Title
Bioelectronics for Wearable and Implantable Electrical Stimulation Therapeutics

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Abstract
This review article discusses self-powered wearable bioelectronics, which have become an emerging field of research due to their unique features such as portability, low power consumption, and wireless connectivity enabled by the Internet of Things (IoT). The focus is on physical bioelectronics, particularly electrical stimulation therapies, which have been used for tissue regeneration processes. The current non-self-powered and self-powered bioelectronics, such as transcranial and transcutaneous electrical stimulation, and triboelectric and piezoelectric nanogenerators, are discussed along with their applications, challenges, and limitations. The article then introduces magnetoelastic generators (MEGs) as a potential alternative for electrical stimulation therapies due to their unique working mechanism and self-powered advantages. The key components and requirements of bioelectronics for therapies are highlighted, and the challenges and limitations of MEGs are discussed. The article concludes with a summary of the current status and potential future applications of MEGs in electrical therapeutics.

1. Introduction

1.1 Self-Powered Wearable Therapeutics And Their Features

Nature and technology have come a long way since the early days of wearable devices. Today, wearable electronics are available in a wide range of forms and offer an array of advanced features. However, users demand increasingly high standards from these devices, including miniaturization, multi-functionality, and intelligence[1]. One of the most critical factors affecting the user experience is the battery life of these devices. Therefore, it is imperative that wearable electronics continue to evolve in order to meet these demands and provide users with a truly exceptional experience.

Portable devices have traditionally been powered by batteries, but the limitations of the battery industry have made it challenging to create truly portable devices, as batteries can take up a significant amount of space and weight. However, the invention of lithium batteries has greatly accelerated the development of wearable devices, as they are lightweight, low-pollution, safe, and have a high specific energy[2]. Nevertheless, the energy consumption of the load part is increasing, particularly with the development of wearable devices, necessitating repeated charging. To address this issue, researchers have turned to self-powered wearable devices that use various forms of energy surrounding the human body to power themselves[3]. Nanogenerators, including triboelectric nanogenerators (TENGs), piezoelectric nanogenerators (PENGs), and magnetoelastic generators (MEGs), have emerged as promising technologies for self-powered wearable bioelectronics due to their high output voltage and energy conversion rates, as well as their ability to collect small-scale mechanical energy and respond to low-frequency mechanical motion[4].

1.1.1 Internet Of Things And Personalized Healthcare

The advancement of the Internet of Things (IoT) has rapidly fueled a new concept that is point-of-care, characterized by a more personalized approach to healthcare with better healthcare outcomes, higher quality care, and lower costs[5]. It combines a variety of medical sensors and performs information exchange and preliminary processing among mobile terminals, embedded computing devices, and medical information processing platforms in accordance with the network agreement[6]. Medical IoT's perception layer is an essential part of helping users obtain their health information and assisting with medical care, and wearable medical devices play a key role in this[7]. The advent of self-powered wearable medical systems has dramatically extended the lifespan of wearable medical devices, enabling both real-time and long-term health monitoring. As a result, collecting energy from the human body for disease treatment also provides tremendous opportunities for telemedicine and long-term health care.

1.1.3 Electrical Impulses And Tissue Regeneration Processes

Electrical stimulation has recently gained a lot of attention as a physical stimulus. Due to its significant experimental performance, it shows great promise in disease treatment, wound healing, and mechanism study[8]. Stimulation of intracellular signaling pathways can influence the intracellular microenvironment, thereby affecting cell migration, proliferation, and differentiation[9]. In tissue engineering, electrical stimulation is used as a novel type of tool in regenerative medicine. Additionally, with the advantages of biocompatible conductive materials coming into view, the combination of electrical stimulation and tissue engineered scaffolds can well combine the benefits of both and is ideal for regenerative medicine. This report reviews the significant advances in self-powered wearable bioelectronics for electrical stimulation therapeutic systems.

2. Current Physical Bioelectronics For Electrical Stimulation In Therapeutics

2.1 Non Self-Powered Bioelectronics

Electricity has been used for various physiological systems to achieve therapeutic effects. The traditional way of delivering electrical therapies is in a non-self-powered fashion, in which the electrical applicators are coupled to a constant voltage source. Electrical stimulation therapies have been widely applied in the human nervous system, due to neurons' excitable property to fire action potentials in response to changes in membrane voltages. The following four technologies involve delivering electrical pulses to various biological systems such as the nervous system and the skeletal system to alleviate or treat a certain pathological state.

2.1.1 Fracture Healing And Bone Regeneration

Electrical pulses have been proven effective in facilitating the bone healing process after fracture. There are three principal ways that electrical current promotes the growth of bone cells

(Figure 1)[10]. First, electrodes coupled with an external power source can be invasively implanted to directly apply electrical current into the fracture site, enhancing osteoblastic activity and collagen synthesis. Second, a local electrical field can be produced by placing electrodes attached to the skin of the fracture site, which will increase calcium ion concentrations at the fracture site due to the capacitive effect. Third, a power source supplying an electromagnetic coil can create a local magnetic field at the fracture site. This inductive coupling method increases bone morphogenesis protein 2 and 4 (BMP2/4) due to the applied magnetic field, further facilitating the growth of bone cells[10]. In all three cases, a constant power source is required to produce electrical or electromagnetic energy to produce changes in the biochemical status of the fracture site.

2.1.2 Transcranial Electrical Stimulation

Transcranial electrical stimulation (TES) is a non-invasive brain stimulation technique that can be used to modulate the excitability of neurons in specific cortical regions[12]. TES includes transcranial direct current stimulation (tDCS), which involves applying a constant direct current to the scalp of the subject, and transcranial alternating current stimulation (tACS), which involves the application of alternating current (Figure 2). These currents are generated by a constant voltage source with a safe magnitude of less than 4mA[13].

Cathodal tES hyperpolarizes the targeted regions, making neurons less likely to fire action potentials and decreasing overall activity in the corresponding region. On the other hand, anodal tES depolarizes the targeted region, making neurons more excitable and increasing overall activity in the corresponding region[13]. By modulating the excitability of neurons in a particular cortical area, the applied electrical current can produce effects in cognitive, motor, or memory functions.

2.1.3 Transcutaneous Electrical Stimulation

Transcutaneous electrical stimulation (TES) is a technique in which electrical pulses are delivered above the skin to alleviate pain (Figure 3)[15]. By targeting the A-beta fibers on the external layer of the skin, TES can modulate the second-order pain transmission to the central nervous system. Acupuncture can penetrate the surface of the skin to reach the nociceptive (pain-related) A-delta fibers. By changing the electrical properties of these nociceptive sensory neurons via delivered electrical pulses, the therapy can modulate the process of pain sensation and transmission.

Patients with diabetes often suffer from neuropathic foot ulcers, which can lead to inconvenience of movement and painful bacterial infections. In severe cases, large-scale infection of diabetic foot ulcers can lead to amputation. The incidence of neuropathic foot ulcers in diabetes is correlated with the decreased conduction velocity of the nerve supplying the tibialis anterior muscle[15]. Researchers have measured the effect of applying TES to the nerve supplying the tibialis anterior muscle of genetically induced diabetic rats, observing a significant increase in the mean conducting signal velocity after applying electricity over the skin of diabetic rats for 7 days[15]. The decreased nerve conduction velocity recovered after researchers stopped applying electricity on day 8 (Figure 4).

Research in human diabetic patients also shows a significant decrease in the amount of subjectively sensed pain after TES (Figure 4)[16]. The increase in sensed pain resurged after removing the stimulation for 1 month. These results demonstrate that TES is effective in alleviating correlated neuropathy of diabetic foot ulcers. Furthermore, TES can be incorporated with smart shoe insoles to deliver therapies.

2.1.4 Deep-Brain Stimulation For Parkinson's Disease

Parkinson's disease patients suffered from the degeneration of dopaminergic neurons in the striatum, which lead to the impairment of motor-related functions. Death of neurons leads to patient's inability to control unwanted movements and produce tremor-like behaviors. By implanting electrodes to apply electrical spikes in the subthalamic nucleus region of striatum, this deep brain stimulation (DBS) could serve a "pulse-making" function for the unregulated neural activities in this region and alleviate symptoms of Parkinson's disease such as tremor. A DBS system primarily consists of three components: an electrode directly innervating the subthalamic nuclei region to deliver electrical pulses, a neurostimulator with a battery source that produces electrical pulses at a particular strength and frequency, and an insulated extension wire that connects the previous two components[16]. The battery in the neurostimulator, which is implanted in the chest of the patients can be wirelessly charged via an external power source placed right outside of the chest.

Researchers at UCSF developed a closed-loop DBS system, which could control the magnitude and time course of electrical pulses applied to striatum based on the real-time recording of motor-related neural signals in the cortical regions[17]. A sensing component involves implanting recording electrodes into the primary motor cortex (M1 region) of Parkinson's disease patient. The recorded neural signals in M1 region, which will be streamed to a computer, provide information about the patient's function in motor control, which could reflect upon the severity in imbalance and tremor. Meanwhile, such signal will be decoded and analyzed by a previously trained models and algorithms. Eventually, physiological information will be concluded about how far the current state deviates from the desired healthy state, which further demand the therapy component by changing the magnitude of electrical pulses applied in sub-thalamic nucleus in the next unit of time. Therefore, this closed-loop system could produce real-time feedback and smart therapies for Parkinson's disease patients.

In these cases, modern medical technology advances use electricity to modulate different physiological systems and achieve therapeutic effects. Though effective in producing the desired treatments of the corresponding conditions, most of these non-self powered electrical therapies require a stable power source or a battery. Except for the implanted DBS, these non-self powered bioelectronics are difficult to provide constant therapies and real-time feedbacks on the physiological state of the subject. Hence, in order to provide efficient real-time monitoring and therapies, self-power generation will be compulsory for next-era smart bioelectronics.

2.2 Self-Powered Bioelectronics

2.2.1 Triboelectric Nanogenerators (TENGs)

2.2.1.1 TENG Operating Principles

For TENGs, the electric field is produced by the transfer of static charge. The charges transferred between two materials can be molecules, ions and electrons. When two materials are separated, some of the bonded atoms tend to maintain the additional transferred electrons, and some tend to give them away, which possibly give rise to the opposite charges on different friction materials. The opposite charges on both friction surfaces can generate a triboelectric potential, which can drive electrons in the back electrode to flow in order to balance the created electric potential drop. On the basis of this principle, four kinds of TENGs with different modes have been invented, as shown in Figure 5.

2.2.1.2 TENG Applications In Therapeutics

2.2.1.2.1 Drug Delivery

Administration of medical drugs in the current healthcare system either most often comes in the form of a pill or invasive injection. Oftentimes, however, this leads to inefficient drug efficacy due to overdelivery or administration that takes time for effect. Additionally, needles can lead to noncompliance among patients, dissuading them from properly following TENGs offer a solution to this problem by creating systems for on-demand drug release that react promptly to stimuli and in a tunable fashion.

One method of tunable stimuli is the use of responsive polymers, such as polypyrrole, that can generate an electric potential when manipulated in both an exogenous and endogenous manner. Ouyang et al. utilized exogenous manipulation of (DEX P)-loaded polypyrrole interfaced with a TENG medical patch to achieve tunable transdermal drug delivery[18]. Iontophoresis, which is the electrically-driven delivery of drug molecules, was achieved by the electric field created by the TENG (Figure 6).

Manual manipulation was used to trigger the TENG circuit and initiate the release of DEX. The radial rotary array TENG used in this device saw a power density of 19 mW/cm^2 and an efficiency of up to 24%, with a max instantaneous voltage output of 250V. With respect to drug delivery efficiency, TENG release rates were compared to the release rates of an industry standard power supply, a potentiostat, while the effective voltage was varied. The researchers were able to conclude that the amount of drug released was directly proportional to the effective voltage and TENGs served as a suitable replacement for potentiostats by demonstrating equivalent performance. As shown in Figure 7, the longer the TENG was charged, the higher continuous voltage output it could produce, leading to a greater iontophoretic effect

Microneedles are also a rapidly popularizing method of transdermal drug delivery as they cause almost no intracellular damage and greatly enhance drug permeability. Microneeldes also offer enhanced sites for electroporation, the forming of small pores in the cell membrane, at the needle-cell interface. Liu et al. created a TENG-nanoneedle system (Figure 8) that takes advantage of this principle to form a tunable, two-fold drug delivery system actuated by manual stimulation[19]. The TENG/nanoneedle delivery saw a 4x increase of drug delivery as compared to just nanoneedle loading. This is believed to be attributed to the electroporation caused by the TENG component. Not only was delivery into the cell enhanced, but the diffusion of the drug into deeper layers of the dermis was found to be much greater (three times the height of the nanoneedles) when acted upon by the TENG. External electrical fields also helped preserve cell viability as previous methods of powering using nanowires have been shown to cause intracellular damage. Methods of powering the TENG included slapping and finger friction, with each displaying different drug release patterns so as to allow for tunability. While the drawbacks of this system are slight invasiveness due to the nanoneedles as well as low area of effect, its superior performance of a delivery efficiency of 90% and cell viability of 94% indicate high promise for localized drug delivery.

Recently, remarkably new ways to utilize TENGs for drug delivery have also been developed. Zhao et al. have created a novel approach for treating cancer based on electrically-stimulated drug release by red blood cells. Cancer tumors are highly vascularized as they spur angiogenesis to allow for nutrient uptake and waste removal. As such, this group decided to exploit the abundance of red blood cells (RBCs) present at the site of the tumor by turning the cells into chemo-therapeutic vehicles[20].

These cells serve numerous advantages over traditional small molecule drugs that are the current paradigm for cancer treatment. RBCs have reduced macrophage uptake, leading to decreased pharmacokinetic clearance and a higher residence time inside the tumor. Obviously being biocompatible and highly stable, there is also little concern of degradation of the vehicle leading to a low delivery efficiency. Finally, the RBCs can respond to an exogenous electric field created by a magnetic TENG (MTENG) to precisely release drugs at the target site through the formation of recoverable nanopores in the cell membrane. Tests *in vitro* for a 2D cell culture confirmed the enhanced cytotoxicity of the D@RBC+EF as compared to solely DOX, with a 20.9% and 70.4% viability rate, respectively.

2.2.1.2.2 Muscle Stimulation

Muscle contraction is mediated by electrical signals sent by the brain to the nervous system. When muscles or the nerve connections become damaged, disuse of the muscle fibers over time can result in atrophy, leaving patients weak and unable to return to their normal lives. Electrical stimulation (E-STIM) is a common form of therapy used for post-operation and rehabilitation purposes. However, current systems for E-STIM are bulky and intrusive, leading to a decreased quality of life. TENGs serve as a solution to this challenge due to their portability and flexibility, allowing them to adhere to the body with minimal perception of an on-body device. With their capability to produce localized electric fields, they have shown promise for systems of electrical muscle stimulation for rehabilitation.

Wang et al. created a self-powering TENG muscle stimulation system that attaches intramuscularly (Figure 9)[21]. Attached at sites of high motion artifacts, this device is able to harvest mechanical energy to turn it into electrical energy. Subsequently, it can use the stored electrical energy to create microcurrent stimulations (35μA) of muscle fibers. The device is tunable by changing the microcurrent waveform polarity and the motor neuron-electrode position.

The researchers used an animal model to demonstrate the TENG muscle stimulator's ability. A mouse had intramuscular electrodes attached to its hind leg muscle fibers and was then sedated to diminish any active movements. Tapping of the TENG led to the repeated kicking of the leg, demonstrating successful performance. Interestingly, this system can also be used to map motor neurons present in the muscle tissue, which can further enhance their connection with the stimulating electrodes.

In another work by Wang et al., a similar system was used but a different phenomena was investigated, namely the frequency of manual manipulation of the TENG. The group remarkably found that fast tapping versus slow tapping would stimulate different motor neurons optimally based on electrode configuration (Figure 10). This modulative ability serves as further tunability for muscle stimulation regarding TENGs. These results indicate the hopeful future for TENG-mediated muscle rehabilitation.

The human body contains three types of muscle: smooth, skeletal, and cardiac. While muscle stimulation is largely focused on skeletal muscle rehabilitation, cardiac muscle has recently entered into the TENG field's focus. Jiang et al. developed a full bioabsorbable TENG device that can be used to synchronously stimulate cardiomyocytes[22]. The device showed no inflammation when implanted *in vivo*, indicating its biocompatibility. Silk fibroin (SF), which is triboelectric in nature, was used as the encapsulation layer for this device. Untreated SF was combined with methanol treated SF in different ratios to tune the degradation rate. To evaluate the system's ability to contract cardiomyocytes, cardiomyocytes were plated on the 2D surface of the TENG electrode. Comparison of the beating cycle frequency before and after TENG stimulation showed a significant increase (Figure 10). Additionally, the researchers found that the beatings were more unified between individual cardiomyocytes. These findings hold promise for future uses of TENGs in pacemaking and AED capabilities.

2.2.1.2.3 Assistive Therapy

Assistive technology is any piece of equipment or system that is used to improve the functional capabilities of persons with disabilities. This includes rehabilitation and the heightening of a sense or muscle that has lost function overtime.

In Bhatia et al., an at-home based rehabilitation system is set up where a patient with an impaired arm plays a motivational game in order to track harvested energy vs. time, or arm strength.[23] This graph allows doctors to see what level of impairment the patient has undergone. A rehabilitation TENG is subsequently used in order to help the patient build up their arm strength over periods of playing this game and eventually build them back to normal strength. Since the TENG can store energy, it serves as a motivating factor for the patient, as well as an index to monitor progression of rehabilitation and any improvements made.

Zheng et al. discuss a pacemaker developed in combination with a TENG. It works in a circuit, with stimulating electrodes helping the heart to pump blood at a rhythmic pace[24]. These electrodes are powered by a TENG connected on the other side of the circuit located directly next to the pacemaker. Through this closed loop circuit, the pacemaker is powered and heart feedback is collected during its use.

Qu et al. constructed a bionic cochlear auditory sensor as a TENG[25]. Nine electrodes are placed in alignment with different selectivity, with the electrodes able to pick up and convert sound to motion for the user who is unable to hear well. Two strips of these electrodes are constructed as layers within the TENG with electrode and acrylic materials.

In Shomly et al., a TENG is implanted under the skin and translates tactile pressure into electrical signals, which it sends from cuff electrodes to healthy sensory nerves, thereby stimulating them to mimic tactile sensation[26]. The extent of this signal is dependent on the level of tactile pressure applied to the device.

2.2.1.2.4 Neural Engineering

Neuroengineering is a field focused on the understanding, repair, and enhancement of the neural systems in the body. In Katiyar et al., a TENG is used to promote functional recovery and structural regeneration following repair of nerve lesions in rats[27]. Furthermore, TENGs are compared to autographs and NGTs for the same functionality. TENGs can be used for chronic nerve morphometry following repair of 2 cm nerve lesions.

Hassani et al. demonstrated the use of a photosensitive TENG-based powered electrical brain stimulation[28]. In a closed loop system, a student is given an exam that they flip through, which harvests mechanical energy. This motion would then power an E-skin device that is stuck to the neck. Finally, the E-skin would be able to send electronic signals that power a light when the student is learning. When the student is focusing and working, the light powers on. When the student is looking away from the paper and taking a break, the light turns off.

Finally, Parandeh et al. focuses on biodegradable and D-TENGs for neural cell differentiation, migration, orientation and axonal regeneration[29]. Here, electrical stimulation can orient a nerve and induce cell conversion. TENGs can then be able to allow cells and axons to change and develop based on different electrical currents, which has huge potential in tissue engineering.

2.2.1.3 Challenges And Limitations To TENGs

TENGs have many limitations, despite their benefits as a newly developing technology in the field of bioelectronics. In order to assess them all, it is best that split them up into four main categories:

I. **Electrical Output**
   Because TENGs need significant contact between the positive and negative pieces to create an electrical current, some implantations may not create very much power. Take for example an item of clothing, here the shirt would have to be perfectly fit and very tight on its user in order to generate the maximum amount of power possible. Additionally, because a user is not perfectly replicating every movement, power frequencies will be irregular and sometimes result in low output. This would be significant if the TENG was powering a blood sugar monitoring device, as not low power could cause the TENG to stop monitoring and potentially miss an irregularity.

II. **Industrialization**
   Due to the intricate nature and complex materials involved in creating a TENG, it could be difficult to mass produce TENGs that would work at the same level as an intricately produced one in the lab.

III. **Standardization**
   Because of the many different types of TENG devices, there has yet to be adequate standardized testing for the device to be able to be put in the market. A big part of this standardized testing has to do with the fact that the device is so new, so we don’t know

the wear and tear of the TENG overtime and how that would affect the user. This means that the device is unable to be sold to customers and has stopped it from conquering the bioelectronics field.

IV. **Sustainability**

TENGs lose their conductivity when in contact with water, so they can't get wet in order to work properly. However, sweat, tears, humidity, and rain can lower the effectiveness of the device, even if by accident. This brings up the issue earlier that with lower output, the device may no longer be reliable. Also, because there has been no ability to test outside the lab for a long term, the durability and how well TENGs will hold up with time outside of the protected conditions of a lab is unknown.

2.2.2 Piezoelectric Nanogenerators (PENGs)

2.2.2.1 Piezoelectric Nanogenerator Principles

Piezoelectric nanogenerators utilize the piezoelectric effect in order to convert mechanical stress to generate an electric charge. As the name implies, these nanogenerators are created using piezoelectric materials. Similar to triboelectric nanogenerators, they are self-powered and capable of producing electricity using biomechanical energy and have been shown to have a wide variety of applications in electrical stimulation therapeutics.

2.2.2.2 Piezoelectric Nanogenerator Applications In Therapeutics

2.2.2.2.1 Fully Implantable Cochlear Implants

Cochlear implants are commonly used to restore hearing in individuals with hearing loss. The implant electrically stimulates auditory nerves, allowing for the user to "hear" despite having damaged cochlear hair cells. Current cochlear implants consist of an external unit that includes the transmitter as well as housing for the microphone, sound processor, and other parts, making the implant cumbersome or impossible to wear around water (Figure 11). Piezoelectric nanogenerators can be incorporated into cochlear implant to make cochlear implants fully implantable; the nanogenerator functions as an acoustic sensor and aids in reducing the overall power requirements of the implant[30].

2.2.2.2.2 Peripheral Nerve Stimulation

Peripheral nerve stimulation refers to the use of electricity to stimulate any nerves outside the brain and spinal cord, and is commonly used in neuroprosthetics and similar therapeutic fields. Piezoelectric nanogenerators can be incorporated into minimally-invasive thin films that can provide electrical stimulation driven by ultrasound[31]. These soft films are battery-free and programmable by acoustic pressure, pulse width, and pulse interval. Ultrasound is an increasingly popular method of driving piezoelectric nanogenerators such as these due to its ability to deeply penetrate tissue in a safe manner.

2.2.2.2.3 Accelerated Wound Healing

Electrical stimulation can be utilized to aid the natural wound healing process by mimicking the body's bioelectric field produced by the epithelial layer. Piezoelectric nanogenerators are used to provide an exogenous electrical field that has been shown to accelerate wound healing[32]. Research has shown that zinc oxide, a popular piezoelectric material due to its inherent biocompatibility, was able to produce the sufficient voltage necessary to stimulate wound healing enhancement with a mere 200-mm bending radius[33]. Similar studies have shown promising results with other popular piezoelectric materials such as poly(vinylidene fluoride-tri-fluoroethylene) (P(VDF-TrFE))[32].

2.2.2.3 Limitations Of Piezoelectric Nanogenerators

Despite the many benefits of piezoelectric nanogenerators such as their ability to function in damp or wet conditions, there are several drawbacks that must be taken into consideration for their use in therapeutics. Firstly, these nanogenerators are limited in material choice due to their utilization of the piezoelectric effect in order to generate electricity. Among these piezoelectric materials, some may not be biocompatible, an important factor for in vivo applications. Additionally, the power output of piezoelectric nanogenerators is limited respective to that of triboelectric generators. With an output range commonly in the mV, piezoelectric nanogenerators are not well-suited for applications requiring high output voltages.

3. Future Applications Of Magnetoelastic Generators For Electrical Therapeutics

3.1 Limitations Of Current Bioelectronics

The two aforementioned self-powered bioelectronics, TENGs and PENGs, suffer from low current output and high intrinsic impedance. TENGs and PENGs may not be suited for electrical therapeutics that require higher current output. Also TENGs are affected by humidity from sources such as sweat and ambient humidity which negatively impacts the electrically based working mechanism of these devices. Due to these limitations, self-powered therapeutic magnetoelastic generators (MEGs) are considered. However, literature on the use of MEGs for electrical stimulation therapeutics is not yet available as the use of MEGs for bioelectronics is relatively new.

3.2 Key Components/Requirements Of Bioelectronics For Therapies

MEGs can be used in bioelectronics for electrical stimulation therapeutics. The key components of a bioelectronic for electrical stimulation include a sensor, a power source, and the electrical stimulation. The sensor can detect a change in the environment so that the therapy can be adjusted accordingly. The power source supplies energy to the device in order to emit the electrical stimulation. MEGs can be a sensor, power source, and an electrical stimulation device. They act as a sensor by detecting mechanical pressures as changes in the magnetoelastic layer shape and emit electrical signals in response. Magnetoelastic generators are self powered through harnessing biomechanical energy in the human body. Lastly, these devices are relevant to electrical stimulation therapies because they output electrical currents which can help aid in things like wound recovery or muscle stimulation.

3.3 MEG Working Mechanism

The MEG is another self-powered device that can potentially be used for electrical stimulation therapies. The MEG couples the magnetoelastic effect with electromagnetic induction through the use of two layers — the magnetomechanical coupling (MC) layer and the magnetic induction (MI) layer. The two layers operate hand in hand by utilizing Faraday's Law of Induction in which an electrical current can be induced in coils through changes in local magnetic fields. The MC layer consists of micromagnets that generate a magnetic flux upon deformation to convert mechanical energy to magnetic energy. The MI layer consists of liquid metal turns that capture the change in magnetic flux to convert magnetic energy to electrical energy through induced currents. The low resistance of the liquid metal turns boosts the current output. The magnetic field is inherently unaffected by moisture since it uses a magnetic field versus charged particles (electric fields) which can be hindered by polar molecules like water due to electrostatic shielding.

The output performance of TENG can be affected by ambient humidity or human sweat. Also, TENG and PENG have low current density and high internal impedance. MEGs, however, have high current output and low internal impedance as well as inherent waterproofness. Zhou et al. demonstrated the potential of the MEG to outperform the previous two self-powered systems.[34] The group fabricated an MEG in a soft polymer system and addressed concerns of sensitivity, humidity, stretchability, and biocompatibility. The device had up to 440% stretchability and had a Young's modulus similar to human tissue. Because the MEG has a similar Young's modulus to human tissues, they are ideal candidates for human implantation since they have a modulus match with surrounding tissues. The modulus match reduces biocompatibility concerns. The pressure sensing range for the MEG was from 3.5 Pa to 2000 kPa, which is within the range of biomechanical pressures produced by the human body. The device was fully waterproof and biocompatible. Similarly to TENG and PENG, the MEG can sense and use biomechanical forces to self-power a device and potentially perform electrical stimulation therapies. However, literature does not yet exist on MEG applications for electrical stimulation therapies.

3.4 Magnetoelastic Generators For Potential Electrical Stimulation Applications

Zhou et al. also invented textile MEGs by weaving one-dimensional soft magnetic fibers[35]. The textile MEGs were able to convert arterial pulses into electrical signals. Making textile devices for electrical stimulation minimizes the user discomfort and improves fashionability and cosmetics. Textiles also allow for various shapes and sizes to fit the function and curvature of the body part. This demonstrates the capability of MEGs to be surgically implanted for electrical therapeutics such as deep brain stimulation, transcranial stimulation, or for drug delivery, as previously mentioned. This demonstrates the capability of MEGs to be worn for electrical stimulation on the skin.

Chen et al. demonstrated the use of the ultrahigh current output of MEGs in Joule-heating textiles for personalized thermoregulation and thermotherapy[36]. MEGs have relatively higher output current than TENGs and PENGs. The wearable MEG was used as a high current power source to drive a Joule-heating textile to increase the temperature of the resistor by 0.2 °C. This wearable MEG can be developed further for on-body electrical stimulation therapeutics.

It has been shown that MEGs are intrinsically waterproof. They are also very stretchable and can be woven into textiles. MEGs have also been shown to be ultrahigh current power sources for wearable bioelectronics. Therefore, MEGs can be used for an electrical stimulation therapeutic device.

Also, MEGs can be incorporated in the shoe insole for power generation during walking. An MEG could generate electricity when it is compressed, bent, or twisted, among which the compression mode produces the largest magnitude of current and voltage. Hence, when the MEG is compressed by the feet stepping upon the ground, it could efficiently transform biomechanical energy into electrical energy. As previously discussed in 2.1.3, transcutaneous electrical stimulations can be applied upon neuropathic diabetic foot ulcers to alleviate pain. For one, MEG possesses the potential to power such transcutaneous therapy during patients' daily walks. Meanwhile, MEG provides sensing applications about any movement-related information of the patients, thereby adjusting the magnitude of therapy based on different situations. Therefore, MEG has the potential to be incorporated in closed-loop sensing and therapy bioelectronics.

3.5 Challenges And Limitations Of MEGs

While MEGs offer numerous advantages over TENGs and PENGs, they do have some limitations that can impact their use in certain applications. One key limitation is their relatively low voltage output, which may make them unsuitable for high voltage applications. Additionally, MEGs are sensitive to external magnetic fields, which can interfere with their performance and cause unintended electrical outputs. This is especially problematic in medical applications, where strong magnetic fields generated by MRI machines or the Earth's magnetic field can lead to interference with MEGs and potentially harm patients.

To address these issues and improve the performance of MEGs, several approaches can be taken. One possibility is to develop MEGs that are more resistant to external magnetic fields, such as by using shielding or other techniques to reduce interference. Another option is to increase the voltage output of MEGs through the use of specialized materials or design features that enhance their electrical properties. Additionally, researchers can explore new applications for MEGs that are less sensitive to external magnetic fields, such as in environmental monitoring or non-medical industrial settings.

Overall, while MEGs have some limitations to their use, there are many ways to improve their performance and expand their range of applications. By addressing these challenges, researchers can unlock the full potential of MEG technology and help to create a better future for both nature and electronics.

4. Conclusion

Electrical stimulation therapeutics have demonstrated significant potential in the treatment of various diseases and wound healing. However, the use of batteries to power non-self-powered electrical stimulation devices is often limited by their bulkiness and short lifespan. As a result, researchers have turned to self-powered bioelectronics like TENGs and PENGs to power electrical stimulation therapeutics using biomechanical pressure as a power source. This technology has the potential to increase the lifespan of wearable medical devices and provide numerous opportunities for telemedicine and personalized long-term healthcare.

MEGs have emerged as a new wearable bioelectronic technology with several advantages, including waterproofness, higher current output, and stretchability. Although there is little published literature on the use of MEGs for electrical stimulation therapeutics, they hold great promise as an alternative power source. MEGs are capable of providing higher voltage output, which is necessary for certain applications, and their waterproofness makes them ideal for use in wound healing applications.

Overall, the field of bioelectronics for electrical stimulation therapeutics is rapidly evolving and expanding, with a wide range of potential applications. As researchers continue to explore new technologies and applications, it is likely that bioelectronic devices will become increasingly mainstream in healthcare systems.

5.Figures

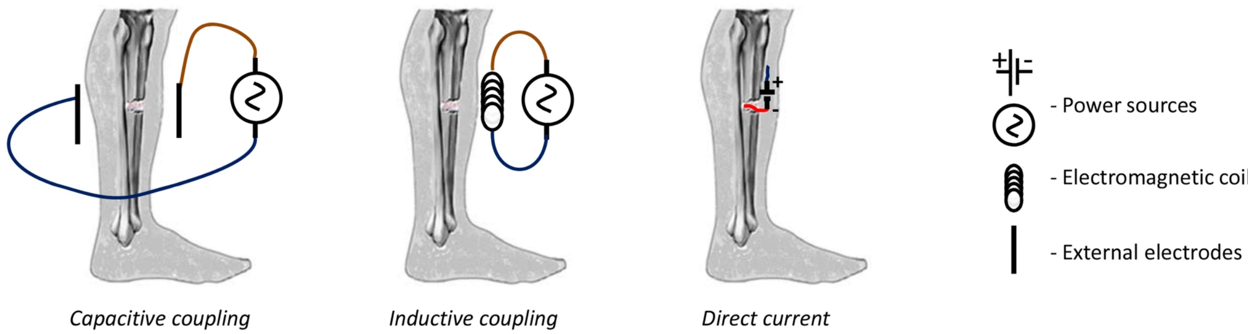

Figure 1. Different configurations of fracture healing with electric stimulation through capacitive inductive coupling, and direct current. (Adapted from Kotsougiani et al.)[37]

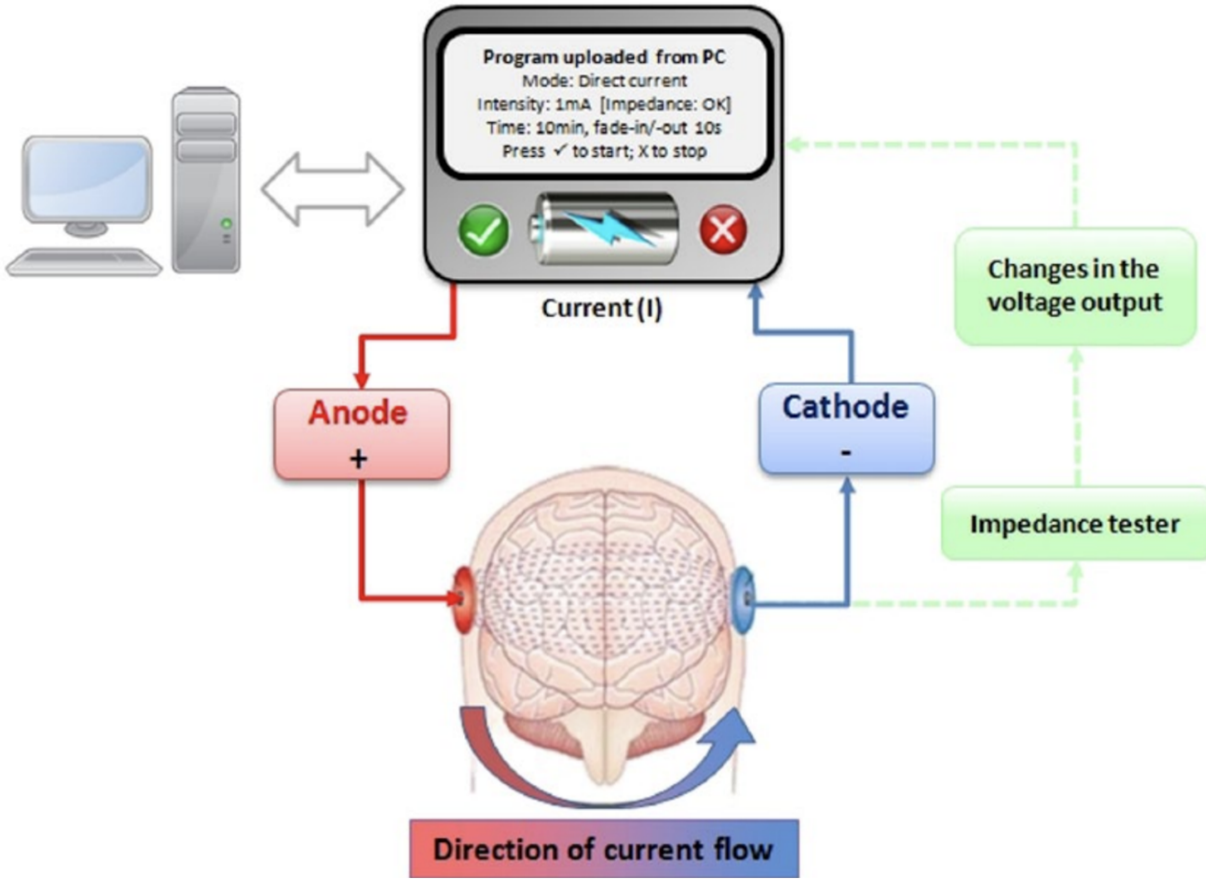

Figure 2. Flow schematics of transcranial electrical stimulation (tES) system. (Adapted from Lapenta et al.)[38]

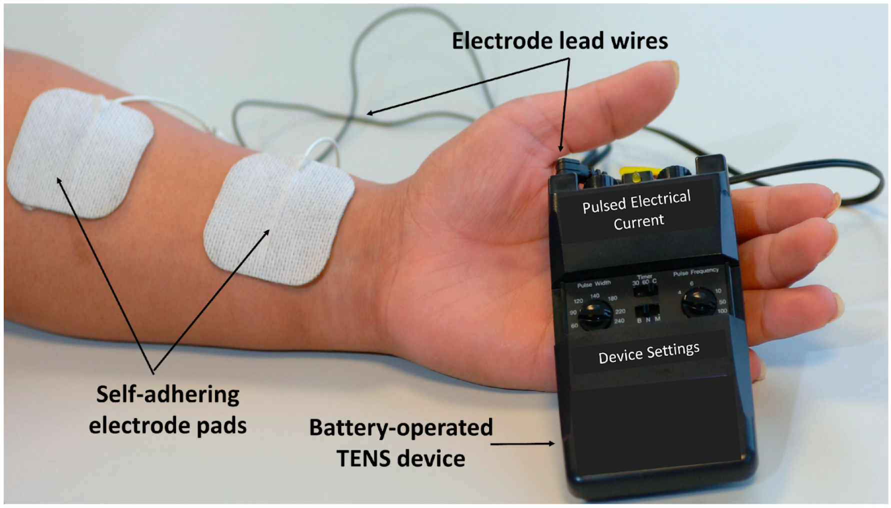

Figure 3. Transcutaneous electrical stimulator with power source, self-adhering electrode pads, and electrode lead wires. (Adapted from Juodžbalys et al.)[39]

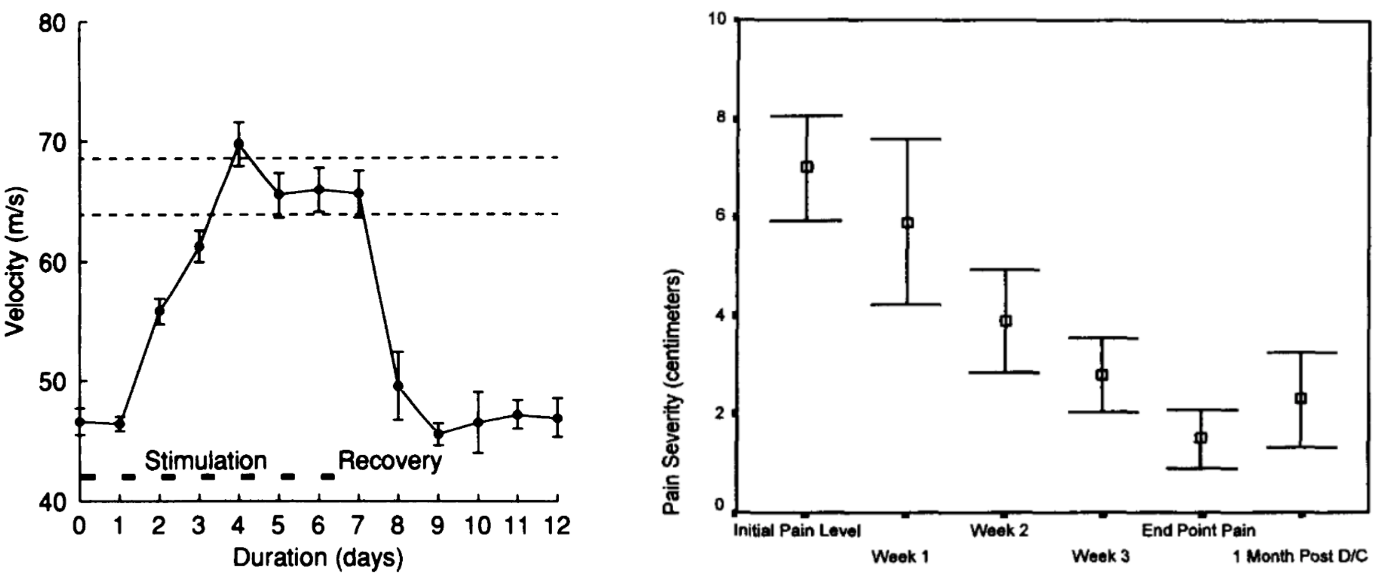

Figure 4. Mean signal conduction velocity in the tibialis anterior after electrical stimulation. Pain severity of diabetic patients after transcutaneous electrical stimulation. (Adapted from Mohamed et al.)[40]

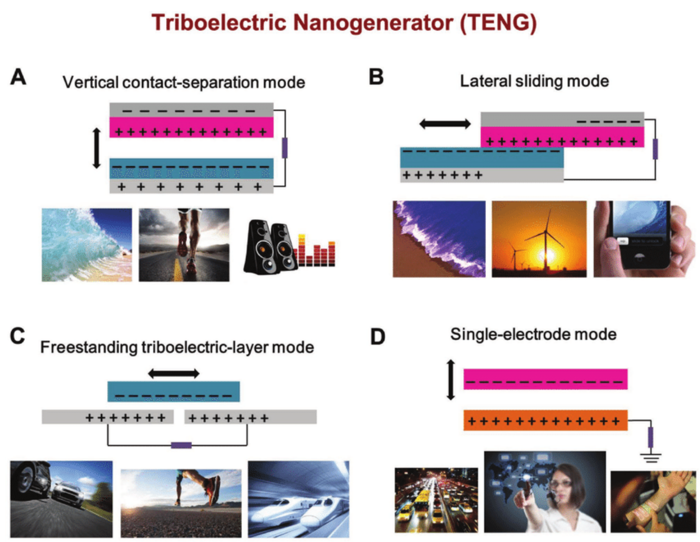

Figure 5. The four fundamental modes of TENGs: A) vertical contact-separation mode; B) Lateral-sliding mode; C) freestanding triboelectric-layer mode, and D) single-electrode mode. (Adapted from Fan et al.)[41]

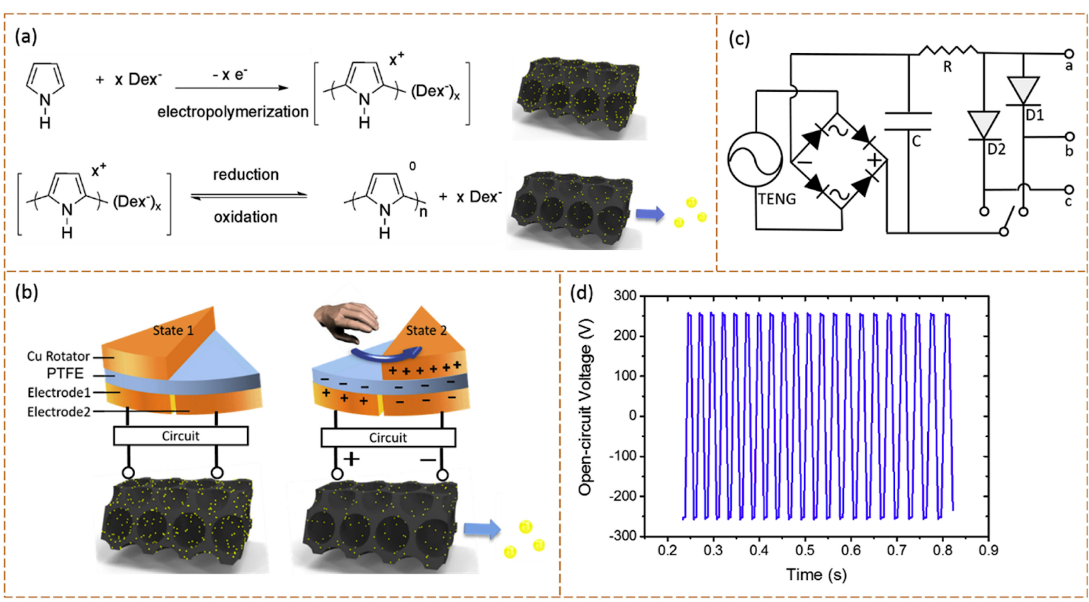

Figure 6. Drug loading of polypyrrole. TENG-mediated release of drug in polypyrrole by electric field. Rotary TENG schematic for drug delivery system. (Adapted from Wang et al.)[42]

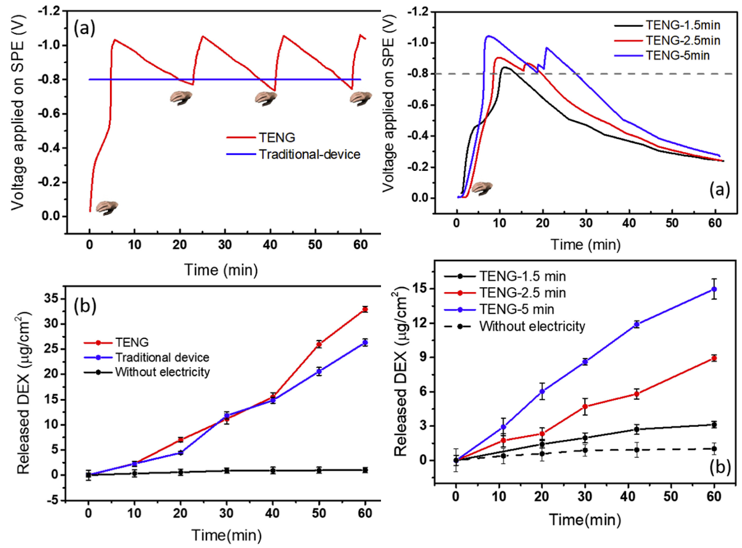

Figure 7. Electrical and drug release performance of TENG transdermal patch. (Adapted from Cai et al.)[43]

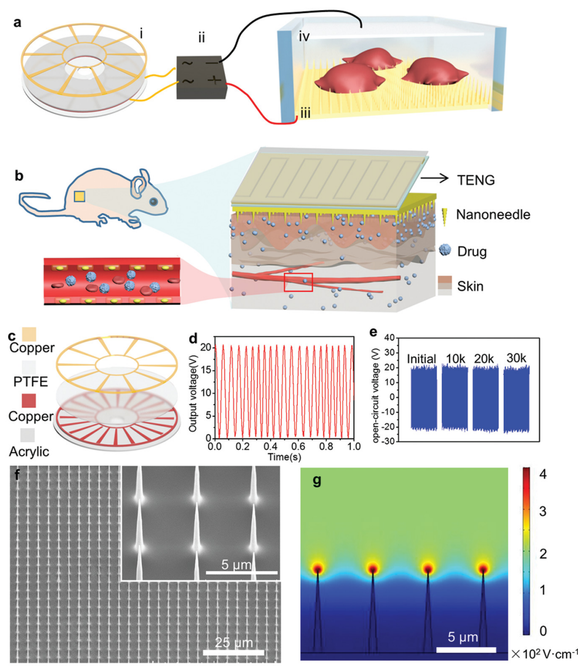

Figure 8. Working principle of nanoneedle/TENG array with SEM images of nanoneedles. (Adapted from Liu et al.)[44]

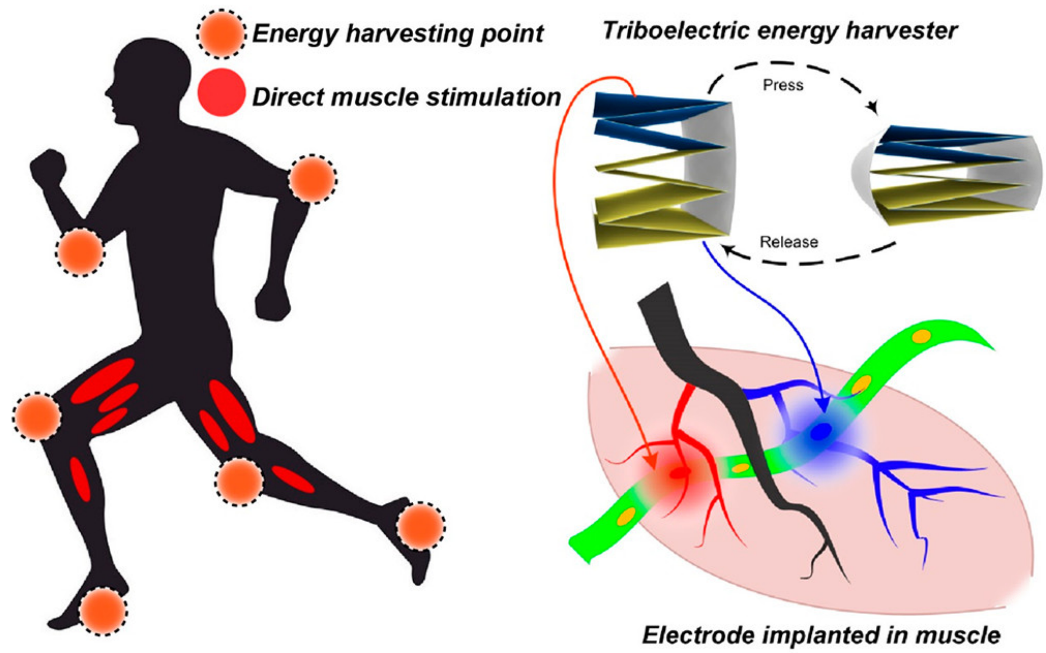

Figure 9. Mechanism of action for self-powering TENG muscle stimulator. (Adapted from Liu et al.)[45]

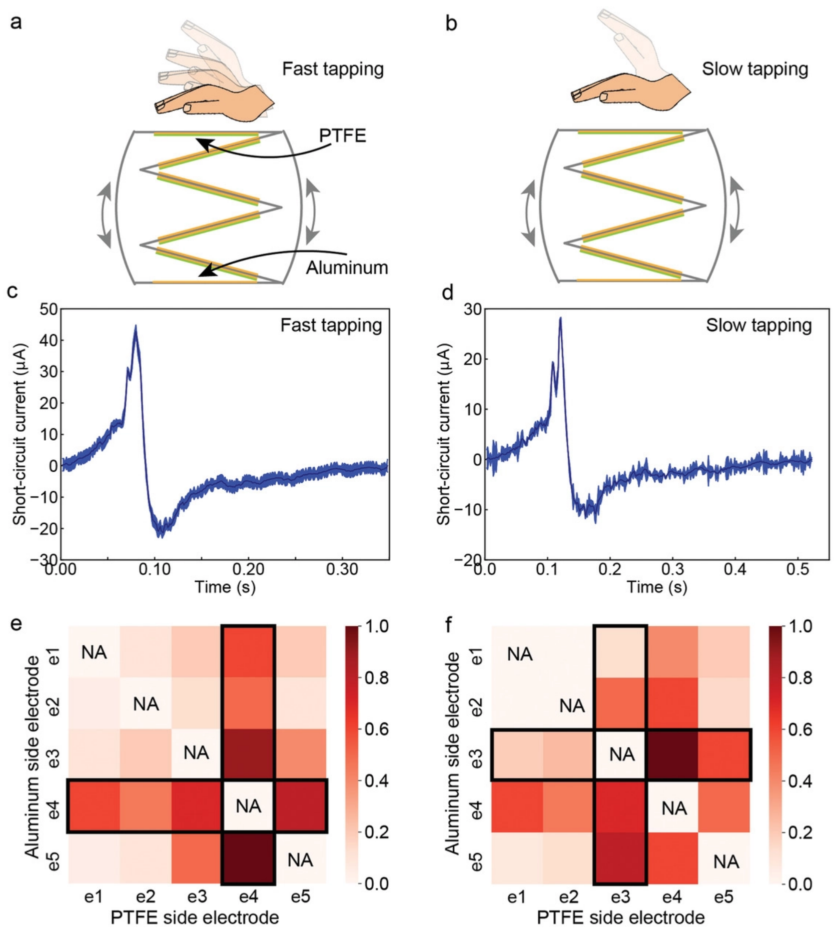

Figure 10. Heat map of stimulation levels of different electrode configurations based on frequency of tapping. (Adapted from Lee et al.)[46]

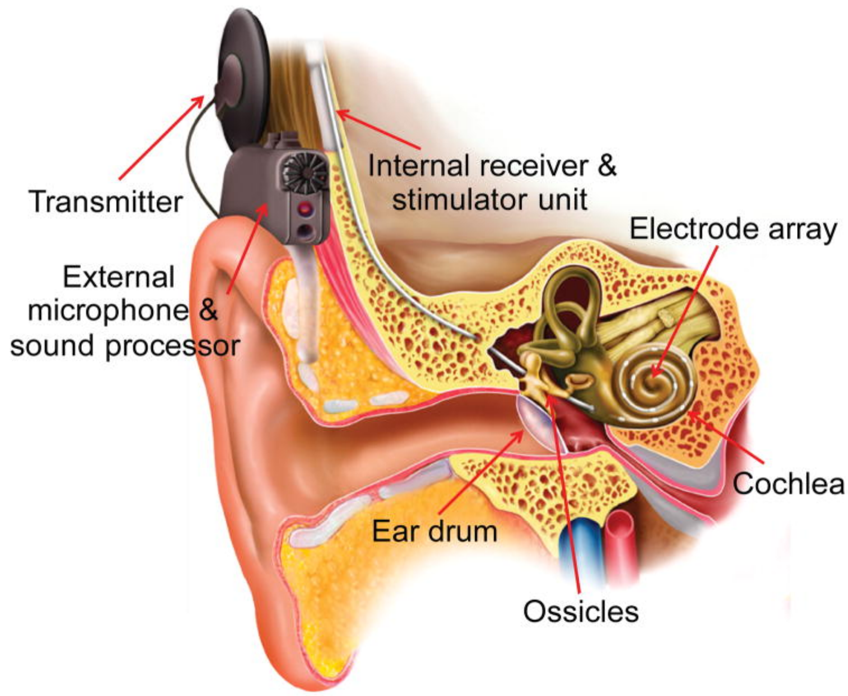

Figure 11. The interfacing of a traditional cochlear implant with the human ear. (Adapted from Chang et al.)[47]

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