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A Narrative Review Exploring Current AI Techniques in Enhancement of Closed-loop Bioelectronic Devices.

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ABSTRACT

Bioelectronic medicine is an emerging field that uses targeted electrical stimulation to treat chronic diseases by modulating physiological signals at the cellular and neural levels. However, the complexity and variability of human biological systems present major challenges in ensuring consistent and precise therapeutic outcomes using already available bioelectronic devices. Artificial Intelligence (AI), particularly through advanced algorithmic frameworks, has demonstrated significant potential in overcoming these limitations by enabling dynamic, adaptive, and patient-specific interventions.

This narrative review explores how AI-enhanced algorithms can significantly improve the functionality of closed-loop systems in bioelectronic medicine. It discusses the integration of various deep learning models, real-time data processing techniques, and intelligent control strategies to enhance precision, adaptability, and patient outcomes.

We examined the current literature and technological advances in AI models such as Convolutional Neural Networks (CNN), Recurrent Neural Networks (RNN), Support Vector Machines (SVM), and Long Short-Term Memory (LSTM) networks, evaluating their applicability in signal interpretation, electrode positioning, and treatment personalization. The review introduces both predictive and non-predictive AI-driven feedback mechanisms used to regulate therapeutic electrical stimulation in chronic conditions. It also outlines system architectures such as multi-level hierarchical control models and embedded AI systems like TinyML, which enable real-time, on-device decision-making with minimal latency.

We found out that AI-powered models allow for the comprehensive mapping of biological systems (e.g., connectomes, electromes, genomes), improving targeting specificity for bioelectronic interventions. Predictive models leverage historical and real-time patient data to adjust stimulation parameters proactively, while non-predictive models enable immediate response to dynamic physiological changes. Hierarchical AI architectures offer multi-tasking capabilities essential for long-term, adaptive treatment. Embedded AI systems and edge computing facilitate real-time diagnostics and remote monitoring, enhancing telemedicine applications and patient compliance, particularly in managing complex chronic diseases such as epilepsy, diabetes, and cardiovascular disorders.

In summary, our article suggests that the integration of AI into bioelectronic medicine has the potential to revolutionize chronic disease management through highly individualized, responsive, and scalable treatment modalities. This review highlights how AI-driven enhancements can transform traditional closed-loop systems into intelligent therapeutic platforms. However, ethical concerns regarding data privacy, bias, accountability, and regulatory oversight remain significant and warrant further investigation. Advancing this synergy between AI and bioelectric systems could open new frontiers in precision medicine and healthcare accessibility.

KEYWORDS

Artificial Intelligence, Machine Learning, Deep Learning, Electromes, Connectomes, Electroceuticals

MAIN ARTICLE

INTRODUCTION

Many Researchers around the world are already fascinated by the intriguing prospect of integrating deep-learning technologies into modern medicine. This compelling amalgamation of Artificial Intelligence with Bioelectric medicine can witness some promising developments in the future, which can revolutionize how doctors can not only manage the changing dynamics of chronic and serious medical conditions like Cardiovascular diseases, Cancer, Diabetes, etc. but also change the perspective of our patients towards their health by taking precautionary measures, resulting in the efficient working of our healthcare system. Artificial Intelligence (also known by the names of deep learning, and machine learning) is a virtual computing science technology fed with tons of algorithms that aims to perform complex tasks in place of human intelligence like learning, reasoning, understanding, and decision making (McCarthy,2007). On the other hand, Bioelectric medicine refers to electrical stimulation of cells, nerves, and tissues to provide treatment of medical diseases (Lee et al.,2024).

This comprehensive review aims to investigate the therapeutic potential of bioelectricity and also showcase how collateral expansion of the intelligent computing space (AI) can beneficially impact bioelectric therapies in addressing its drawbacks and upscaling its capabilities in public healthcare.

This review will be covering the different aspects by which bioelectric science works, the techniques implemented by artificial intelligence to decipher the barriers of bioelectricity, and its limitations. It does not take into account the use of this medicine in acute illnesses, but the direction is more towards management of chronic diseases. Furthermore, the aim of this study is not intended to be on the notion of having our hardworking healthcare professionals in hospitals being replaced with an AI.

This article is structured as follows. Section 2 presents the Background and Related works of Bioelectric medicine found in the literature. Section 3 involves the AI approach in mending the voids to expedite this fields growth. Section 4 dwells into the Fallacies of AI and Future Research Directions. Section 5 shows the Conclusion.

BACKGROUND AND RELATED WORKS OF BIOELECTRIC MEDICINE

The concept of bioelectricity arose in the late 16th Century with the discovery of 'animal electricity' by Luigi Galvani (Piccolino,1998; Funk,2009). After four centuries, critical studies by research analysts began to find out the potential role of electricity produced by human cells in development and disease (Funk,2009; McCaig et al.,2005). Bioelectric medicine has emerged as a fast-growing field; with the market size currently having surpassed $20 billion and expected to hit $60 billion in the next five years (Asirvatham et al.,2020). This share is heavily divided between the bioelectronics for retinal, cochlear implants, cardiac solution for rhythm problems, and nervous system stimulation for epilepsy [Peeples,2019].

A human body is a highly biological intricate system made up of large groups of different cells, nerves and tissues. All of these generate their own intrinsic bioelectricity to communicate with each other to regulate different systemic functions in the body. The ability to modulate this bioelectricity with the aid of extrinsic electrical signals by an electronic device for therapy purpose is referred to as Bioelectric Medicine [Levin and Stevenson,2012]. There are 4 distinct types of Bioelectric Therapies-a) Transcutaneous Electric Nerve Stimulation (TENS) b) Electric Muscle Stimulation (EMS) c) Functional Electric Stimulation(FES) d) Micro-current Stimulation (MCS). TENS is done at the motor neuron level (Johnson,2014; Kim et al.,2023), EMS and FES at the tissue level (Karatzanos et al.,2012; Greve et al.,1993) while, MCS is done at a cellular level (Lee et al.,2023; Wirsing et al.,2015) typically utilising current in the range of microamperes (less than 1 milliamps) (Al-Tubaikh,2016; Kolimechkov et al,2023).

The vagus nerve is known to play an instrumental role in the functioning of vital organs such as the heart, the intestines and the liver. Its additional usage in controlling the immune system was never heard about, up until an experiment done on rats, published in *Nature* in the year 2000 by Tracey and his colleagues (Borovikova et al,2000). Later on, studies followed showed that by electrically exciting this nerve in humans, there is an enhanced release of acetylcholine, which triggers a cascade of effects leading to inhibition of cytokine production and thereby, reducing systemic inflammation in the body. This can be path-breaking, especially to adapt to the changes required to be made in treating chronic inflammatory diseases like rheumatoid arthritis (Koopman et al.,2016). Triggering the vagal fibres, the carotid sinus nerve and liver parenchymal tissue with electrical currents have also found out to be efficacious in cutting down the sugar levels by releasing insulin and reducing obesity in Type 2 diabetes patients (Chen et al.,2010; Shikora et al 2013; Shikora,SA et al.,2015;

Sacramento et al.,2018). Moreover, high frequency electric fields in cancer can cause the process of cell division to stop (known as Tumour Treating Fields) (Kirson et al.,2004; Gera et al.,2015; Giladi et al.,2015); and can also induce pores inside cancerous cells (Electroporation), in which a chemotherapeutic drug can be injected (Electro-chemotherapy) (Lucia et al.,2019). Inducing these currents to neuromuscular fibres in stroke patients undergoing rehabilitation has seen great success as well (Takeda et al,2017).

A bioelectric action potential at the level of every cell is formed due to the unequal motion of ions and electrons across its plasma membrane via various ion-pumps, voltage gated ion channels and redox mediated systems such as enzymes (Zerfaß C et al.,2019). In many chronic conditions like cancer, ischaemic heart problems and diabetes, impaired functioning of this potential occurs (Robinson et al.,2021; Klabunde,2017; Rorsman and Ashcroft,2018). An electronic device equipped with a sensor can easily detect and monitor these differences in the cells bioelectrical circuitry which can help in prognosis and staging of cancer (Robinson et al.,2021) and other chronic health issues. Exogenous electrical stimulation can alter behaviour of a cell to construct functional neural tissues in spinal cord injuries (da Silva LP et al.,2020). Hence, bioelectric medicine has a very captivating future in tissue engineering and regenerative medicine.

THE AI APPROACH

The future possibilities in bioelectric solutions are astounding, but monumental barriers are falling in its path. Firstly, there are scarcities relating to information about neural circuitry, large genomic expressions, and electrical activities, thus making its extensive mapping a great desire. **With this clarity in sourcing large amounts of human databases, AI can aid in selecting the best placement for an electrode.** Secondly, commonly used bio-electronic devices like cardiac pacemakers, neural implants for epilepsy, and others are installed with traditional static closed-loop algorithms, **which struggle dealing with the non-linear, time-varying nature of human responses. This results in suboptimal performance of the devices in estranged situations**. Therefore, deep collusion between the mapped data and a **smart** software system to continuously interpret these **signals in choosing the best frequency to stimulate human tissues** and overcoming unpredictable dynamics of interfering agents like biosensor fouling (Rocchitta et al.,2016; Liu et al.,2019), scar tissue build-up (Polikov et al.,2005), and changes in cell behavior and gene expression (Jafari et al.,2023), or human factors like a diabetic patient eating food at uncertain times during the day causing fluctuations in glucose levels is required.

This is where the AI (deep learning algorithms), with its smart intelligence, can continuously update its parameters in real-time and generate faster responses to achieve cell homeostasis **and prevent the risk of under or overstimulation**. (Rocchitta et al.,2016).

The following is how AI can leverage the therapeutic efficacy of these devices-

a) Comprehensive Mapping of the Human System to enhance Target Specificity for Optimal Electrode Positioning:-

To single out comprehensive mapping of each electrical dimension of cells (electromes), genes(genome), and nerve fibers (connectomes), can substantially increase the precision as well as specificity of this treatment. Generating these as input data would tremendously be large. Consequently, the 'SPARC' research program funded by the Common Fund at the National Institute of Health, has already embarked upon forming a detailed map of the human nervous system (Peeples,2019). The AI has proven to process about 250 million of clinical images per day and sequencing of 100,000 exomes has transpired at Geisinger Health in Pennsylvania (Beam AL and Kohane IS,2016; Topol,2019), showing its ability to store and process high-volume of information. A computing algorithm developed into *'Flood Filling Network' (FFN)* has tracked the shape of neurons using electron microscopy from a male zebra finch brain (Januszewski et al.,2018). The technique resulted in a mean error-free neurite path length of 1.1 mm and successfully integrated segmentation of all neurons. Subsequently, *SVM (Support Vector Machine), K-NN (K-Nearest Neighbors), and ANN (Artificial Neural Network)* were able to recognize electrical activity patterns in plants (e Oliveira et al.,2023). Large Datasets of over 650000 DNA Genome sequencing from patients suffering from Autism spectrum disorder, spinal muscular atrophy, and nonpolyposis colorectal cancer were input into a computational model. The model was able to predict disruption to RNA splicing precisely to classify disease-causing variants (Xiong et al,2015). **Hybrid models involving Convolutional Neural Networks (CNN) and Recurrent Neural Networks (RNN) can effectively capture spatial and temporal information from bioelectric signals. These combined neural architectures have implied great success in classifying and recognizing sequential output and signals from EEG, ECG, and EMG, which can help in the optimal positioning of electrodes (Yu Hu et al,2018; F Manzouri et al 2022). This would also help in the elimination of noisy or poor-quality of signals been picked up by the devices.**

Deep Learning algorithms have been organized into forming their insight from collecting loads of medical details of patients (Dilsizian SE and Siegel EL,2014; Patel VL et al,2009; Jha S and Topol EJ,2016). With this approach, artificial learning technologies can predict the desired response of a tissue or a cell meticulously by picking up changes within the electrical and neural systems. Deep Care method involves *'Sequential Recurrent Neural Network'(RNN)* and *'Long Short Term Memory'(LSTM)* algorithmic framework coupled with patient input data have accurately projected the progression of a disease and anticipated future disease risk predictions (Pham et al.,2016). **By understanding the nature of different disease mechanisms and utilizing pre-mapped biological data, AI can precisely stimulate the correct region for maximising therapeutic efficacy. For example, in Chronic pain, AI would target regions in the spinal cord while in Stroke, it might focus either on the motor cortex or peripheral nerves.**

Overall, AI has the caliber to mount targeted algorithms to each neuron, genome, electrome, etc**., and also take into account patient specific factors, such as their existing medical conditions,** which can help in the prior methodological understanding, **recognizing and classifying** the behavior of cells in ambiguous environments to accelerate the creation of functional neuro-modulation or genetic modulation devices by predicting the best placement and stimulation site for these devices**.** This can result in massive strides been made into catering to tailor-made treatment protocols for every individual (Personalised/Precision medicine).

b) Intelligent Fusion between AI and Mapped Human Data to enhance closed-loop systems for therapy: -

A realistic ML strategy would be to extensively digest sensing and response data in real-time from these interfacing implanted devices, resulting in synchronized learning from a database in an ML-based controller to select an appropriate placement for electrode and waveform, and also tackle estranged complexities arising in the human system in real-time (Jafari, M et al.,2021).

i) Adaptive Accuracy in Electrotherapeutic Stimulation:-

Electric stimulus healing can work with both Predictive and Non-predictive frameworks, and this is how ML can vastly expand the therapeutic accuracy of bio-electronic devices (Hagan and Demuth,1999; Spooner et al.,2004). **This would help determine the best frequency**

and waveform to excite human tissues and prevent any adverse effects arising from overstimulation.

In the Predictive model (indirect approach), detailed data about biological properties is already known. This is achievable through previously mapped data records and continuous patient learning. Intelligent anticipation of these biological variations regarding electrical stimulus is constructed regularly and proactive adjustments to apply the correct stimulation frequency are made swiftly to attain cell homeostasis throughout (Jafari, M et al.,2021). **AI-architecture models like Reinforcement Learning(RL) and Bayesian Optimization have implemented this indirect approach, which can dynamically optimize stimulation frequency parameters in closed-loop systems (Oliviera et al., 2023; Kenneth et al.,2021).**

In the Non-Predictive model (direct approach), only limited information on the changing dynamics of a system is present. The device actively senses knowledge about patients' internal health and actuates real-time changes to achieve cell stability (Hosseini et al.,2021). **Models like RNNs or LSTMs, Adaptive Neural Controllers, and Deep Q-Networks (DQN) work on this model by actuating responses in real-time.**

Thus, problems of biosensor fouling, scar tissue build up, and a change in gene expression can be rapidly addressed for the continuous peak performance of these devices.

For example, A wider application of these ML-based strategies (Predictive and Non-Predictive) in neural implants for epileptic seizures would work as follows:- The Electroceuticals can **actively sense (Direct approach) as well as forecast the onset of epileptic episodes (Indirect approach) in presence of a fresh scar tissue accumulation and therefore might apply a higher frequency or waveform in comparison to previous patterns for appropriately stimulating the region promptly or in advance**, thereby maintaining stable neural circuitry within the brain. This will remarkably diminish the requirements for higher doses of epileptic medicines, and exceptionally improve the quality of life in these patients**. A similar work of these AI-equipped bioelectric devices could be utilized in actively managing chronic pain (spinal cord stimulator), maintaining heart rate (cardiac pacemaker) and sugar levels (Pancreas stimulation device) , etc., which would be a remarkable breakthrough in modern medicine.**

ii) AI-Powered Real-Time Diagnostics & Management :-

Traditional static closed-loop algorithms like ECG-Holter monitoring, Implantable Cardioverter Defibrillators, etc. can store limited, predefined signals. However, unlike AI-enhanced closed-loop devices, which can capture and process multiple physiological parameters over a broader range and also send these signals remotely to the hospital servers in real-time for complete assessment by the clinician. This is where Embedded ANNs and Edge Computing Models have a crucial role to play.

Embedded ANNs such as TinyML (Sun, B et al,2023), CNN, LSTM etc., operate independently without relying on any external server and therefore consume low power. It is designed to run locally on a device, which can smartly analyse a wide range of parameters like ECG rhythms, EEG Patterns, Spatial motion data, Blood Pressure and Glucose levels etc., to identify irregularities or anomalies. Based on the deviations, Embedded ANNs can instantly make active decisions on the device itself which could be in the form of electric stimulation or sending alert notifications to wearable devices of patients or their caregivers. This ensures reduced latency, and also sensitive patient data is processed locally on-device.

Edge Computing Models uses cloud server processing of data held on device. A project called '*EH4CR'* was able to retrieve and analyse real-time data from electronic medical records (EMR) of patients remotely with algorithms like Apache Kafka/Storm, which can aid in executing closed-loop adaptive feedback mechanisms to the device without significant delays (De Moor G et al.,2015). This will impart rapid and flexible therapeutic interventions that can be consistent with treating impaired homeostatic mechanisms in real-time from a distance (Neill DB,2013). The deep fusion of AI in analysing the data from electronic health records of patients (EHR) and bio-electronic devices in real-time at a distance can provide a comprehensive overview of our patient's health for clinicians and speed up the role for Tele-medicine. **These devices can also connect to hospital servers which can be helpful in invasive monitoring of patients vital health parameters**. This can shorten the time required to make accurate decisions about diagnosis, boost follow-ups, and step up the process to seamlessly transition patients onto new treatments.

Bio-electronic provisions mixed with AI constantly senses changes in the electrical system of cells and neurons can be well-utilized for studying specific patterns matched with patients health behavioural practices. For example, not having adequate exercise, insufficient sleep, eating unhealthy food for a long time etc., has the potential ability to alter body's electrical

and neuronal functions, especially in chronic conditions. Detecting this variation in real time on a device can have AI suggest vital health related tips which can be ground-breaking as it will consequently raise awareness among the public to take their health seriously.
ML-based bioelectric devices sensing remotely can also make patients with memory problems or learning disability issues adhere to their medicines. For Instance, most diabetic patients forget to take their medicines on time in today's fast-paced world. An increase in sugar levels can incite changes in the cell potential being captured by the device and communicated remotely to the patient's mobile phones as an alert notification.

iii) Dynamic Multi-Task Processing Efficiency:

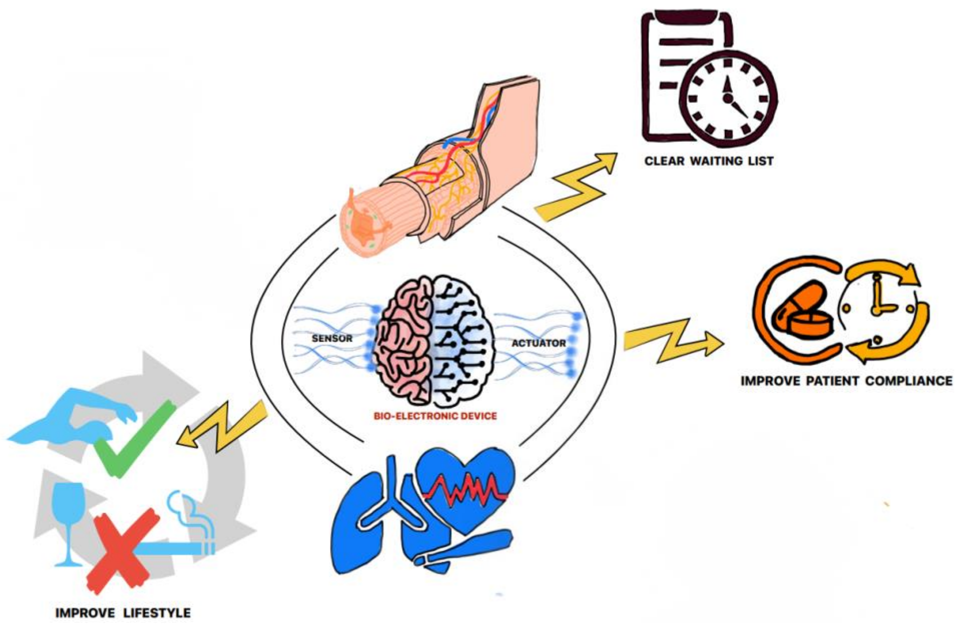
Various activities in the body function at different timeframes from just a few seconds to years (Lehninger et al.,2008; Bean,2007; Pérez-Ortín JE et al.,2007; Costa, MR et al.,2011; Seiler et al,2014). A smart AI-powered bioelectronic device could prioritize and manage tasks based on a multi-level hierarchical system, which allocates simpler tasks to lower levels while complex, critical tasks are managed at higher levels.
A Multi-Level Hierarchical system of biological control would perfectly complement ML-based strategies (Selberg et al.,2020). Frequently maneuvering and predicting these changes at regular intervals would set a new benchmark in the treatment of long-term processes like the healing of wounds (Anisuzzaman et al.,2022; Mostafalu et al.,2018; Veredas et al.,2015; Carrión et al.,2022) and other chronic illnesses**. Models such as Hierarchical Reinforcement Learning (HRL) (Dietterich, T.G, 2000), Multi-Agent Systems(MAS), Hierarchical Bayesian Models (Gelman, 2006) have demonstrated multi-level decision making process abilities and can be installed into bioelectric instruments/devices**.
The presence of Higher, Medium, and Lower levels is vital for Efficient Task Delegation, Better System Load Balancing, and Dynamic level switching in case of failures.
A Higher level in an epilepsy case might be responsible for identifying future trends or patterns of brain functioning that might trigger seizures to adjust stimulation parameters, a Medium Level might involve in actively processing and recognizing abnormal seizure signals in real-time and a lower level might involve delivering electric impulses to the specific region. In any case a level fails, the other level compensates. This system utilises a Multi-Decision making process which additionally can also strengthen the long-term durability and prevent sudden system shut-downs in these devices.

4. FALLACIES OF AI & FUTURE RESEARCH DIRECTIONS

On the contrary, the AI may backfire dramatically. It may develop bias, which could potentially cause hindrance in offering treatment to an individual who may not need it. There may be an added threat of the AI getting hacked and its data being manipulated (Brundage et al.,2018; Finlayson et al.,2018), thus maintaining patient health privacy is a major concern. **Another risk beyond the patient data getting hacked, would be to determine accountability largely in cases of adverse events. This would be challenging and thereby, clear guidelines would be required to state who is responsible- whether it's the healthcare providers, device manufacturers, or the patients themselves (Brown and Patel,2023). Moreover, these devices are actively making decisions on behalf of patients. It can hamper patient autonomy. Therefore, it is very important to ensure that patients are fully informed about how these gadgets make decisions and that they consent to their use (Taylor et al,2023).** Without appropriate and strict regulatory standards structured at every step, the AI's execution could be detrimental to patient safety.

On the whole, patient's health privacy cannot be compromised at any circumstance to AI, having its own mind. And that's why, more research on health data ownerships for the patient is required to absolutely eliminate privacy risks with AI to gain patient confidence. Studies on effacing bias out of AI can furthermore enhance the delivery of treatments. Being comfortable to wear or affordable to buy these devices are both tangible areas of concern to fasten its reach globally and must be plausibly worked upon.

Figure 1- Analogy of AI-equipped Bio-electronic Device in Global Healthcare Practice.



5.Conclusion

This review proposes to shower light on the collateral works done in the field of AI which can potentially address the gaps in bioelectric medicine. **The various algorithmic networks like FNN, SVM, K-NN can be very useful in outlining each neuron, genome and electromes. Hybrid models like Convolutional Neural Networks (CNN) and Recurrent Neural Networks (RNN) can analyse spatial configurations from signals to optimise electrode placement. Furthermore, RNN and LSTM Networks can derive insights from patient related medical factors which along with enhanced mapping of the human system can enable precise stimulation of targeted regions. Additionally, these models fused with Predictive and Non-Predictive strategies can further strengthen the core foundation of this therapy continuously by selecting the right waveform and frequency to prevent any unwanted complications and to effectively navigate the complexities and uncertainties of the human physiological systems. Furthermore, real-time local and remote monitoring facilitated by Edge Computing and embedded ANNs may enhance clinician input and instant on-device decision making process for advanced treatment. Finally, multi-level hierarchical models can organise and allocate various tasks for optimal functioning of these devices throughout.** Cutting down waiting lists by expanding opportunities in Telemedicine, implementing the right lifestyle, increasing patient compliance to medicines, and obtaining personalized treatment are some of the many other advantages bioelectric medicine can offer by integration of advanced AI algorithms. **However, concerns such as accountability for incidents, patient autonomy and consent issues, data privacy safeguarding risks, and bias in AI algorithms persist and still need to be extensively studied.**

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