst potential is dominated by the low and high concentration of Na^+ ions inside and outside of the cell respectively. It triggers the slower opening of voltage-activated K^+ channels, which will re-polarize the membrane towards the resting potential (Lacroix et al., 2013). The fast gating kinetics of Na^+ ion channels do not have to be as selective as K^+ channels. One of the most critical functions of K^+ channels is their high selectivity for K^+ over Na^+ while allowing high-throughput ion conduction (Roux, 2017).

Cell membrane also encloses hyperpolarizing and depolarizing channels. Hyperpolarizing channels make the membrane more negative, allowing negative ions (such as chloride) to get into the cells and positive ions to flow out. On the other hand, depolarizing channels make the membrane potential more positive, where Na^+ and calcium (Ca^{2+}) ions flow into the cell. These channels can be categorized to ligand-gated and voltage-gated channels (Bates, 2015). In addition, ions can go through gap junctions (from central pores in the cell membrane called hemichannels) to a neighboring cell and in case of their absence, ions will flow to the extracellular matrix (Söhl et al., 2004). Furthermore, there have been studies about the relationship of ion channels and their conductance with cellular proliferation. The conduction across ion channels can regulate cell proliferation through K^+ channels. Studies on impact of ion channels in disease development concluded that increasing K^+ current promotes proliferation and inhibition of voltage-gated K^+ channels will slow the proliferation of diseased cells

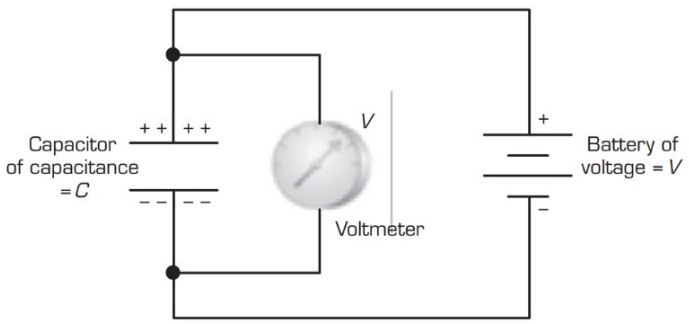

Fig. 5. The capacitor the voltage of the battery causes an electron to go from one plate and accumulate in the other, until the gradient is the same as the battery. (Reproduced with permission from World Scientific (2008). Copyright 2008 World Scientific)[80].

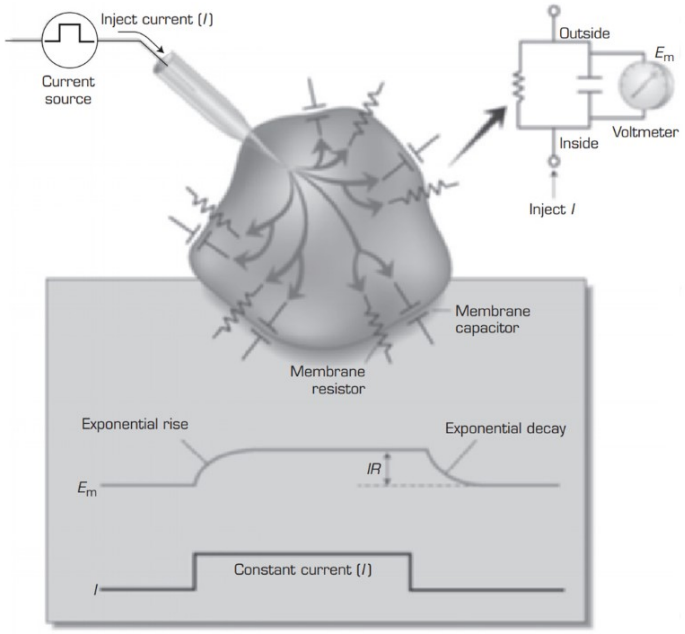

Fig. 6. Comparison of the cell as an electrical system (Reproduced with permission from World Scientific (2008). Copyright 2008 World Scientific) [80].

(Abdul and Hoosein, 2002a, Abdul and Hoosein, 2002b; Chang et al., 2003; Fraser et al., 2000; Menéndez et al., 2010). Regulation of cell proliferation through ion channels occurs due to two reasons: 1. The channels activate signals that would modify molecular cell cycle protein. 2. Ion channels are responsible for regulating cell volume, which in turn regulates the concentration of cell cycle regulatory protein, hence affecting cell cycle progression (Rouzaire-Dubois et al., 2000). Ion channels are also known to intervene with cellular migration. Chioni et al. research found a relationship between the overexpression of Na^+ channel subunits in breast cancer cells and metastasis (Chioni et al., 2009). Reasons were explained that currents help the cell change shape while its volume contracts at the trailing edge and increases at the leading edge, which results in cell migration (Mcferrin and Sontheimer, 2006).

Due to the relationship between ion channels, migration and proliferation of cells, researchers have studied how they can manipulate the electrical properties of cells in order to treat diseases such as cancer. Irreversible electroporation is an ablation modality that uses electric pulses or an electric field to create defects (nanopores) in the cell membrane on a nanoscale (Wagstaff et al., 2016). The irreversibility is due to passing a specific electric threshold by which the nanopores become permanent. Using this technique, nanopores or conductive pores permit molecules to go through the cell membrane (Chang and Reese, 1990; Lee et al., 2012; Wagstaff et al., 2015). The method could be used in treatment of pancreatic, hepatic and prostate carcinomas, as it can be localized in their specific cells (Wagstaff et al., 2016). Electroporation can also be used for gene delivery, through nanopores where DNA is able to migrate inside of the cell (Young and Dean, 2015). This helps with understanding functional properties of simpler organisms leading to investigating the more complex forms (Meglic and Kotnik, 2017). Gene delivery using electroporation will be further discussed in the next section. Electroporation can also be combined with electrolysis in case of tissue ablation. Philips et al. used this method to inflict a more effective damage to cells using a smaller applied charge per electrode area.

After understanding how each of the subunits operate from an electronic perspective and how we can use their intrinsic electrical charge transports, we will be focusing on how and in what scale each will be used in addressing biological issues such as wound healing and

neurodegenerative diseases. The next section will discuss the above mentioned in detail.

5. Biological application of biomolecule's electronic properties

To put all the above information into clinical meaning, several studies have been done on manipulation of physical properties of DNA, proteins and cells to attend a systemic problem in the human body (Chuang et al., 2008; Hondroulis et al., 2014; Mozneb et al., 2020; Shah et al., 2014; Tong et al., 2019; Yu et al., 2014b, 2014a; 2013; Zhu et al., 2013a). Their controlled reconstruction and manipulation has been employed in developing biosensors for toxicity assessment (Shah et al., 2016; Zhu et al., 2013a), cell trapping, development, molecular uptake and comprehensive analysis (Chuang et al., 2008; Hondroulis et al., 2014; Shah et al., 2014; Tong et al., 2019), photocurrent harvesting from plant cells (Yu et al., 2014b, 2014a, 2013) and so many other applications. Here we will be discussing their different applications in wound healing, gene therapy, neurodegenerative diseases such as Parkinson's Disease (PD), electroencephalography (EEG) and electrocardiogram (ECG) studies.

5.1. Wound healing

There are natural electrochemical signals in different parts of human body such as brain, skin, muscle and bones. These signals are generated from endogenous bioelectric system of the body. The current of such electrochemical signal is carried by charged ions, since there are no free electrons available. When the skin is injured, there is a short-circuit and electrical leak in the trans-epithelial electric potential, in which the main components of the current are: Ca^{2+}, Na^{+}, K^{+} and Cl^{-} (FOULDS and BARKER, 1983). This current generates an electrical potential of 10–60 mV in which center of the wound is the negative pole and its edge is positive pole (Reid et al., 2005; Zhao et al., 2006). This potential induces the cell migration towards the injury until the wound is healed or dries out due to prolonged opening (McCaig et al., 2005). Generally, the wound healing process is made up of four distinct stages of: hemostasis, inflammation, proliferation and remodeling. During the wound healing, each of these stages can be affected by local factors such as infection, foreign body invasion and blood supply, as well as systemic factors such as age, gender, obesity, medication or lifestyle.

Electrical stimulation (ES) is a non-invasive, inexpensive and easy to use method to mimic the current of injury, therefore, accelerate the healing process of the wound. Studies on the effect of electrical stimulation on the various cells playing a role in wound healing such as macrophages (Hoare et al., 2016), fibroblasts (Kim et al., 2015; Rouabhia et al., 2016; Wang et al., 2016), epidermal cells (Cohen et al., 2014; Gao et al., 2015; L. Li et al., 2012), endothelial cells (Bai et al., 2011) and bacteria (Gomes et al., 2015) shows changes in cell proliferation, migration and orientation. In vivo (Ahmed et al., 2012; Asadi et al., 2013; Borba et al., 2011; Cinar et al., 2009; Gürgen et al., 2014; Kim et al., 2014; Morris et al., 2009) and clinical (Ahmad, 2008; Franek et al., 2012; Houghton et al., 2010; Janković and Binić, 2008; Margara et al., 2008; Santamato et al., 2012; Sebastian et al., 2011; Ud-Din et al., 2015, 2012; Wirsing et al., 2015) studies also showed accelerated wound closure and increased healing rate when using electrical stimulation. There are four different techniques available for wound healing using electrical stimulation; Direct Current (DC), Alternative Current (AC), Pulsed Current (PC), and Transcutaneous Electrical Nerve Stimulation (TENS). Application of DC is shown to be more effective in reducing wound area, whereas AC is more effective on wound volume (Reger et al., 1999). On the other hand, PC is the most frequently used method of electrical stimulation and it has been shown to be useful for enhanced wound closure in the treatment of chronic, venous and diabetic ulcers (Janković and Binić, 2008; Margara et al., 2008; Santamato et al., 2012; Sebastian et al., 2011). The biomolecular mechanisms responsible for sensing and responding to electrical stimulation is not completely understood, however, it is believed that an asymmetric signal is formed between two poles of the cells in the electrical field parallel to the electrical field lines. This signal is generated as a result of the electrical potential gradient in extracellular environment. The electrical potential of cell membrane is around 70 mV. This potential can vary based on the activity of the cell, meaning that an increase in the electrical activity of membrane is observed with upregulation and increased general activity of the cells. Similarly, if the membrane becomes electrically inactive, there is a downregulation of cells and therefore their functional capacity decrease (Zhao et al., 2003). It is therefore assumed that by applying electrical stimulation, the activity of cells' membrane can be increased. Studies (Wang and Zhao, 2010; Xiong et al., 2015) have shown that the activation of ion channels and protein transport is only due to application of electric current and intracellular polarization and is independent of extracellular chemical gradient and ionic flow (Caddy et al., 2010). When applying the electrical current, the behavior of cells can be divided to two different categories based on the direction of migration. Some cells migrate toward the anode while others migrate toward the cathode (Pu and Zhao, 2006; Zhao et al., 2003). For instance, corneal epithelium cells have been shown to change the direction of migration based on the polarity of external electrical current, meaning that if this current has the same polarity of endogenous electrical current, then wound closure would be accelerated, whereas if they are with opposite polarity, the migration of cells are directed toward the edge of the wound and resulting in further opening up the wound (Pu and Zhao, 2006). Another mechanism by which the electrical current affects wound healing is its antibacterial effect which acts either directly, by disrupting the bacterial membrane, or indirectly by changing pH and temperature within the wound, producing electrolysis products and increasing migration of macrophages and leukocytes (Hunckler and de Mel, 2017). Also, Bayat, et al. had reviewed the effect of ES in wound healing by evaluating the results of the available clinical trials(Ud-Din and Bayat, 2014).Table 1 summarizes some of the clinical trials on the effect of ES on wound healing (Hunckler and de Mel, 2017).

An important phenomenon in wound healing is angiogenesis, and when there is insufficient angiogenesis, it could lead to chronic wound formation, while aggressive angiogenesis can lead to abnormal scarring. Electrostimulation has shown to increase the number of blood vessels in the wound and enhance angiogenesis (Borba et al., 2011; Ferroni et al., 2005; Ud-Din et al., 2015, 2012) which results in local tissue oxygenation (Barrientos et al., 2008). Electrotherapy can also be used in regenerative applications to overcome the limitation of human body in repairing the damaged area. Since repair and regeneration processes in human body are regulated by ionic flows and endogenous electrical current, exogenous electrostimulation can be applied to promote healing and regeneration (Reid et al., 2009). The most important thing for best healing process and least scar formation is to recognize the relation between electrostimulation polarity and the stage of wound healing. In early stage of wound healing, cathodal (negative) stimulation attracts macrophages and promotes inflammatory phase, while in the late stage of wound healing, anodal (positive) stimulation promotes fibroblasts resulting in advanced remodeling phase (Ahmed et al., 2012).

5.2. Electrical gene therapy

One effective method for transferring DNA into the cells in a tissue is cell electroporation/electropermeabilization as it has been discussed in the previous section, in which electrophoresis is the basis for DNA transfer (Orlowski and Mir, 1993). In this method, the plasma membrane permeability of the cells is momentarily increased via exposure of short and intense electrical pulses. Relatively long pulses (tens of milliseconds) are required to achieve the most efficient results (Bureau et al., 2000; Mir et al., 1999). Also, in order for cells to be recoverable and efficiently express the genes of the electro-transferred DNA molecule, the electropermeabilization should be performed using long duration pulses (20 ms or more) and moderate electric field intensity

Table 1
Clinical trials on the effect of ES on wound healing (Hunckler and de Mel, 2017).

Type of ES	Type of wound	ES parameters	ES Effects	Ref.
DC	- Mixed ulcers	- 1.5 μA	- Reduction in wound area	Wirsing et al. (2015)
	- Pressure ulcers	- Not reported	- Wound closure and reduction in wound area	Adunsky and Ohry (2005)
AC	Diabetic venous ulcers	80 Hz, 1 ms pulse width	- Wound closure and reduction in wound area	Lundeberg et al. (1992)
PC	Chronic wounds of diabetic and nondiabetic	5 V, pulse width 200 μs, 30 Hz, 20 mA	The reduction in wound area in diabetic wounds were higher that nondiabetic ones	Lawson and Petrofsky (2007)
Low Voltage PC (LVPC)	- Mixed ulcers	- 300–500 μA and 500–700 μA	- Reduction in wound area	Carley and Wainapel (1985)
	- Pressure ulcers	- 300–600 μA, 0.8 pps	- Wound closure	Wood et al. (1993)
High Voltage PC (HVPC)	- Mixed ulcers	- 29.2 V, maximum 29.2 μA, 64–128 pps - 100 μs, 150 V, 100 Hz	- Reduction in wound area	Feedar et al. (1991) Houghton et al. (2003)
	- Pressure ulcers	- 100 pps, 200 V, 500 μA - 50 μs pulse duration, 50–150 V, 20 min at 100 Hz, 20 min at 10 Hz and 20 min off cycle - 100 V, 100 μs, 100 Hz	- Reduction in wound area - Wound closure and reduction in wound area - Reduction in wound area	Griffin et al. (1991) Houghton et al. (2010) Anna et al. (2012)
	- Venous leg ulcers	- 100 V, 100 pps, monophasic		Franek et al. (2000)
	- Diabetic foot ulcers	- 50 V, 100 μs, 80 pps for 10 min then 8 pps for 10 min, and 40 min standby cycles	- Wound closure and reduction in wound area	Peters et al. (2001)
SVPC	Mixed ulcers	- 300 V, 1000 Hz, 10–40 μs, 100–170 μA	- Reduction in wound area	Janković and Binić (2008)
	Chronic leg ulcers		- Wound closure and reduction of pain	Magnoni et al. (2013)
	Diabetic foot ulcers		- Reduction in wound area	Margara et al. (2008)
	Venous ulcers		- Reduction in wound area	Santamato et al. (2012)
	Healthy volunteers, acute wounds	- 0.004 mA, 20–80 V, 60 Hz, degenerative waves	- Increase angiogenic response - Increased blood flow and hemoglobin levels	Ud-Din et al. (2015) Ud-Din and Bayat (2014)

(200–250 V/cm for the skeletal muscle). This criteria dictates a reversible electroporation process (Aihara and Miyazaki, 1998; Bureau et al., 2000; Mir et al., 1999). It was shown that in the electro-transfer of the skeletal muscle, the gene expression has been increased by two to three orders of magnitude (Mir et al., 1999), therefore it is considered to be a promising method for gene therapy (Aihara and Miyazaki, 1998; Bureau et al., 2000; Mir et al., 1999). Also, the properties of DNA electro-transfer method such as expression of therapeutic genes, makes this method an attractive approach for the correction of genetic diseases, vaccination and cancer treatment (Bettan et al., 2000; Rizzuto et al., 1999).

There are several preclinical and clinical trials on using electrical gene therapy for treatment of cancer (Daud et al., 2008), systemic disorders (Çeliker et al., 2002; Samakoglu et al., 2001) and wound healing (Ferraro et al., 2009; Marti et al., 2004).

Electrical Stimulation of Parkinson's and other neurological diseases.

Deep brain stimulation (DBS) is the most widely used form of electrical stimulation for the treatment of PD and is effective for relief of motor and some non-motor symptoms (Kurtis et al., 2017). In this method a relatively high-frequency (higher than 100 Hz) electrical impulses are delivered via implanted electrodes to the sub-cortical regions of the brain (Lozano et al., 2018). In traditional forms of DBS, the probes were cylindrical providing an omnidirectional field. This type of stimulation has however some drawbacks such as parasthesias and dysarthria (Fytagoridis et al., 2013). Recently, the electrode design is modified to enable the formation of complex stimulation fields by breaking the cylindrical shape into three radial aspects or more multi-contact designs. Studies have shown that the preferred orientation of the stimulation has enhanced therapeutic effect compared to the omnidirectional or alternate directions (Dembek et al., 2017; Tinkhauser et al., 2018). DBS is known to provide extensively focal, yet nonspecific form of neuromodulation, with high-frequency pulse trains, therefore, it can cause unfavorable effects such as impulsivity (Hälbig et al., 2009), postural instability and weight gain, as well as previously mentioned parasthesias and dysarthria (Guehl et al., 2006). Therefore, another delivery method for stimulation is introduced which is called on-demand stimulation. On-demand stimulation delivers DBS only when pathological neural activity (related to disease symptoms) are detected (Little et al., 2016), therefore, enhances PD motor scores and decreases the side effects compared to the high-frequency DBS(Little et al., 2016).

Another type of electrostimulation is transcranial direct current stimulation (tDCS), which has recently been developed extensively (Nitsche and Paulus, 2000). In this type of stimulation also novel electrode configurations are designed to provide even more focal stimulation. It was shown that anodal tDCS has potential impact on gait and motor symptoms (Lefaucheur et al., 2017), also it has improved survival and integration of neurons that synthesize dopamine in a rat model of PD (Winkler et al., 2017). Also, it can be used along with rehabilitative strategies to improve recovery/motor learning (Benninger and Hallett, 2015; Lefaucheur et al., 2017). It should be noted that the area of electrical intervention in the brain is determined by the shape of electric field in tDCS stimulation. Therefore, the number (multifocal targeting and greater specificity (Dannhauer et al., 2011; Ruffini et al., 2014) with greater number of electrodes), arrangement (center-surrounded (Datta et al., 2010) or concentric rings (Gbadeyan et al., 2016)) and geometry of electrodes as well as the complex conductivity of the brain should be considered.

Transcranial alternating current stimulation (tACS) is another method that was used in a few studies in PD patients. And its applications on PD symptomology mostly remains experimental. Using depressed beta-band cortico-muscular coupling during contraction and lower amplitudes in tACS has led to the altered pathophysiological brain state, which is responsible for its responsiveness to PD (Krause et al., 2014). In another study by Shill et al. (2011), using high-frequency (77.5 Hz), high-amplitude (15 mA) stimulation has shown to be effective in accelerating the motor responses in healthy individuals. Therefore, this method could be used for the treatment of bradykinesia (Joundi et al., 2013). The effect of alternating current on the

neurochemical processes should be considered when studying tACS, since studies sometimes aimed at increasing the sub-threshold modulations in the membrane potential (Thut et al., 2017) or changing the neurotransmitter concentrations and cortical plasticity (Nowak et al., 2017).

5.3. EEG and ECG

Neurons are responsible for the electrical charge in the brain. As discussed in section 4, this electrical charge is due to the migration of ions through transmembrane proteins of their membrane. There is a continuous exchange of ions in neurons and their extracellular milieu. When ions of the same charge are transported to the extracellular environment at the same time, they will repel each other so that a wave-like volume conduction will be formed. In EEG, metal electrodes can be used to detect this wave of ions when they reach the scalp as these ions can attract or repel the electrons of metal on the electrode. By using multiple electrodes on the scalp, the potential difference between each electrode can be measured over the time. This noninvasive technique can be used as a monitoring method to record the activity of brain, however, it can also be used invasively in electrocorticography Electrocorticography (ECoG), or intracranial electroencephalography (iEEG), where the electrodes are directly mounted on the surface of the brain (Oehler et al., 2008).

Similarly, in electrocardiography, an ECG is produced by measuring the electrical activity of the heart (in terms of voltage versus time). Here, this measured potential difference is due to the cardiac muscle depolarization and repolarization in a cardiac cycle. Three main regions of each ECG are: the P wave which reflects the depolarization of the atria, the QRS complex and the T wave, which demonstrates the depolarization and repolarization of the ventricles, respectively (Schläpfer and Wellens, 2017). The electrical conduction system of the heart is studied by ECG and deviations from normal conduction (predictable pattern) might reveal pathological conditions (Force, 2018).

6. Discussion

Several scientists today are struggling with embedding electronic components and conducting layers into complicated microfabricated devices for sensing and stimulating applications of biological samples such as sensing metabolic profiles from spheroids in an organ on chip system (Abe et al., 2015b; Weltin et al., 2017). If the solution lies in tampering with smaller dimensions or higher quantities, accessibility and interference with some of these distinct fields are a major challenge (complicated nano-microfabrication techniques). Synthesis of new material, polymers and nanotechnology-based fixes have become an emerging field to pave the path for solving such questions. However, taking advantage of the already-existing organic material with intrinsic electron transfer properties that could be manipulated to our needs, seems the most efficient solution. Group of these scientists have taken the route to explore more on state-of-the-art applications of such organic material in Artificial Intelligence (AI) and biological data integration, synthetic biology and wearable biocompatible bioelectronic-based devices, which will be discussed in the next few paragraphs.

With the fast-emerging knowledge of artificial intelligence and its healthcare applications such as neuronal network mapping, there always is a crucial need for more efficient and accurate data processing and storage. All current storage devices for almost 44 trillion gigabytes of data that is available in the world is either electrically powered or on the cloud, which neither are highly reliable for long durations of time. An international power outage or a strong hacking system that affects online data, can compromise vital information like patient data files and result in dangerous chaos. Hence, researchers have investigated alternatives that can keep the data over millions of years without being damaged. As we've discussed earlier, not only DNA but also proteins like Azurin, Cytochrome C and bacteriorhodopsin have the ability of storing and transferring electrons both within the protein itself and from one protein to another. They can be activated as charge carriers, transistors and capacitors. Due to millions of years of evolution, the capability of a DNA/protein with intrinsic properties of charge transfer/3D data storage, has been optimized to the fastest level transfer and can triumph pioneering microfabricated capacitors and transistors. Harvard scientists leveraged the science behind DNA's amino acids electron storage and fabricated an oligopeptide-based data storage, successfully capable of storing 400 Kb of data, which could be read using a mass spectrometer (Cafferty et al., 2019). An oligopeptide is noticeably smaller and easier to handle than a DNA and is known to survive for thousands of years. Looking at the roadmap for small organic electronics, currently existing computational devices can be improved on their data processing and storage, and with integration of deep learning, could be an answer to revealing how complex diseases are formed and function (Ma et al., 2009) (Nicolau et al., 2016).

On the other hand, understanding the underlying physical properties of biological entities has made it possible for re-designing them into useful systems for current needs, known as "Synthetic Biology". Using the latest simulations as well as experimental designs, investigating the complex nature of biological systems has become more feasible over the years, making it more possible for fabricating a replica or manipulating it to a new model. With decreasing cost of DNA synthesis, one major investment in the field of synthetic biology has gone towards isolating bacterial DNAs and redesigning them into applications such as bio-fuel products, renewable chemicals and health care technology such as genetic engineering. Incorporating newly found Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) into gene editing, has made it possible for scientists to input engineered biology into applications such as complex cellular formation/nuclear localization (Pickar-oliver et al., n. d.) and DNA functionality changes towards DNA repair (Taghbalout et al. n. d.). In the case of electrical properties, re-routing the charge transfer within DNA and proteins as well as surface modification for negative/positive charge designs, has gained lots of interest for implantation in new biological processes and production of newly-formed natural products. Taking advantage of synthetic biology has made it a cheaper and faster endeavor in complex problem-solving not only in the field of biology but also environmental and computational engineering.

A more advanced field of research in applications of bioelectrically active material was wearable organic electronics for fabrication of organic light-emitting diodes (OLEDs) (Grünbaum et al., 2019; Zhang et al., 2019) and organic solid-state field effect transistors (FET) (Li et al., 2019). A major advantage of organic electronic material, like small molecule-based dielectrics and semiconductors, is their lightweight properties and mechanical flexibility and mouldability, which could be characterized and used as soft electronics. Their conjugation into modern 3D bio-printers, has made it possible for accurate design of green printed circuit board (PCBs) for a variety of applications such as logic operations (Zhan and Wool, 2013). Combination of these green PCBs with their biocompatibility and flexibility features, make small biological molecules that are capable of transporting electrons, the primary choice of soft wearable electronic fabrication. The design will go not only towards a large-scale assembly like OLEDs on fabric, textile with lithium ion batteries and smart glasses, but also towards smaller scale wearable such as tattoo-based biosensors for sensing physiological properties such as hydration, glucose, blood pressure, etc.(Zhu et al., 2017).

Nevertheless, every revolutionary field in science will have their own challenges and setbacks that should be considered in the early phases to avoid possible future negative outcome. In the case of applying organic electronics, especially data storage, one should consider the adaptability of their application in our fast-growing technological world. With development of new computer languages, retrieving their information in the next thousand years might seem primal. Another important aspect is their sustainability. Although it's been mentioned that the design will be

durable yet thought should be given to sustainability of their endurance. A better system would be self-sustainable and resistant to changes in temperature, pH, pressure, etc. With the abovementioned considerations, the electronic properties of biological material will be of outmost use as an alternative to other sources of energy and an organic future.

7. Conclusion

The advancement of knowledge and technology in studying and manipulating the sub-micron world has sparked a revolution in developing organic bioelectronics, employing biological elements such as DNAs, proteins and cells as conductors or semiconductors. Use of such elements in fabrication of bioelectronics is considered a promising strategy not only to decrease the costs associated with fabrication and maintenance, but also to achieve an efficient sustainability post production of such devices. It's been proven through many studies that not only the DNA, but also proteins and cell structures can both transport charge and store it, making up an organic interface for fabricating the next generation of electronics and quantum computers. There are several concepts behind charge transport and charge transfer within these small molecules, which could result in a different application in today's medical devices such as wound healing equipment, electroencephalograms and gene detection machines. Among them, DNA provides the best and most flexible conductor, while proteins could be applied to a vast application of not only electronic but also electromagnetic devices. On the other hand, manipulating cellular electronics and ionic channel gradients can result in cancer treatment strategies and targeted Nano-delivery of therapeutic drugs. Moreover, their unique application is resonated also in the fields of AI, synthetic biology and wearable/biocompatible bioelectronic devices. In the present review, we have attempted to mirror the importance of understanding the concepts behind how conduction occurs in small biological material, their characterization methodology and techniques, followed by state-of-the-art application in today's medical device industry. It is expected that advancement of information on organic bioelectronics will make them a fundamental element in the future fabrication of sustainable medical devices and complex quantum computers.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Olmon, Eric D., Hill, Michael G., B, J.K., 2011. Inorg. Chem. 50, 12034–12044.
Carter, Joshua D., LaBean, Thomas H., 2011. Am. Chem. Soc. 5, 2200–2205.
Abdul, M., Hoosein, N., 2002a. Oncol. Rep. 9, 961–964.
Abdul, M., Hoosein, N., 2002b. Anticancer Res. 22, 1727–1730.
Abe, H., Ino, K., Li, C.Z., Kanno, Y., Inoue, K.Y., Suda, A., Kunikata, R., Matsudaira, M., Takahashi, Y., Shiku, H., Matsue, T., 2015. Anal. Chem. 87, 6364–6370.
Adunsky, A., Ohry, A., 2005. Arch. Gerontol. Geriatr. 41, 261–269.
Ahmad, E.T., 2008. Ann. Burns Fire Disasters 21, 124–128.
Ahmed, A.F., Elgayed, S.S.A., Ibrahim, I.M., 2012. J. Adv. Res. 3, 109–117.
Aihara, H., Miyazaki, J., 1998. Nat. Biotechnol. 16, 867–870.
Alfinito, E., Pousset, J., Reggiani, L., 2015. J. Phys. Conf. Ser. 647.
Alwarappan, S., Cissell, K., Dixit, S., Li, C.Z., Mohapatra, S., 2012. J. Electroanal. Chem. 686, 69–72.
Amdursky, N., Marchak, D., Sepunaru, L., Pecht, I., Sheves, M., Cahen, D., 2014. Adv. Mater. 26, 7142–7161.
Anna, P., Taradaj, J., Kucio, C., 2012. Ostomy Wound Manag .
Arnold, A.R., Grodick, M.A., Barton, J.K., 2016. Cell Chem. Biol. 23, 183–197.
Artés, J.M., Díez-Pérez, I., Gorostiza, P., 2012. Nano Lett. 12, 2679–2684.
Asadi, M.R., Torkaman, G., Hedayati, M., Mofid, M., 2013. J. Rehabil. Res. Dev. 50, 489.
Aschi, M., Zazza, C., Spezia, R., Bossa, C., Di Nola, A., Paci, M., Amadei, A., 2004. J. Comput. Chem. 25, 974–984.
Assan, D., Mozneb, M., Lai, J.C.K., Leung, S., 2015. Sens. Transducers 6–12.
Bai, H., Forrester, J.V., Zhao, M., 2011. Cytokine 55, 110–115.
Barrientos, S., Stojadinovic, O., Golinko, M.S., Brem, H., Tomic-Canic, M., 2008. Regen 16, 585–601.
Bates, E., 2015. Annu. Rev. Cell Dev. Biol. 31, 231–247.
Benninger, D.H., Hallett, M., 2015. NeuroRehabilitation 37, 11–24.
Bettan, M., Emmanuel, F., Darteil, R., Caillaud, J.M., Soubrier, F., Delaere, P., Branelec, D., Mahfoudi, A., Duverger, N., Scherman, D., 2000. Mol. Ther. 2, 204–210.
Borba, G.C., Hochman, B., Liebano, R.E., Enokihara, M.M.S.S., Ferreira, L.M., 2011. J. Surg. Res. 166, 324–329.
Bren, K.L., Eisenberg, R., Gray, H.B., 2015. Proc. Natl. Acad. Sci. Unit. States Am. 112, 13123–13127.
Brück, E., Arons, R.R., Buschow, K.H.J., De Boer, F.R., 1936. J. Magn. Magn Mater. 157–158, 395–396.
Bukhari, M.H., Batool, S., Raza, D.Y., Bagasra, O., Rizvi, A., Shah, A., Razzaki, T., Sultan, T., 2018. Electromagn. Biol. Med. 37, 169–174.
Bureau, M.F., Gehl, J., Deleuze, V., Mir, L.M., Scherman, D., 2000. Biochim. Biophys. Acta Gen. Subj. 1474, 353–359.
Caddy, J., Wilanowski, T., Darido, C., Dworkin, S., Ting, S.B., Zhao, Q., Rank, G., Auden, A., Srivastava, S., Papenfuss, T.A., Murdoch, J.N., Humbert, P.O., Boulos, N., Weber, T., Zuo, J., Cunningham, J.M., Jane, S.M., 2010. Dev. Cell 19, 138–147.
Cafferty, B.J., Ten, A.S., Fink, M.J., Morey, S., Preston, D.J., Mrksich, M., Whitesides, G. M., 2019. ACS Cent. Sci.
Cahen, D., Bostick, C.D., Lederman, D., Pecht, I., Mukhopadhyay, S., Sheves, M., 2018. Rep. Prog. Phys. 81, 026601.
Cantero, M. del R., Villa Etchegoyen, C., Perez, P.L., Scarinci, N., Cantiello, H.F., 2018. Sci. Rep. 8, 1–10.
Carley, P., Wainapel, S.F., 1985. Arch. Phys. Med. Rehabil. 66, 443–446.
Çeliker, M.Y., Ramamurthy, N., Xu, J.W., Wang, M., Jiang, Y., Greenwald, R., Shi, Y.E., 2002. Arthritis Rheum. 46, 3361–3368.
Chaban, Y., Boekema, E.J., Dudkina, N.V., 2014. Biochim. Biophys. Acta Bioenerg. 1837, 418–426.
Chang, D.C., Reese, T.S., 1990. Biophys. J. 58, 1–12.
Chang, K.W., Yuan, T.C., Fang, K.P., Yang, F.S., Liu, C.J., Chang, C.S., Lin, S.C., 2003. J. Oral Pathol. Med. 32, 606–611.
Chen, B., Xiao, Y., Liu, C., Li, C., Leng, F., 2010. Research 38, 3643–3654.
Chiolerio, A., Draper, T.C., Mayne, R., Adamatzky, A., 2019.
Chioni, A.M., Brackenbury, W.J., Calhoun, J.D., Isom, L.L., Djamgoz, M.B.A., 2009. Int. J. Biochem. Cell Biol. 41, 1216–1227.
Choi, Seong Ho, BongSoo Kim, C.D.F., 2008. Science 320 (80), 1482–1486.
Choi, K., Park, H.G., 2017. ACS Nano 11, 5223–5226.
Chuang, C.H., Li, C.Z., Yeh, C.C., Hsu, Y.M., 2008. 3rd IEEE Int. Conf. Nano/Micro Eng. Mol. Syst. NEMS 938–942.
Cinar, K., Comlekci, S., Senol, N., 2009. Laser Med. Sci. 24, 735–740.
Cohen, D.J., Nelson, W.J., Maharbiz, M.M., 2014. Nat. Mater. 13, 409–417.
Conant, G., Lai, B.F.L., Lu, R.X.Z., Korolj, A., Wang, E.Y., Radisic, M., 2017. Stem Cell Rev. Rep. 13, 335–346.
Dannhauer, M., Brooks, D., Tucker, D., MacLeod, R., 2011. Conf. Proc. IEEE Eng. Med. Biol. Soc. 23, 1–7.
Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., Bikson, M., 2010. 2, 201–207.
Daud, A.I., DeConti, R.C., Andrews, S., Urbas, P., Riker, A.I., Sondak, V.K., Munster, P.N., Sullivan, D.M., Ugen, K.E., Messina, J.L., Heller, R., 2008. J. Clin. Oncol. 26, 5896–5903.
Dembek, T.A., Reker, P., Visser-Vandewalle, V., Wirths, J., Treuer, H., Klehr, M., Roediger, J., Dafsari, H.S., Barbe, M.T., Timmermann, L., 2017. Mov. Disord. 32, 1380–1388.
Dietz, H., Douglas, S.M., Shih, W.M., 2009. Science 325 (80), 725–730.
Douglas, S.M., Dietz, H., Liedl, T., Högberg, B., Graf, F., Shih, W.M., 2009a. Nature 459, 1154.
Douglas, S.M., Marblestone, A.H., Teerapittayanon, S., Vazquez, A., Church, G.M., Shih, W.M., 2009b. Nucleic Acids Res. 37, 5001–5006.
Dwyer, D.S., 2001. J. Biomol. Struct. Dyn. 18, 881–892.
Elias, B., Shao, F., Barton, J.K., 2008. J. Am. Chem. Soc. 130, 1152–1153.
Engelkes, V.B., Beebe, J.M., Frisbie, C.D., 2004. J. Am. Chem. Soc. 126, 14287–14296.
Feedar, J.A., Kloth, L.C., Gentzkow, G.D., 1991. Phys. Ther. 71, 639–649.
Ferraro, B., Cruz, Y.L., Coppola, D., Heller, R., 2009. Mol. Ther. 17, 651–657.
Ferroni, P., Roselli, M., Guadagni, F., Martini, F., Mariotti, S., Marchitelli, E., Cipriani, C., 2005. In: Vivo (Brooklyn), vol. 19, pp. 949–958.
Force, U.S.P.S.T., 2018. J. Am. Med. Assoc. 319, 2308–2314.
FOULDS, I.S., BARKER, A.T., 1983. Br. J. Dermatol. 109, 515–522.
Franek, A., Polak, A., Kucharzewski, M., 2000. Med. Eng. Phys. 22, 647–655.
Franek, A., Kostur, R., Anna, P., Taradaj, J., Szlachta, Z., Blaszczak, E., Dolibog, Patrycja, Dolibog, Pawel, Koczy, B., Kucio, C., 2012.
Fraser, S.P., Grimes, J.A., Djamgoz, M.B.A., 2000. Prostate 44, 61–76.
Friesen, D.E., Craddock, T.J.A., Kalra, A.P., Tuszynski, J.A., 2015. Biosystems 127, 14–27.

Fytagoridis, A., Åström, M., Wårdell, K., Blomstedt, P., 2013. Clin. Neurol. Neurosurg. 115, 65–71.
Gao, J., Raghunathan, V.K., Reid, B., Wei, D., Diaz, R.C., Russell, P., Murphy, C.J., Zhao, M., 2015. Acta Biomater. 12, 102–112.
Gbadeyan, O., Steinhauser, M., McMahon, K., Meinzer, M., 2016. Safety, tolerability, brain stimul. Basic, transl. Clin. Res. Neuromodulat. 9, 545–552.
Genereux, Joseph C., Barton, Jacqueline K., 2011. Chem. Rev. 110, 1642–1662.
Gerling, T., Wagenbauer, K.F., Neuner, A.M., Dietz, H., 2015. Science 347 (80), 1446–1452.
Gharooni, M., Alikhani, A., Moghtaderi, H., Abiri, H., Mashaghi, A., Abbasvandi, F., Khayamian, M.A., Miripour, Z.S., Zandi, A., Abdolahad, M., 2019. ACS Sens. 4, 353–362.
Gomes, R.C., Brandino, H.E., Alves De Sousa, N.T., Santos, M.F., Martinez, R., De Jesus Guirro, R.R., 2015. Wound Repair Regen. 23, 403–411.
Gorodetsky, A.A., Barton, J.K., 2006. Langmuir 22, 7917–7922.
Gray, H.B., Winkler, J.R., 2003. Q. Rev. Biophys. 36, 341–372.
Griffin, J.W., Tooms, R.E., Mendius, R.A., Clifft, J.K., Vander Zwaag, R., El-Zeky, F., 1991. Phys. Ther. 71, 433–442.
Grodick, Michael A., Muren, Natalie B., B, J.K., 2015. Biochemistry 54, 962–973.
Grünbaum, T., Bange, S., Kronseder, M., Back, C.H., Lupton, J., 2019. J. Phys. D Appl. Phys.
Guehl, D., Cuny, E., Benazzouz, A., Rougier, A., Tison, F., Machado, S., Grabot, D., Gross, C., Bioulac, B., Burbaud, P., 2006. Eur. J. Neurol. 13, 963–971.
Guo, C., Wang, K., Zerah-Harush, E., Hamill, J., Wang, B., Dubi, Y., Xu, B., 2016. Nat. Chem. 8, 484–490.
Gürgen, S.G., Sayın, O., Çetin, F., Tuç Yücel, A., 2014. Inflammation 37, 775–784.
Hafez, I., Kisler, K., Berberian, K., Dernick, G., Valero, V., Yong, M.G., Craighead, H.G., Lindau, M., 2005. Proc. Natl. Acad. Sci. Unit. States Am. 102, 13879–13884.
Hälbig, T.D., Tse, W., Frisina, P.G., Baker, B.R., Hollander, E., Shapiro, H., Tagliati, M., Koller, W.C., Olanow, C.W., 2009. 16, 493–497.
Hihath, J., Xu, B., Zhang, P., Tao, N., 2005. Proc. Natl. Acad. Sci. U. S. A 102, 16979–16983.
Hoare, J.I., Rajnicek, A.M., McCaig, C.D., Barker, R.N., Wilson, H.M., 2016. J. Leukoc. Biol. 99, 1141–1151.
Hodgkin, A.L., Huxley, A.F., 1952. J. Physiol. 117, 500–544.
Hondroulis, E., Melnick, S.J., Zhang, X., Wu, Z.Z., Li, C.Z., 2013. Biomed. Microdevices 15, 657–663.
Hondroulis, E., Zhang, R., Zhang, C., Chen, C., Ino, K., Matsue, T., Li, C.Z., 2014. Theranostics 4, 919–930.
Hou, Y., Liu, J., Hong, M., Li, X., Ma, Y., Yue, Q., Li, C.Z., 2017. Biosens. Bioelectron. 92, 259–265.
Houghton, P.E., Kincaid, C.B., Lovell, M., Campbell, K.E., Keast, D.H., Woodbury, M.G., Harris, K.A., 2003. Phys. Ther. 83, 17–28.
Houghton, P.E., Campbell, K.E., Fraser, C.H., Harris, C., Keast, D.H., Potter, P.J., Hayes, K.C., Woodbury, M.G., 2010. Arch. Phys. Med. Rehabil. 91, 669–678.
Hunckler, J., de Mel, A., 2017. J. Multidiscip. Healthc. 10, 179–194.
Janković, A., Binić, I., 2008. Arch. Dermatol. Res.
Johnson, B.N., Lancaster, K.Z., Hogue, I.B., Meng, F., Kong, Y.L., Enquist, L.W., McAlpine, M.C., 2015. Lab Chip 16 (Ahead of Print).
Joundi, R.A., Brittain, J.-S., Green, A.L., Aziz, T.Z., Brown, P., Jenkinson, N., 2013. Clin. Neurophysiol. 124, 565–573.
Kaushik, A., Yndart, A., Kumar, S., Jayant, R.D., Vashist, A., Brown, A.N., Li, C.Z., Nair, M., 2018. Sci. Rep. 8, 3–7.
Kelley, S.O., Barton, J.K., Jackson, N.M., Hill, M.G., 1997. Inside Chem. 8, 31–37.
Kelly, S.M., Jess, T.J., Price, N.C., 2005. Acta - Proteins Proteomics 1751, 119–139.
Kim, B., Choi, S.H., Zhu, X.Y., Frisbie, C.D., 2011. J. Am. Chem. Soc. 133, 19864–19877.
Kim, T.H., Cho, H., Lee, S.M., 2014. Tohoku J. Exp. Med. 234, 1–6.
Kim, M.S., Lee, M.H., Kwon, B.J., Koo, M.A., Seon, G.M., Park, J.C., 2015. Biophys. Res. Commun. 460, 255–260.
Krause, V., Wach, C., Südmeyer, M., Ferrea, S., Schnitzler, A., Pollok, B., 2014. Front. Hum. Neurosci. 7, 1–10.
Kurtis, M.M., Rajah, T., Delgado, L.F., Dafsari, H.S., 2017. NPJ Park. Dis. 3, 1–12.
Lacroix, J.Ô.J., Campos, F.V., Frezza, L., Bezanilla, F., 2013. Neuron 79, 651–657.
Lawson, D., Petrofsky, J.S., 2007. Med. Sci. Monit. 13, 258–263.
Lee, E.W., Wong, D., Prikhodko, S.V., Perez, A., Tran, C., Loh, C.T., Kee, S.T., 2012. J. Vasc. Intervent. Radiol. 23, 107–113.
Lee, S.H., Shim, K.Y., Kim, B., Sung, J.H., 2017. Biotechnol. Prog. 33, 580–589.
Lefaucheur, J.-P., Antal, A., Ayache, S.S., Benninger, D.H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M.A., Padberg, F., Palm, U., Poulet, E., Priori, A., Rossi, S., Schecklmann, M., Vanneste, S., Ziemann, U., Garcia-Larrea, L., Paulus, W., 2017. Clin. Neurophysiol. 128, 56–92.
Legant, W.R., Pathak, A., Yang, M.T., Deshpande, V.S., McMeeking, R.M., Chen, C.S., 2009. Proc. Natl. Acad. Sci. Unit. States Am. 106, 10097–10102.
Leung, S.W., Mozneb, S.M., Lai, J.C.K., Assan, D., 2014, 2014 Tech. Proc. 2014 NSTI Nanotechnol. Conf. Expo, NSTI-Nanotech. 2, 188–191.
Levin, M., 2012. Bioessays 34, 205–217.
Zhong, Li C., Nishiyama, K., Taniguchi, I., 2000. Acta 45, 2883–2888.
Li, C.Z., Long, Y.T., Kraatz, H.B., Lee, J.S., 2003. J. Phys. Chem. B 107, 2291–2296.
Li, C.Z., Long, Y.T., Lee, J.S., Kraatz, H.B., 2004. Chem. Commun. 4, 574–575.
Li, C.Z., Liu, Y., Luong, J.H.T., 2005. Anal. Chem. 77, 478–485.
Li, C.-Z., Alwarappan, S., Zhang, W., Scafa, N., Zhang, X., 2009. Am. J. Biomed. Sci. 274–282.
Li, C., Liu, G., Prabhulkar, S., 2009. Am. J. Biomed. Sci. 1, 303–311.
Zhong, Li C., Taniguchi, I., Mulchandani, A., 2009. Bioelectrochemistry 75, 182–188.
Li, C.Z., Karadeniz, H., Canavar, E., Erdem, A., 2012. Acta 82, 137–142.
Li, D., Gannett, P.M., Lederman, D., 2012. Nanotechnology 23.
Li, L., Gu, W., Du, J., Reid, B., Deng, X., Liu, Z., Zong, Z., Wang, H., Yao, B., Yang, C., Yan, J., Zeng, L., Chalmers, L., Zhao, M., Jiang, J., 2012. Wound Repair Regen. 20, 840–851.
Li, W., Sepunaru, L., Amdursky, N., Cohen, S.R., Pecht, I., Sheves, M., Cahen, D., 2012. ACS Nano 6, 10816–10824.
Li, H., Shi, W., Song, J., Jang, H.J., Dailey, J., Yu, J., Katz, H.E., 2019. Chem. Rev. 119, 3–35.
Linko, V., Paasonen, S.T., Kuzyk, A., Törmä, P., Toppari, J.J., 2009. Small 5, 2382–2386.
Little, S., Tripoliti, E., Beudel, M., Pogosyan, A., Cagnan, H., Herz, D., Bestmann, S., Aziz, T., Cheeran, B., Zrinzo, L., Hariz, M., Hyam, J., Limousin, P., Foltynie, T., Brown, P., 2016. J. Neurol. Neurosurg. Psychiatry 87, 1388–1389.
Liu, B., Bard, A.J., Li, C.Z., Kraatz, H.B., 2005. J. Phys. Chem. B 109, 5193–5198.
Long, Y.T., Li, C.Z., Kraatz, H.B., Lee, J.S., 2003a. Biophys. J. 84, 3218–3225.
Long, Y.T., Li, C.Z., Sutherland, T.C., Chahma, M., Lee, J.S., Kraatz, H.B., 2003b. J. Am. Chem. Soc. 125, 8724–8725.
Long, Y.T., Li, C.Z., Sutherland, T.C., Kraatz, H.B., Lee, J.S., 2004. Anal. Chem. 76, 4059–4065.
Long, Y.T., Abu-Irhayem, E., Kraatz, H.B., 2005. Chem. Eur J. 11, 5186–5194.
Lozano, C.S., Tam, J., Lozano, A.M., 2018. Mov. Disord. 33, 36–47.
Lundeberg, T.C.M., Eriksson, S.V., Malm, M., 1992. Ann. Plast. Surg. 29.
Ma, Q., Teter, B., Ubeda, O.J., Morihara, T., Dhoot, D., Nyby, M.D., Tuck, M.L., Frautschy, S.A., Cole, G.M., 2009. Nat. Chem. Biol. 27, 14299–14307.
Magnoni, C., Rossi, E., Fiorentini, C., Baggio, A., Ferrari, B., Alberto, G., 2013. J. Wound Care 22, 525–533.
Margara, A., Boriani, F., Obbïalero, F.D., Bocchiotti, M., 2008. Chirurgia (Buchar.).
Marti, G., Ferguson, M., Wang, J., Byrnes, C., Dieb, R., Qaiser, R., Bonde, P., Duncan, M. D., Harmon, J.W., 2004. Gene Ther. 11, 1780–1785.
McCaig, C.D., Rajnicek, A.M., Song, B., Zhao, M., 2005. Physiol. Rev. 85, 943–978.
Mcferrin, M.B., Sontheimer, H., 2006. Neuron Glia Biol. 2, 39–49.
Meglic, S.H., Kotnik, T., 2017. Handb. Electroporation 3, 2153–2169.
Menéndez, S.T., Rodrigo, J.P., Allonca, E., García-Carracedo, D., Álvarez-Alija, G., Casado-Zapico, S., Fresno, M.F., Rodríguez, C., Suárez, C., García-Pedrero, J.M., 2010. J. Pathol. 221, 402–410.
Mir, L.M., Bureau, M.F., Gehl, J., Rangara, R., Rouy, D., Caillaud, J.-M., Delaere, P., Branellec, D., Schwartz, B., Scherman, D., 1999. Proc. Natl. Acad. Sci. Unit. States Am. 96, 4262–4267.
Mirtaheri, E., Dolatmoradi, A., El-Zahab, B., 2019. Anal. Chem.
Morris, K.A., McGee, M.F., Jasper, J.J., Bogie, K.M., 2009. Arch. Dermatol. Res. 301, 323–327.
Mostafalu, P., Akbari, M., Alberti, K.A., Xu, Q., Khademhosseini, A., Sonkusale, S.R., 2016. Microsyst. Nanoeng. 2.
Mozneb, M., Mirza, A.M., Li, C.-Z., 2020. Anal. Chem. 92, 2244–2250.
Nicolau, D.V., Lard, M., Korten, T., Van Delft, F.C.M.J.M., Persson, M., Bengtsson, E., Månsson, A., Diez, S., Linke, H., Nicolau, D.V., 2016. Proc. Natl. Acad. Sci. U. S. A 113, 2591–2596.
Nitsche, M.A., Paulus, W., 2000. J. Physiol. 527, 633–639.
Nowak, M., Hinson, E., Van Ede, F., Pogosyan, A., Guerra, A., Quinn, A., Brown, P., Stagg, C.J., 2017. J. Neurosci. 37, 4481–4492.
Nyein, H.Y.Y., Tai, L.C., Ngo, Q.P., Chao, M., Zhang, G.B., Gao, W., Bariya, M., Bullock, J., Kim, H., Fahad, H.M., Javey, A., 2018. ACS Sens. 3, 944–952.
Oehler, M., Ling, V., Melhorn, K., Schilling, M., 2008. Physiol. Meas. 29, 783–793.
Orlowski, S., Mir, L.M., 1993. Biophys. Acta - Rev. Biomembr. 1154, 51–63.
Pauling, L., Coryell, C.D., 1936. Proc. Natl. Acad. Sci. Unit. States Am. 22, 159–163.
Peters, E.J., Lavery, L.A., Armstrong, D.G., Fleischli, J.G., 2001. Arch. Phys. Med. Rehabil. 82, 721–725.
Petrov, E.G., Shevchenko, Y.V., Teslenko, V.I., May, V., 2001. J. Chem. Phys. 115, 7107–7122.
Pickar-oliver, A., Black, J.B., Lewis, M.M., Mutchnick, K.J., Klann, T.S., Gilcrest, K.A., Sitton, M.J., Nelson, C.E., Barrera, A., Bartelt, L.C., Reddy, T.E., Beisel, C.L., Barrangou, R., Gersbach, C.A., n.d. Nat. Biotechnol.
Prabhulkar, S., Li, C.Z., 2010. Biosens. Bioelectron. 26, 1743–1749.
Prabhulkar, S., Piatyszek, R., Cirrito, J.R., Wu, Z.Z., Li, C.Z., 2012a. J. Neurochem. 122, 374–381.
Prabhulkar, S., Tian, H., Wang, X., Zhu, J.J., Li, C.Z., 2012b. Antioxidants Redox Signal. 17, 1796–1822.
Priel, A., Ramos, A.J., Tuszynski, J.A., Cantiello, H.F., 2006. Biophys. J. 90, 4639–4643.
Pu, J., Zhao, M., 2006. J. Cell Sci. 118, 1117–1128. https://doi.org/10.1242/jcs.01646. Golgi.
Rajendran, A., Endo, M., Sugiyama, H., 2012. Chem. Int. Ed. 51, 874–890.
Reger, S.I., Hyodo, A., Negami, S., Kambic, H.E., Sahgal, V., 1999. Artif. Organs 23, 460–462.
Reid, B., Song, B., McCaig, C.D., Zhao, M., 2005. Faseb. J. 19, 379–386.
Reid, B., Song, B., Zhao, M., 2009. Dev. Biol. 335, 198–207.
Ribet, F., Stemme, G., Roxhed, N., 2017. Biosens. Bioelectron. 90, 577–583.
Rizzuto, G., Cappelletti, M., Maione, D., Savino, R., Lazzaro, D., Costa, P., Mathiesen, I., Cortese, R., Ciliberto, G., Laufer, R., La Monica, N., Fattori, E., 1999. Proc. Natl. Acad. Sci. U. S. A 96, 6417–6422.
Ron, I., Sepunaru, L., Ltzhakov, S., Belenkova, T., Friedman, N., Pecht, I., Sheves, M., Cahen, D., 2010. J. Am. Chem. Soc. 132, 4131–4140.
Rothemund, P.W.K., 2006. Nature 440, 297–302.
Rouabhia, M., Park, H.J., Zhang, Z., 2016. J. Cell. Physiol. 231, 1814–1821.
Roux, B., 2017. Essays Biochem. 61, 201–209.
Rouzaire-Dubois, B., Milandri, J.B., Bostel, S., Dubois, J.M., 2000. Pflugers Arch. Eur. J. Physiol. 440, 881–888.

Ruffini, G., Fox, M.D., Ripolles, O., Miranda, P.C., Pascual-Leone, A., 2014. Neuroimage 89, 216–225.
Saaem, I., Labean, T.H., 2013. Rev. Nanomedicine Nanobiotechnology 5, 150–162.
Sabir, I.N., Usher-Smith, J.A., 2008. pp. 1–36.
Samakoglu, S., Fattori, E., Lamartina, S., Toniatti, C., Stockholm, D., Heard, J.M., Bohl, D., 2001. Blood 97, 2213–2220.
Santamato, A., Panza, F., Fortunato, F., Portincasa, A., Frisardi, V., Cassatella, G., Valente, M., Seripa, D., Ranieri, M., Fiore, P., 2012. Rejuvenation Res. 15, 281–287.
Schläpfer, J., Wellens, H.J., 2017. J. Am. Coll. Cardiol. 70, 1183–1192.
Sebastian, A., Syed, F., Perry, D., Balamurugan, V., Colthurst, J., Chaudhry, I.H., Bayat, A., 2011. Wound Repair Regen. 19, 693–708.
Sek, S., 2013. Biopolymers 100, 71–81.
Shah, P., Zhu, X., Chen, C., Hu, Y., Li, C.Z., 2014. Biomed. Microdevices 16, 35–41.
Shah, P., Zhu, X., Zhang, X., He, J., Li, C.Z., 2016. ACS Appl. Mater. Interfaces 8, 5804–5812.
Shill, H.A., Obradov, S., Katsnelson, Y., Pizinger, R., 2011. Mov. Disord. 26, 1477–1480.
Skourtis, S.S., 2013. Biopolymers 100, 82–92.
Slinker, Jason D., Muren, Natalie B., Renfrew, Sara E., B, J.K., 2011. Nature 3, 230–235.
Söhl, G., Odermatt, B., Maxeiner, S., Degen, J., Willecke, K., 2004. Brain Res. Rev. 47, 245–259.
Song, J., Yin, F., Li, X., Dong, N., Zhu, Y., Shao, Y., Chen, B., Jiang, W., Li, C.Z., 2018. Analyst 143, 1593–1598.
Stephen, B., Joyce, E., Ronald, P., 1981. Int. J. Quant. Chem. 20, 307–316.
Stracke, R., Böhm, K.J., Wollweber, L., Tuszynski, J.A., Unger, E., 2002. Biophys. Res. Commun. 293, 602–609.
Sukumaran, P., Thazhe Veettil, V., Rajappa, S., Li, C.Z., Alwarappan, S., 2017. Sensor. Actuator. B Chem. 247, 556–563.
Taghbalout, A., Du, M., Jillette, N., Rosikiewicz, W., Rath, A., Heinen, C.D., Li, S., Cheng, A.W., n.d. Nat. Commun. 1–12.
Taniguchi, I., Li, C.Z., Ishida, M., Yao, Q., 1999. J. Electroanal. Chem. 460, 245–250.
Thut, G., Bergmann, T.O., Fröhlich, F., Soekadar, S.R., Brittain, J.-S., Valero-Cabré, A., Sack, A.T., Miniussi, C., Antal, A., Siebner, H.R., Ziemann, U., Herrmann, C.S., 2017. Clin. Neurophysiol. 128, 843–857.
Tinkhauser, G., Pogosyan, A., Debove, I., Nowacki, A., Shah, S.A., Seidel, K., Tan, H., Brittain, J.-S., Petermann, K., di Biase, L., Oertel, M., Pollo, C., Brown, P., Schuepbach, M., 2018. Mov. Disord. 33, 159–164.
Tong, L., Mozneb, M., Bravo, E., Ferrando, V., Li, C.Z., 2019. TrAC Trends Anal. Chem. (Reference Ed.).
Tran, P., Alavi, B., Gruner, G., 2000. Am. Phys. Soc. 85, 12–15.
Triberis, G., Dimakogianni, M., 2009. Nanotechnology 3, 135–153.
Tuszynski, J.A., Carpenter, E.J., Huzil, J.T., Malinski, W., Luchko, T., Ludueña, R.F., 2006. Int. J. Dev. Biol. 50, 341–358.
Ud-Din, S., Bayat, A., 2014. Healthcare 2, 445–467.
Ud-Din, S., Perry, D., Giddings, P., Colthurst, J., Zaman, K., Cotton, S., Whiteside, S., Morris, J., Bayat, A., 2012. Exp. Dermatol. 21, 758–764.
Ud-Din, S., Sebastian, A., Giddings, P., Colthurst, J., Whiteside, S., Morris, J., Nuccitelli, R., Pullar, C., Baguneid, M., Bayat, A., 2015. PloS One 10, 1–22.
Uppalapati, M., Huang, Y.M., Jackson, T.N., Hancock, W.O., 2008. Small 4, 1371–1381.
van der Helm, M., van der Meer, A., Eijkel, J., van den Berg, A., Segerink, L., 2016. Tissue Barriers 8370.
Wagstaff, P.G.K., de Bruin, D.M., Zondervan, P.J., Savci Heijink, C.D., Engelbrecht, M.R. W., van Delden, O.M., van Leeuwen, T.G., Wijkstra, H., de la Rosette, J.J.M.C.H., Laguna Pes, M.P., 2015. BMC Canc. 15, 1–7.
Wagstaff, P.G.K., Buijs, M., van den Bos, W., de Bruin, D.M., Zondervan, P.J., de la Rosette, J.J.M.C.H., Laguna Pes, M.P., 2016. OncoTargets Ther. 9, 2437–2446.
Wang, K., 2018. J. Funct. Biomater. 9.
Wang, E.-T., Zhao, M., 2010. Chin. J. Traumatol. - English Ed. 13, 55–61.
Wang, K., Hamill, J.M., Wang, B., Guo, C., Jiang, S., Huang, Z., Xu, B., 2014. Chem. Sci. 5, 3425–3431.
Wang, Y., Rouabhia, M., Zhang, Z., 2016. Biochim. Biophys. Acta Gen. Subj. 1860, 1551–1559.
Weltin, A., Hammer, S., Noor, F., Kaminski, Y., Kieninger, J., Urban, G.A., 2017. Biosens. Bioelectron. 87, 941–948.
Wettig, S.D., Li, C.Z., Long, Y.T., Kraatz, H.B., Lee, J.S., 2003. Anal. Sci. 19, 23–26.
Winkler, C., Reis, J., Hoffmann, N., Gellner, A.K., Münkel, C., Curado, M.R., Furlanetti, L., Garcia, J., Döbrössy, M.D., Fritsch, B., 2017. eNeuro 4, 1–11.
Wirsing, P.G., Habrom, A.D., Zehnder, T.M., Friedli, S., Blatti, M., 2015. Int. Wound J. 12, 693–698.
Wood, J.M., Evans III, P.E., Schallreuter, K.U., Jacobson, W.E., Sufit, R., Newman, J., White, C., Jacobson, M., 1993. JAMA Dermatol. 129, 999–1009.
Xin, H., Woolley, A.T., 2003. J. Am. Chem. Soc. 125, 8710–8711.
Xing, W., Cheng, J., 2006. Front. Biochip Technol.
Xiong, G.M., Do, A.T., Wang, J.K., Yeoh, C.L., Yeo, K.S., Choong, C., 2015. J. Biol. Eng. 9, 1–10.
Xu, B., Tao, N.J., 2003. Science 301 (80), 1221–1223.
Xu, T., Scafa, N., Xu, L.P., Su, L., Li, C., Zhou, S., Liu, Y., Zhang, X., 2014. Electroanalysis 26, 449–468.
Xuan, X., Yoon, H.S., Park, J.Y., 2018. Biosens. Bioelectron. 109, 75–82.
Yang, H., Li, Z., Wei, X., Huang, R., Qi, H., Gao, Q., Li, C., Zhang, C., 2013. Talanta 111, 62–68.
Young, J.L., Dean, D.A., 2015. Adv. Genet.. Elsevier Ltd.
Yu, Y., Zuo, F., Li, C.Z., 2013. Electrochim. Acta 113, 603–608.
Yu, Y., Zuo, F., Li, C., 2014a. Biophys. J. 106, 181a.
Yu, Y., Zuo, F., Li, C.Z., 2014b. Electrochim. Acta 144, 263–267.
Zhan, M., Wool, R.P., 2013. Compos. Part A Appl. Sci. Manuf. 47, 22–30.
Zhang, Q.C., Xiao, H., Zhang, X., Xu, L.J., Chen, Z.N., 2019. Coord. Chem. Rev. 378, 121–133.
Zhao, M., Bai, H., Wang, E., Forrester, J.V., McCaig, C.D., 2003. J. Cell Sci. 117, 397–405.
Zhao, M., Song, B., Pu, J., Wada, T., Reid, B., Tai, G., Wang, F., Guo, A., Walczysko, P., Gu, Y., Sasaki, T., Suzuki, A., Forrester, J.V., Bourne, H.R., Devreotes, P.N., McCaig, C.D., Penninger, J.M., 2006. Nature 442, 457–460.
Zhu, X., Hondroulis, E., Liu, W., Li, C.Z., 2013a. Small 9, 1821–1830.
Zhu, X., Shah, P., Li, C., 2013b. Proc. - 29th south. Biomed. Eng. Conf. SBEC 125–126, 2013.
Zhu, X., Shah, P., Stoff, S., Liu, H., Li, C.Z., 2014. AAnalyst 139, 2850–2857.
Zhu, X., Liu, W., Shuang, S., Nair, M., Li, C.Z., 2017. Med. Biosens. Point Care Appl. 133–150.