Advances and Challenges in Closed Loop Therapeutics: From Signal Selection to Optogenetic Techniques

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Abstract – The main objective of this paper is to develop closed-loop therapeutic systems by reviewing various neurological disorders. We propose a system that incorporates a biosensor, controller, and infusion pump to provide closed-loop feedback management of medicine delivery. To address the specific therapeutic requirements of a medication called Dox, they made precise adjustments to the system's functioning. The device incorporates a biosensor capable of real-time assessment of medicine levels in the bloodstream. The method utilizes aptamer probes that have been labeled with an electrochemical tag. When these probes connect to the drug target, they undergo a reversible change in shape, leading to a modification in redox current. A little quantity of blood is consistently extracted from the animal's circulatory system inside a microfluidic device, which is used for this measurement. The paper examines the challenges of seizure detection and the use of advanced learning algorithms and classification methods to enhance real-time seizure detection in closed-loop systems. Following the successful use of optogenetic techniques in epilepsy models, the authors discuss the potential of these technologies for controlling brain activity.

Keywords – Closed Loop Infusion Control System, Biosensor, Proportional Integral Derivative Feedback Algorithm, Infusion Pump, Closed Loop Therapeutics, Electrophysiological Signals.

I. INTRODUCTION

Closed-loop systems (CLS)[1] use feedback between input signals and the system's output to exert control over the system. CL feedback is very beneficial when signs undergo rapid changes due to internal or external sources, or when signs occur in short bursts with normal function periods in between. The advancement of real-time, or automated CLS becomes advantageous in such circumstances. These technologies have already shown therapeutic efficacy for several neurological disorders. However, in order for closed-loop systems to effectively operate in clinical settings, four essential components are required: (1) Sensors capable of detecting crucial pathological signals; (2) Algorithms capable of processing these signals in real-time while being computationally feasible; and (3) Actuators and effectors of delivering the appropriate parameters to the designated location.

A closed-loop system allows for the use of diverse physiological signals and intervention techniques [2]. An instance of this is the use of accelerometer data to enablethe delivery of real visual stimuli, aiming to develop gait disability in individuals with Parkinson's illness.Two Anesthesiologists effectively use on-demandtreatment, whereby medicines are administered based on continuous monitoring of physiological data, to provide consistent and optimal anesthetic levels throughout surgical procedures. This approach might potentially be extended to additional cohorts of patients. However, the most effective CLS for neurological administrationhave mostly employed intervention tactics that enable better

temporal precision, specifically the transmission of on-demandelectrical miniature to the central nervous system. Within this article, we will explicitly focus on these tactics.

Cheng, Sen, and Yu [3] have developed a system that integrates aninfusion, controller, and biosensor pump to provide closed-loop feedback control of medication administration. The biosensor utilizes electrochemically labeled aptamer probes to quantify the accumulation of medicine in the stream of blood. The controller employs a feedback mechanism to determine the rate of drug administration, while the infusion pump dispenses the medication at that designated rate, enabling the desired concentration to be attained. Nicoletto and. Ofner [4] optimized the medication Dox's reaction time, stability, and resilience to meet its specific clinical requirements (CR). Research by Du et al. [15] have development the designing of biosensors by utilizing electrochemically-labeled aptamer probes. The probes undergo a conformational transition when it comes to interactions with the drug target. As a result of the conformational transitions, there is a corresponding difference in redox current, allowing for precise and rapid computation of the drug concentration in organisms.

It is fundamental to simulate the feedback loop based on the application of computer system and then optimize in vivo controllers through simulations. The findings obtained from the systems provide credence to the perspective that closed-loop therapies may produce high clinical outcomes than the open-loop treatment in terms of both efficacy and effectiveness. It should be noted that bosting therapeutic stimulation metrics and establishing new closed-loop system is a complex operation. Selecting the appropriate sensors for closed-loop modulation among the range of sensors designed to collect pathological signals is a challenging task. Enhanced sensors, such as electrodes or arrays with higher spatial and temporal resolution, have the potential to enhance the precision and sensitivity of closed-loop therapies.

According to [6], current seizure detection algorithms depend on several sources of data, which adds complexity to the process. The Food and Drug Administration (FDA) has currently authorized just one closed-loop device, which is used for the purpose of detecting and adjusting trial and error settings. This method utilizes electrocorticography or implanted depth electrodes to collect signals. Optogenetic approaches include the manipulation of cellular activity via the integration of genetics and optics, representing a cutting-edge methodology. Another kind of activators that do not rely on light are present. Optogenetics has shown promise in epilepsy models by inhibiting seizures in the thalamocortical and temporal lobes. However, optogenetic methods are now inaccessible to the general population due to safety considerations. Noninvasive closed-loop actuators, such as transcranial electrical stimulation (TES) [7], are clinically attractive because to their potential to reduce costs and minimize unpleasant effects associated with devices. TES[8] treatment has effectively decreased the magnitude of tremors and averted the occurrence of absence seizures in individuals diagnosed with Parkinson's disease.

This research focuses on many neurological disorders as its main objectives, with the goal of developing closed-loop therapeutic systems. The authors propose a system that combines a biosensor, controller, and infusion pump to effectively regulate the distribution of medicine and offer continuous feedback. In order to cater to the distinct therapeutic requirements of a medication called Dox, they made precise adjustments to the functioning of the system. The device incorporates a biosensor capable of real-time assessment of medicine levels in the bloodstream. The method utilizes aptamer probes that have been labeled with an electrochemical tag. When these probes connect to the drug target, they undergo a reversible change in shape, leading to a modification in the redox current. A little quantity of blood is continuously extracted from the animal's circulatory system inside a microfluidic device, which is used for this measurement. The paper examines the challenges of seizure detection and the use of advanced learning algorithms and classification methods to enhance real-time seizure detection in closed-loop systems. The authors discuss the potential of optogenetic techniques in manipulating brain activity, particularly in epilepsy models.

The remainder of the article has been organized as follows: The closed-loop therapeutic control system and related experimentations have been discussed in Section II. In Section III, a discussion of pathological signals for closed-loop modulation in disease status has been provided. Section IV focusses on the advances in sensor technology for closed-loop therapeutics. Fast and reliable pattern detection algorithms for close-loop stimulation are reviewed in Section V, which optogenetic techniques and non-invasive actuators are discussed on Section VI. Lastly, Section VII presents a conclusion on the advances and challenges of close-loop therapeutics.

II. CLOSE-LOOP THERAPEUTIC CONTROL AND RELATED EXPERIMENTATIONS

The close-loop therapeutic control process involves three steps: To begin, a biosensor measures the medication levels in the stream of blood. Second, a controller uses a proportional-integral-derivative (PID) [9]method of feedback to calculate the requiredrate of drug administration to gain the target accumulation. Lastly, an infusion pump administers the drug at the rate specified by the controller. The closed-loop infusion control system in **Fig 1a** was optimized to address the specific CR of Dox, focusing on stability, reliability, and response time. However, this general configuration may be used to manage the administration of nearly any small-molecule intravenous medicine that can be targeted by an aptamer probe.

According to Ibsen et al. [10], the system was engineered to promptly react, capable of maintaining and achieving alterations in the set point of concentration within a time frame of 10 minutes, which corresponds to the typical duration for Dox to be eliminated from the bloodstream during its α-phase. Furthermore, the system was designed to replicate the typical infusion periods used during Dox treatment, which include more than 2 hours of uninterrupted operation, in order to maintain consistent Dox concentrations. Furthermore, due to significant variations in Dox plasma clearance rates across

patients, we developed our approach to provide robust control over a wide range of pharmacokinetics. Attaining these response speeds, stability, and longevity required careful calibration of the biosensor and controller systems.

The biosensor we previously developed needed significant revision in order to meet these requirements (see **Fig 1b**). Simply said, this biosensor utilizes aptamer probes that have been electrochemically labeled. These probes are specifically designed to change their shape when they bind to the targeted medication, leading to a change in the electrical power between the electrode and the electrochemical label. The electrochemical estimation conducted within a microfluidic gadget allows for the rapid, quantitative, and precise evaluation of drug concentration in vivo. This gadget, as shown in supplementary **Fig 1**, samples a smallamount of bloodstream from the animal's circulation. At first, this sensor could be utilized for processing data after the fact. However, to enable closed-loop control, it is necessary to have real-time knowledge of the in vivo drug concentration. These supposes processing the sensor data in real-time, which includes baseline correction, data smoothing, and calibration.

Fig 1a demonstrates that our real-time biosensor constantly samples the circulation while a programmed infusion pump injects the animal with medication. This feedback controller analyses the acquired electrochemical drug concentration readings, determines the infusion rate (IR) required to sustain the target circulating drug set point at that particular moment, and then automatically modifies the IR based on this calculation.

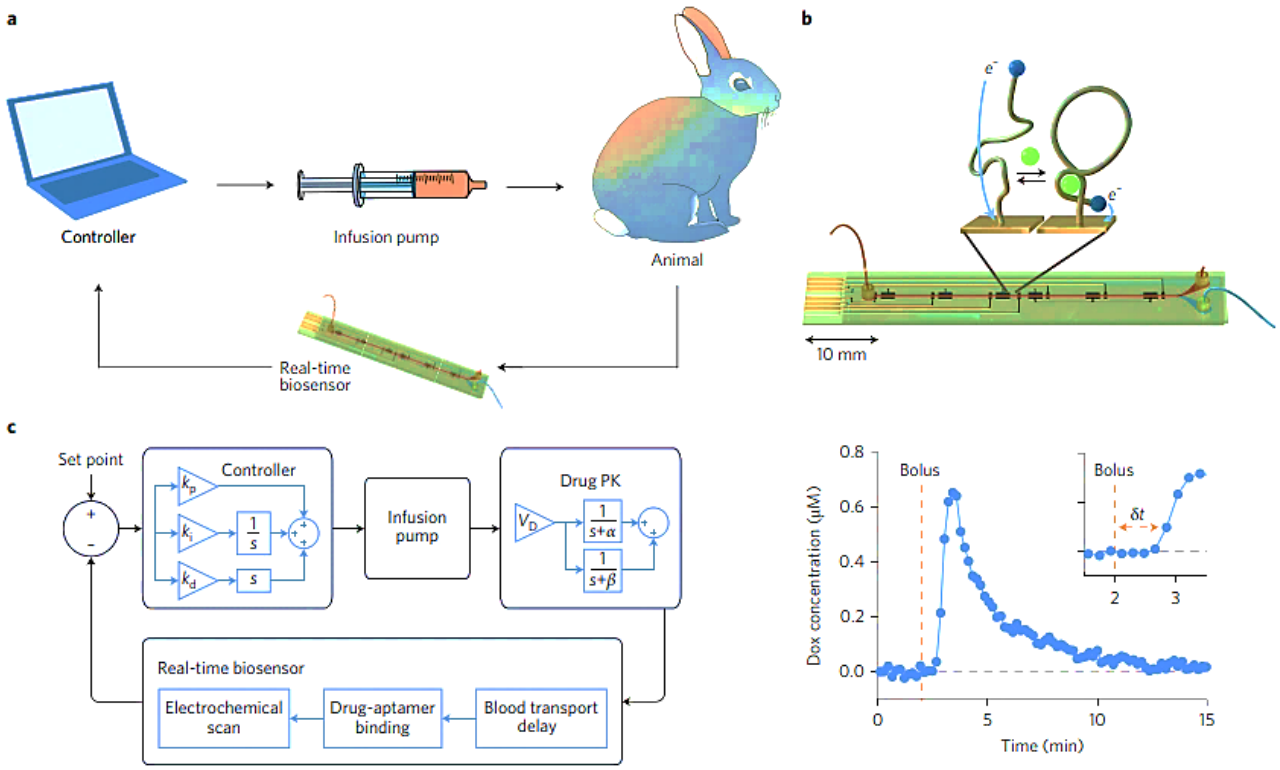

Fig 1. Closed-Loop Medication Level Management in Vivo via Real-Time Biosensing

Fig 1b aims to test drug concentrations in whole blood in real time, the real-time biosensor uses a microfluidic device with shape-shifting electrochemical aptamer probes. When these probes experience conformational changes upon attaching to the target molecule (green), the rate of electron relocation to a microfabricated electrode from an electrochemical redox marker (blue) varies. We can continuously monitor the Dox PK stages in live rabbits using our real-time biosensor (RTB), which has a measurement latency (δt) of 0.8 minutes and a point-to-point temporal precision of 11 s (as shown in the inset). Dox bolus injection times are shown by the vertical dashed lines. The blue dots represent measurements taken from a single rabbit, while the grey dashed lines indicate that there is 0 μM Dox. **Fig 1c**, anin-silico model of the feedback loop is possible. The following components make up this model: the controller, which includes β-phase elimination and exponential α-rates as well as derivative, integral, and proportionalgains k_d, k_i, and k_p,; the drug PK; the infusion pump, which has an impactive dissolution volume VD; and the RTB is the transfer-function version of the complex Laplace variable. This approach paves the way for in vivo control tuning and in silico controller simulation.

Cunningham et al. [11] performed a closed-loop experiment in an animal model, specifically employing a chimpanzee named Paddy. This experiment is likely one of the first of its kind. Paddy's brain was equipped with an implanted telemetric device called a "stimoceiver". This device was able to administer feedback stimulation to the central gray area of the brain when it detected spindle patterns from circuits believed to originate in the amygdala. During the behavioral tests, Paddy exhibited less vocalization, lower attention, and diminished motivation, whereas the unpleasant stimulation had a diminishing influence on the occurrence of spindles. Fröhlich and Townsend [12] examined the feasibility of using

closed-loop feedback stimulation as a therapeutic approach for neurological symptoms such as panic attacks, seizures, and other illnesses. Despite the long-standing existence of neurostimulation and its efficacy in treating many neurological disorders, the closed-loop technique was not feasible for clinical use due to multiple technical obstacles. Modifying the parameters of spinal cord stimulation using accelerometer-derived body position data enhances pain relief and enhances the overall well-being of those suffering from chronic neuropathic pain.

During this time, closed-loop control was maintained by using glucose data obtained from fingerstick measurements. During this experiment, BGC fell below the hypoglycemic threshold on three occasions. However, while doing blood glucose measurements using both fingerstick and YSI methods, only one of them was verified to indicate genuine hypoglycemia. In all three instances, supplementary foods were supplied until BGC returned to the usual range. Various forms and quantities of insulin may exhibit distinct pharmacodynamic characteristics, as can the impact of meals on blood glucose control (BGC). In order to simulate real-life conditions, different meals were offered in each individual trial. Possible factors contributing to the observed elevated BGC levels in this experiment include: The distribution of continuous glucose monitoring (CGM) data for six closed loop tests and three open-loop days is shown in **Fig 2**. The individuals were randomly picked from their respective history data sets. In all instances, the closed-loop trials consistently exhibit a lower average glucose levels. Furthermore, the box-whisker plots indicate that the median value of CGM falls within the typical pre- and postprandial ranges, which are between 70–180 mg/dL. The majority of the data is clustered inside the usual range.

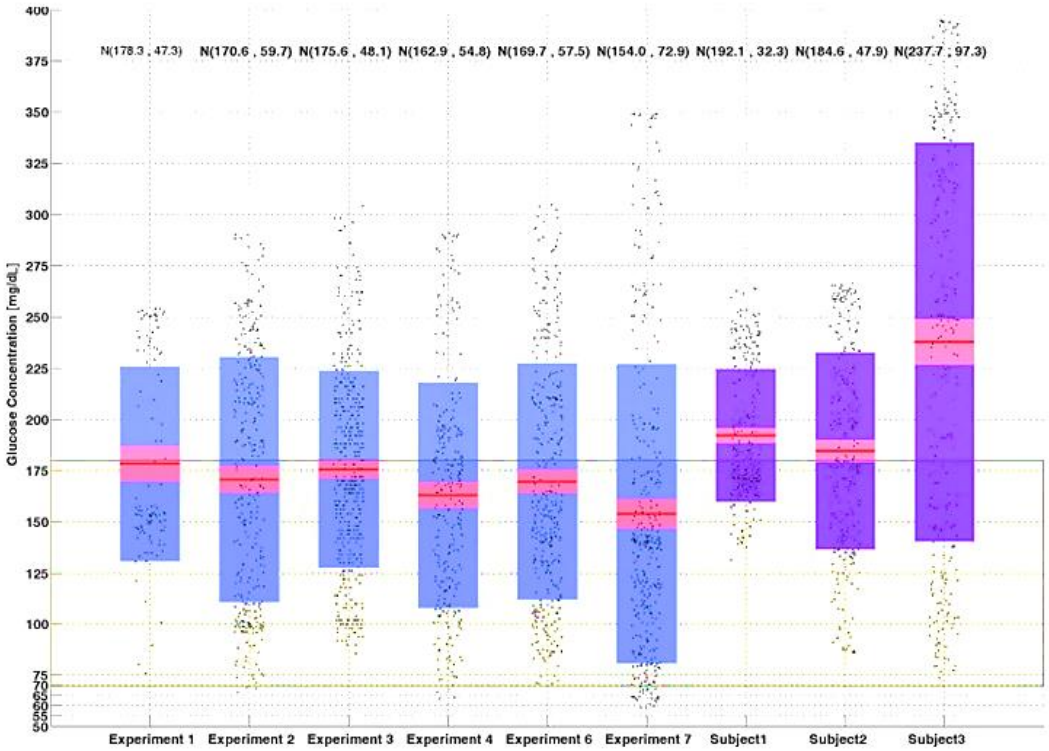

Fig 2. Distribution of Continuous Glucose Monitoring (CGM) Data

The data obtained from the usage of these gadgets provide evidence that CL treatments may enhance the effectiveness and clinical advantages of stimulation, while reducing the detrimental effects of stimulation, in comparison to open-loop protocols. Although there are potential advantages, it is still challenging to create novel CL technologies and optimize stimulation settings in a clinical environment. In this discussion, we explore instances where the use of state-of-the-art procedures and analytical methodologies in a research environment might enhance many aspects of a CL therapeutic system.

III. PATHOLOGIC SIGNALS FOR CLOSED-LOOP MODULATION IN DISEASE STATES

Identifying the suitable pathological alerts to serve as triggersfor CL regulation in different disease conditions continues to be a significant obstacle. For instance, parkinsonism is linked to different characteristics seen in electrophysiological signals and electromyography recordings from cortical areas or basal ganglia (BG). In order to determine the appropriate features to include in a CL paradigm, it is necessary to have a thorough comprehension of the kind of signals that are significantly improved in the circuit of pathology, rather than just being correlated. Without this understanding, the process of selecting these qualities becomes a trial-and-error method. Wichmann, Bergman, and DeLong [13] performed an experiment in which they inserted recording electrodes into the basal ganglia (BG) and cortical areas of nonhuman monkeys. The researchers discovered that the use of responsive deep brain stimulation (DBS), which is influenced by the action capability in the motor cortex (MC), effectively improved motor function. Additionally, this treatment led to a

significant decrease in pallidal vibration activity. In contrast, stimulating DBS according to the occurrence of action capabilities in the pallidum, rather than the MC, resulted in an increase in pallidal vibratoryactivity and a deterioration in motor function. These analysisconfirmed the pathological significance of these vibrations and, along with other important clinical and research observations, stimulated the clinical investigation of CLS in patients with Parkinson's illness. This stimulation is triggered by the vibratory activity detected in the BG.

According to Supèr and Roelfsema [14], the use of animal models in experimentation has the benefit of being able to record alerts from both independent neurons and groups of neurons in brain areas that are often difficult to reach for clinical noting in people. Additionally, it allows for the opportunity to record from numerous scattered brain regions at the same time. These techniques provide more accurate understanding of network-level processes at the spatial and temporal scale of connections between neurons, which is becoming more widely acknowledged as important in neurological illnesses. Closed-loop techniques have effectively been used to specifically identify and eliminate or amplify hippocampus sharp wave ripples using optogenetic or electrical stimulation. These oscillations have been shown to be vital in the unificationof memory traces. Nonetheless, the efficacy of converting discoveries from animal research to therapeutic applications depends on the usefulness of the animal framework employed. This underscores the need of continuous communication among scholars engaged in clinical and animal investigations of a certain condition.

IV. ADVANCES IN SENSOR TECHNOLOGY FOR CLOSED-LOOP THERAPEUTICS

After identifying the essential signals, it is necessary to get suitable sensors to acquire these signals. In order to accurately capture electrophysiological signals, it is important to position the sensors close to the source of the abnormal signal and ensure that they have the ability to record with a high level of temporal resolution. Changes in neuronal spiking patterns or rates are associated with the start of deterioration and seizures of parkinsonian symptoms in people. These changes might possibly be used to initiate interference in a CLS. Nevertheless, the majority of clinical electrodes that are positioned on the surface of the brain (known as electrocorticography electrodes) or inserted into deep structures (referred to as depth electrodes) are too big and often fail to properly convert signals, hence limiting their ability to detect high- threshold activity in the action potentialsform. Enhanced spatiotemporal resolution in electrodes or arrays might greatly increase the specificity and sensitivity of CL therapies.

The effective management of seizures serves as a prominent demonstration of the possible significance of advanced triggering processes, recording methodologies, and selection of signals. Research has shown that intervening at an early stage enhances the probability of effectively halting seizures. In a study conducted by Jangwan et al. [15], twenty- one High-density MA (microelectrode arrays), namely Cyberkinetics Neurotechnology model’s NeuroPort, were surgically implanted into the brain of individuals suffering from medically resistant epilepsy. This enabled researchers to view micro seizures occurring in the seizure-onset zone prior to their detection by the clinical subdural electrodes. The research electrodes detected distinct variations in the spiking activity of several units, indicating a variation between the initiation of ictal rhythms, as determined by traditional electrodes, and duration of the rapid and synchronized activation of neurons. Therefore, using advanced electrodes able to capture accurate data on spike resolution might possibly act as more efficient stimuli for investigating the role of cortical layers in epilepsy.

As stated by Jones et al. [16], the practical importance of MA in CL therapy is currently limited because to its restricted 4 mm by mm spatial coverage, uneven monitoring of activities within a unit during a certain time, and the potential for cortical damage linked to array implantation. These obstacles might possibly be surpassed by advancements in electrodedesign. The continuous mechanical damage resulting from the small movements of implanted electrodes significantly adds to the instability of recordings and the activation of glial cells after the implantation. A sinusoidal probe made from versatile products has been created to reduce this movement and has effectively captured alerts of physiology for over 2 years without causing significant harm to the rabbit's neural tissue. A different method is identifying the occurrence of rapid bursts of electrical activity on the outer layer of the human brain by using flexible, compatible with living tissue, and easily expandable arrays of electrodes made from conducting polymers (NeuroGrid). Additional research is necessary before using this technology in regular clinical practice. However, these innovative sensors have the potential to enhance detection sensitivity and reduce the negative consequences associated with sensor installation.

According to Sadaghiani, Brookes, and Baillet [17], progress in sensor technology extends beyond the field of electrophysiology. Neurons not only produce electrical fields but also create neurochemical fingerprints in the extracellular space as a result of neurotransmitter release. Neurological illness is linked to alterations in several neuroactive chemicals. The most well recognized is the deficit of dopamine in the pallidum in Parkinson's illness. Fast-scan cyclic voltammetry (FSCV) is a technique used to monitor the dynamic fluctuations in the levels of electroactive substances (such as dopamine, norepinephrine, serotonin, and adenosine) outside of cells. This is achieved by observing the oxidation and reduction processes that occur at a carbon fiber electrodein real-time. FSCV has been integrated into a wireless, real-time neuromodulator accumulation sensing device to measure changes in adenosine liberate after inserting a DBS electrode in patients with essential tremor.30 Comparable sensors might function as the input element of CLS designed to sustain consistent extracellular levels of a certain neurochemical, like dopamine in Parkinson's illness.

V. FAST AND RELIABLE PATTERN DETECTION ALGORITHMS FOR CLOSE-LOOP STIMULATION

Efficient and dependable pattern identification techniques with a minimal occurrence of false alarms are required to ensure the safety and effectiveness of closed-loop stimulation in clinical environments. While techniques are necessary for all CL devices, the challenges and potential for implementing new tactics are particularly apparent when it comes to detecting seizures in patients with epilepsy.

Seizure identification is a challenging problem since seizures may vary greatly in their features, both within the same patient and across different individuals. Additional research has been conducted on seizure detection using a single characteristic, namely entropy and its sub-types including approximate entropy (AE) and sample entropy (SE) [18, 19, 20]. The entropy characteristic is used to analyze the randomness of EEG signals and provides a useful measure of signal impurity [21, 22]. The entropy characteristic has been extensively used in cases where data is in the form of signals, such as ECG, EEG, and ECoG. This contributes to subsequent stages of the detection model. Shoeibi et al. [23] provide a visual representation of the model used for detecting seizures from an EEG/ECoG seizure dataset. This representation is shown in **Fig 3**. The procedure consists of four steps: Data Collection, Data Preparation, Application of Machine Learning Classifiers, and Performance Evaluation.

The detection algorithms have relied on signal features obtained from various sources such as video recordings, electroencephalography, accelerometry, electrocorticography, electrocardiography, and electromyography. However, the only CLD that has received approval from the FDA, known as the NeuroPace system [24], utilizes recorded signals from implanted depth and electrocorticography electrodes.The gadget has three adjustable detection settings (linear length, area, and bandpass) that may be customized by the physician to improve the specificity and sensitivity for each victim`s electrodiagnosis seizure sequence. While this method for capturing is very enough in terms of computing speed, the process of fine-tuning the detection parameters relies on trial and error, which may be time-consuming for both the physician and the patient.

One possible resolution to this problem is to use sophisticated algorithms of learning or categorization techniques, which are becoming more prevalent in diverse fields such as pharmaceutical research and image analysis. Seizure detection methods that have been attempted include Markov modelling, support vector machines, fuzzy logic models, and artificial neural networks.These systems usually include a training phase, when previously obtained data is analyzed and important characteristics that indicate the beginning of a seizure are identified. Subsequently, a real-time classifier is developed and used to identify future seizures. During training, data from several patients may be used to develop a classifier that can be applied to a wide range of cases. Alternatively, a significant quantity of information from a single patient can be employed to create a classifier that is particular to that person. An important obstacle faced by these methods is to enhance the efficiency of the actual-time classifier in order to promptly identify seizures with an acceptable delay forCL applications.

VI. OPTOGENETIC TECHNIQUES AND NONINVASIVE ACTUATORS

Optogenetics is the combination of genetics and optics to manipulate the activity of cellular function and proteins. It involves using light to influence the functioning of modified or genetically-targeted cells. Optogenetics enables the manipulation of several biological activities, such as migration, cell stimulation/inhibition, intracellular signaling, and gene activation. Optogenetics has the capability to manipulate several types of cells, such as cancer cells, neurons, stem cells, and heart cells. However, since the main emphasis of this study is on optics, let us concentrate on regulating a specific function (such as inhibition or stimulation) of neural cells. The lack of targeted inhibition or stimulation of particular groups of neurons in the peripheral or brain system using traditional non-optical and electrical techniques has been a significant obstacle to the use of stimulation tactics for therapeutic reasons.

According to Pulvermüller [25], the investigation of the role of particular neurons in the natural neural network requires meticulous manipulation of their activity. This entails performing dissection procedures to ensure the correct placement of stimulating electrodes. Consequently, it has shown to be intrinsically challenging to carry out targeted stimulation in live animals using non-optical methods such as electrical or magnetic stimulation. The issue of selective activation remains unresolved, despite the use of light-assisted glutamate uncaging or ultrafast laser stimulation. Scientists are considering the potential of using a remote-controlled switch in the brain by combining optics and genetics via emerging approaches. The process of implementing optogenetic stimulation involves four key stages, as shown in **Fig 3**.

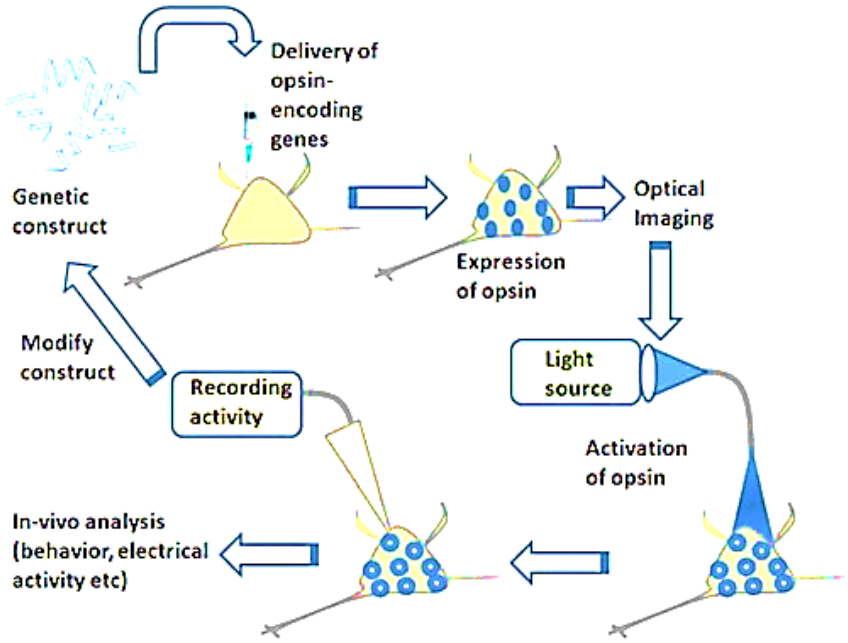

Fig 3. The procedure of Optogenetic Stimulation

A genetic construct containing the opsin gene is artificially created, transported, and activated inside certain cells. Cells harboring opsins are triggered by light. Measurements are conducted, and the structure is altered to enhance optical manipulation.

The optimal stimulation parameters for a closed-loop system would be those that reinstate typical patterns of brain activity once they have become pathological. Although certain diseases may need focused stimulation, broader and more widespread stimulation, or inhibition of activity throughout the whole cortex may be beneficial for other conditions. The impact of electrical inducement on groups of neurons is often ambiguous, and several types of cells in the brain may undergo modifications, making it difficult to practically establish these parameters. During the onset of a seizure, it may be beneficious to subdue the activity of excitatory cells instead of inhibitory. Optogenetic methods, which will be explored in detail below, have made it possible to investigate the effects of manipulating certain cell types on pathological conditions in a cost-effective way.

The fundamental basis of optogenetics is on the targeted synthesis of light-sensitive proteins. These opsins, known as synthetic proteins, are not naturally synthesized.Consequently, optogenetic techniques have only undergone experimentation on animals in previous studies. By restricting the manifestation of the photosensitive proteins, it becomes possible to precisely control certain groups of neurons. In addition, there exist many photosensitive proteins, such as excitatory channels (which facilitate increased firing of active neurons) and inhibitory channels and pumps (which impede the fast firing of active neurons). Therefore, on-demandoptogenetics (ODO) enables precise manipulation of the modulation direction (i.e., excitation or inhibition), selectivity to certain cell types, and precise control over the timing of electrical stimulation. An instance of this is the recent advancement in animal experimentation that enables the targeted suppression of certain subclasses of neurons in particular brain locations during specified time periods. Currently, on-demand optogenetics is a very effective experimental approach due to its ability to precisely intervene in particular areas. Additionally, discoveries made in this field might potentially be used in practical ways in a clinical setting.

Specifically, the use of ODO has been effective in mice frameworks of temporal lobe and thalamocortical epilepsy, which are two forms of epilepsy that have been investigated by optogenetic methods. A recent research examined the feasibility of using optogenetics to exhibiting cells selectively target the thalamus and stop seizures produced by experimental cortical stroke, which has been shown to induce thalamocortical epilepsy. In this study, the ventrobasally thalamus, which is on the same side as the induced cortical stroke, was targeted to generate arepressive opsin termed halo Rhodopsin in. The purpose was to suppress the output of the thalamus. The implementation of automated light supply was triggered as a reaction to seizures that were detected online utilizing the line-length frequency crossing method. This ODO method successfully addressed the abbreviated thalamocortical seizures.

Several diverse ODO techniques have been explored for the treatment of temporal lobe seizures. The first stage was the introduction of halo rhodopsin, a light-sensitive chloride pump that inhibits neuronal activity, into cells that are normally excitatory. The activity of these cells was inhibited and the occurrence of seizures was much reduced when light stimulation was applied to the hippocampus as needed. A further experiment was conducted on Channel rhodopsin, which is a light-activated cation channel that stimulates particular inhibitory neurons. Less than five percent of neurons belong to this type. To suppress the activity of excitatory neurons in the hippocampus, it was essential to provide light stimulation to the inhibitory cells when needed. This technique effectively decreased temporal lobe seizures by specifically suppressing a limited number of inhibitory interneurons. These findings provide evidence for both the effectiveness of a targeted

intervention that focuses on certain cell types, and the accuracy of a timely intervention that may be initiated as needed to control seizures. Stimulating the midline cerebellum using optogenetics leads to a unique and enduring decrease in the initiation of seizures. This approach may be used as needed and has recently shown its efficacy in reducing seizures in the temporal lobe. These results provide the foundation for the possible use of on-demand optogenetics in future studies on the networks and cell types that have a crucial impact on seizures.

Similarly, optogenetics has provided insights into the specific output targets associated with distinct cell types in Parkinson's illness. Optogenetic stimulation of direct route medium nerves in the neostriatum reversed bradykinesia in mice with parkinsonismproduced by 6-hydroxydopamine, bringing their movement speed back to the levels seen before the injury. Conversely, the stimulation of medium spiny neurons in the indirect route led to the development of Parkinsonin mice that had previously shown normal motor function.These results indicate the activity of the basal ganglia affected by these pathways and that the symptoms of Parkinson's disease may be relieved by specifically activating these channels. A different optogenetic approach revealed that mice with hemi parkinsonism did not experience sufficient improvement in parkinsonian symptoms by deep brain stimulation (DBS), despite DBS being the purported mechanism of action. The researchers used a transgenic mouse that generated channel rhodopsin under the control of the Thy1 promoter to selectively excite fibers originating from the cortex rather than neurons that are subthalamic.A possible novel anatomical location for stimulation in this condition may have been identified, since this stimulationwas capable of replicating the therapeutic impact of deep brain stimulation (DBS) in these animals.

The necessity for gene therapy techniques to stimulate the expression of opsin, since they are not endogenously synthesized, raises safety issues, hence restricting the availability of optogenetic treatments for patients. However, many viral vectors have demonstrated safety in gene therapy for Parkinson's disease. Additionally, Retro Sense Therapeutics' viral vector-based channelrhodopsin has been classified as an orphan drug, indicating its potential use in clinical trials to restore actuator vision in victims with retinitis pigmentosa using optogenetic techniques. Optogenetic techniques have the potential to function as in CL therapeutic gadgets, expanding their role beyond just adjusting output parameters.

Currently, the most prevalent approach for implementing actuators in CL neurological systems is the alteration of brain electromagnetic fields by targeted electrical stimulation. The NeuroPace system utilizes depth leads or subdural strips for the administration of electrical current, whereas the DBS Therapy device from Medtronic, Inc. employs a depth electrode equipped with four columnar contacts. However, the improvement of noninvasive CL actuators is a subject of significant therapeutic importance because to its potential to decrease the adverse effects and expenses associated with devices. The precise timing capabilities of transcranial electrical stimulation (TES) are thought to make it a viable noninvasive tool for treating paroxysmal neurological illnesses. Furthermore, transcranial magnetic stimulation (TMS) is both more expensive and more burdensome in comparison to TES.

Recently, there has been a significant amount of research conducted on various uses of TES in human subjects, demonstrating the excitement around its potential. These applications include addiction treatment, rehabilitation for stroke patients, enhancement of spatial tactile acuity, and improvement of reading skills. Various ways are available for delivering transcranial electrical stimulation, including as alternating current and direct current methods. Pruritus, paresthesia, and fatigue are among the limited number of recognized moderate adverse reactions associated with transcranial electrical stimulation, which is normally regarded as innocuous.Yavari et al. [26] have shown that the impact of transcranial electrical stimulation (TES) differs according on the brain's state. By combining Transcranial Electrical Stimulation (TES) with a CLS, it is feasible to improve symptom management and reduce unnecessary intervention.

Pinault [27] examined the use of transcranial electrical stimulation (TES) in a rat framework of thalamocortical epilepsy (also known asabsence epilepsy) found that OD involvement may give dominant seizure management. Long-Evans rats with absence seizures, defined by spontaneously repeating spike-and-wave occurrences, had electrodes surgically inserted. The objective was to document the activities of neurons during seizure occurrence. The three recording electrodes, shown as A, B, and C in **Fig 4**, were positioned at increasingly higher levels inside the neocortex. The current source density (CSD) trace was obtained by applying formular $CSD = -(a + c) + 2b$to the amplified and filtered recorded signal. Subsequently, transcranial stimulating electrodes were used to administer TES. This was done by placing the electrodes on the skull after swiftly identifying spike-and-wave events online. These events were detected as crossings of voltage of a certain frequency level of the CSD trace (see **Fig 4**).

The researchers looked at the effects of two types of stimulation: OD inducement (50-millisecond gaussian waveshapes affected by online seizure detection) and continuous, OD 1-Hz sinusoidal inducement. Sinusoidal inducement did not decrease the time of spike-and-wave events, rather, it had the potential to synchronize neuronal firing (measured as multiunit firing) and alter their magnitude. **Fig 4F** demonstrates that the duration of animal seizures was significantly reduced by the application of on-demand transcranial electrical stimulation (TES), therefore restricting the length of the convulsions. These data demonstrate two significant factors. One primary advantage of TES is its capacity to effectively inhibit absence seizures. Furthermore, using an on-demand approach might potentially enhance the efficacy of seizure management.

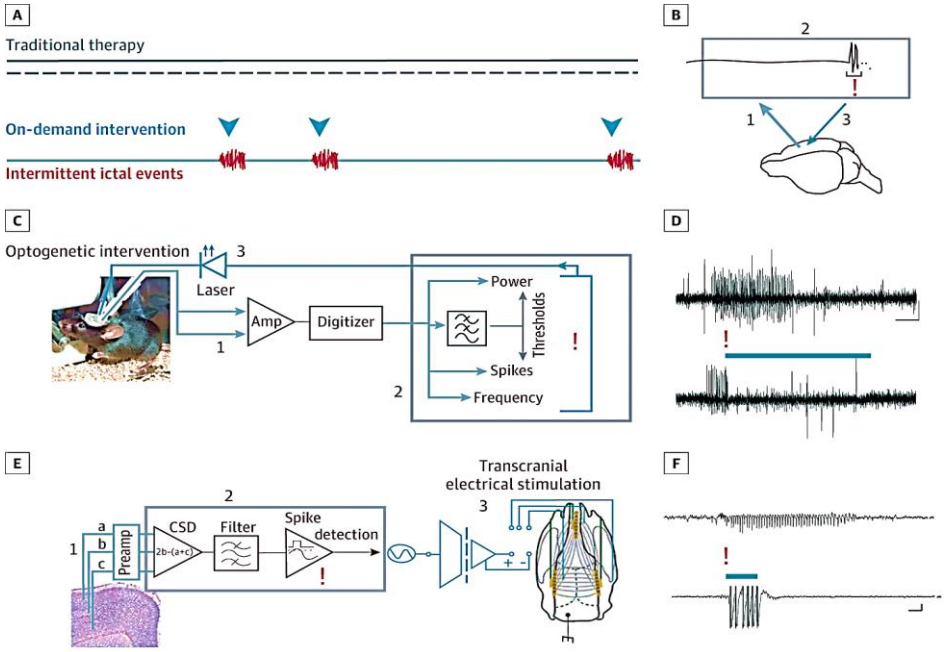

Fig 4. Closed-Loop Intervention for Spontaneous Seizure Detection

In A, unlike conventional therapeutic methods (represented by black lines), which are administered consistently or according to a predetermined schedule without considering the brain's condition or the appearance of pathological events like seizures, on-demand interference aims to synchronize the interference (depicted by blue arrowheads) with the specific events that necessitate involvement, such as seizures (depicted in red). B states that closed-loop techniques use continuous brain activity information to decide the timing of intervention. The brain's electrical impulses are recorded (the first step - gray) and assessed in the second step, which is the upper rectangle to identify the events in real time (denoted by "!"). The discovery process promptly initiates involvement (step - blue), modifying brain activity and completing the feedback loop. The CL optogenetic system in C is used to identify impulsive seizures for temporal lobe by analyzing several signal parameters such as frequency, spiking, and energy components.

The illustration in D reports that the seizure length was shortened by inhibiting excitatory cells using on-demand optogenetics. The upper trace depicts an unassisted seizure, whereas the lower trace illustrates a seizure with little assistance in the form of light stimulation. E reports the use of a CL TES system of intervention to suppress seizures absence in rats. The system is explained widely in the Actuators and Effectors part of the objective article. CSD is an abbreviation for current source density. F states that OD TES involvement reduces the duration of absence seizures. The upper trace displays an unassisted seizure that occurred naturally, while the lower trace exhibits an online-detected seizure (indicated by a red exclamation point) that prompted an intervention involving TES. The intervention period is represented by a blue bar. It is worth noting that the large amplitude signal observed during TES has been shortened. The scale bars for (D) are 0.5 mV and 500 ms, whereas for (F) they are 5 s and 100 μV.

An analogous method has been used as a pilot study to diminish tremors in individuals diagnosed with Parkinson's disease. In this instance, Transcranial Electrical Stimulation (TES) was specifically administered to the MC, targetingthe frequency of patient`s tremor, which was measured using a wrist-mounted accelerometer. Closed-loop stimulation, which achieved precise phase alignment between TES and MC, was more successful than OL inducement in reducing the amplitude of the shock. While the effectiveness of this approach has only been shown in short-term situations, it highlights the potential effectiveness of noninvasive technology when employed in a CL manner. Although TES-based CL paradigms have been successful, the precise processes via which TES acutely and chronically changes neuronal activity in particular brain areas are still not well understood. Hence, it is essential to conduct meticulously planned investigations to elucidate the fundamental physiological mechanisms responsible for the reported effects, while simultaneously advancing the development of TES devices. investigations conducted in animal models have started to make advancements in comprehending the alterations in local sector spiking and potential activity that take place in animals during TES. These investigations use invasive neural recordings coupled with TES.

VII. CONCLUSIONS

This article focuses on the advancement of closed-loop therapy systems for diverse neurological illnesses. The authors suggest a closed-loop infusion control system that integrates a biosensor, controller, and infusion pump to accomplish closed-loop feedback control of medication administration. The system's performance was tuned to align with the precise clinical needs of the administered medicine. We also address the difficulties and progress made in controlling abnormal signals in various illness conditions via closed-loop modulation. We emphasize the importance of understanding the

signals that are important for the disease circuitry and the need for ongoing communication between researchers involved in animal and clinical research. The development of sensor technology plays an important role in the treatment in a sealed cage. The authors explore the need for sensors with high temporal accuracy and improved spatiotemporal precision to promote the sensitivity and specificity of closed-loop therapies and additionally discuss how to use fast scan cyclic voltammetry used to assess real-time changes in neurochemical profiles.

The authors address the challenges in seizure detection, focusing on the problems of selecting appropriate features, making real-time classifiers used in closed-loop applications more efficient. We discuss the use of sophisticated classification techniques and machine learning algorithms for threat detection. The authors also explore the development of optogenetics and noninvasive operators for closed-loop therapies. The findings highlight the potential of photogenetics to regulate brain function and examine specific cell types and interactions associated with epilepsy, however, the use of photogenetics in humans is currently restricted due to safety concerns. Transcranial electrical stimulation, a type of non-invasive intervention, is effective in preventing seizures and reducing tremor magnitude. Generally, this study provides important insights into closed-loop neurotherapy of treating diseases. Further research is needed to increase the stimulation process, improve the sensor technology, and optimize the detection algorithm to achieve effective closed-loop modulation

Data Availability
No data was used to support this study.

Conflicts of Interests
The author(s) declare(s) that they have no conflicts of interest.

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Ethics Approval and Consent to Participate
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Competing Interests
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