

## SPECIFIC AIMS

Epilepsy affects approximately 70 million people worldwide [12]. About 30% of epilepsy patients are drug resistant and must consider invasive alternatives such as resection and electrical stimulation therapy. Surgical candidates must have a well-localized focus in an area outside of eloquent brain structures [13]. Although surgery can dramatically improve the lives of patients, it is irreversible and outcomes are highly variable (30-70% success rates) [14]. Electrical stimulation, on the other hand, is reversible and has great potential [15-17]. Chronic open-loop stimulation has shown some efficacy, but does not account for dynamic brain activity and the continuously changing state of the patient, making it suboptimal and crude. In order to maximize therapeutic effects, new methods must be developed for fine dynamic tuning of stimulation parameters in a patient-specific manner. **Closed-loop electrical stimulation therapy** provides an attractive option that minimizes intervention by limiting the stimulation to times when the patient is in need [18,19].

Efforts have been made to develop closed-loop stimulation strategies using different protocols, yet none provide a highly effective and reliable solution. The recently FDA approved responsive neurostimulator (RNS, NeuroPace, Mountain View, California) uses electrical stimulation in response to seizure event detection. Stimulation typically reduces seizure frequency acutely in 40% of the implanted patients [20]. However, only 20% of patients become seizure-free [16]. This device is too sensitive (hundreds of false alarms per day) and the responsive mode does not adapt its stimulation intelligently to the current state of brain activity. There have been other closed-loop strategies proposed and studied [21-27], but *all* are actually “responsive switches” rather than **continuous feedback control**, and have not produced reliable results that translate to the clinic. These strategies *wait* until a seizure is detected (via an algorithm) and then stimulate with a *fixed* pattern to suppress the seizure. In contrast, **we aim to implement real closed-loop control that continuously steers the neural network away from seizure genesis entirely using adaptive stimulation patterns that change with feedback from EEG measurements—avoiding seizures altogether** [28].

To meet this objective, we plan to use *in vivo* experimental data to develop an innovative mathematical model that characterizes fundamental neural dynamics during seizure genesis, and the effects of different electrical stimuli on neural activity leading to seizure genesis. Based on this model, we will then design and implement a feedback controller that monitors neural activity in real-time to prevent seizures from evolving in the network. In particular, the controller will steer temporal patterns of stimulation to disrupt preseizure activity with minimal energy consumption. To accomplish our goals, we have assembled a highly interdisciplinary team with expertise in system identification [29,30], control [31,32], and experimental neurophysiology [1,9,33,34]. Our computational framework will be constructed through the following aims:

**Aim 1: Identify features of network behavior sensitive to neural activity that leads to seizure initiation.** We will implement a chronic rat model of epilepsy that simulates sclerosis in the mesial temporal lobe. We will perform intrahippocampal application of a chemoconvulsant to induce focal Spontaneous Recurrent Seizures (SRS) that resemble the dynamics of seizures in humans [2,3,33,34]. To monitor neural activity, Local Field Potentials (LFPs) will be recorded using Microelectrode Arrays (MEAs). Offline computational analyses will then be performed to design a feature extraction algorithm that derives a signal or vector of signals from the LFPs to track the dynamics of the epileptogenic network. We hypothesize that the derived signals will be informative features that show a recurring pattern during pre-seizure initiation [29,35]. These features will become the output of our control system (Aim 2) and will enable us to characterize the dynamics of the epileptic network behavior as it approaches seizure onset.

**Aim 2: Design and validate closed-loop feedback controller to prevent seizure initiation.** This aim involves two parts. Aim 2a: System Identification. We study how closed-loop stimulation affects neural activity as the seizure onset approaches by performing a grid search over the electrical stimulus parameters (signal period, frequency, duty cycle and gain). This will identify a dynamic relationship between stimulus parameters and neuronal activity. Specifically, we will record LFP data from the *in vivo* chronic model under various stimulation settings and measure the behavior of the informative features derived in Aim 1. These input-output responses will inform a closed-loop data-driven model [30,31] of preictal dynamics. Aim 2b: Control Design and Validation We will design a model-based controller that, given real-time estimation of informative features, constructs stimulation settings that prevent seizure onset by stabilizing around desired baseline neural activity using minimum energy consumption. The algorithm will update the stimulation parameters to prevent the epileptic network from reaching a neuronal state that will initiate a seizure, ultimately preventing seizures in a safe and efficient manner. The feedback controller will then be validated *in vivo* on the chronic animal model.

These aims will lead to a nuanced understanding of how electrical stimulation impacts preictal dynamics, ultimately facilitating the design of a novel control strategy for preventing seizures before they begin.

## RESEARCH STRATEGY

### A. SIGNIFICANCE

Partial seizures are the most common type of seizures; with or without secondary generalization, partial seizures are found in more than 50% of epilepsy patients [36]. From these patients, only about half have their seizures controlled with antiepileptic drugs (AEDs) [37]. If a patient fails to achieve seizure control with AEDs, the chance of doing so with additional AED therapy utilizing new or old agents is less than 5% [38]. Drug resistant patients must therefore consider invasive treatments such as surgical resection, which is irreversible and has highly variable outcomes (30-70% success rates post-surgery) [15]. However, many patients are not candidates for surgical resection (e.g. because focus is in eloquent cortex), and therefore a significant number of patients need new treatment options [39].

Electrical stimulation is a powerful tool capable of altering neuronal activity with the potential to become a highly effective form of treatment for seizure therapy [15-17]. So far, stimulation has been implemented in a chronic or responsive mode. Chronic stimulation aims to produce neuromodulation of interictal background activity to reduce seizure frequency [16]. Alternatively, responsive therapy aims to detect and suppress ictal activity at the seizure focus within a window of opportunity after electrographic onset but before the onset of disabling clinical symptoms [20]. Responsive stimulation has clear benefits in that therapy is minimized and restricted to periods of time when the patient is in need. Recent studies using responsive stimulation have reported similar results to chronic stimulation studies, with a 40% decrease in seizure frequency over a 3-month period. An explanation for the similarities in results could be because of the low specificity shown in the responsive stimulation trials. Results showed over 500 detections and subsequent therapies per day [15] and a limited number of patients become seizure-free [16,17,20]. Furthermore, these stimulation modalities use a fixed pattern stimulation signal, which is not ideal given the rapid rate of change in neurological activity seen in seizures. Hence, we hypothesize that the stimulus should be dependent on the ongoing state of neurological activity. This motivates the development of new intelligent algorithms that can fully-exploit the capabilities of neurostimulation to offer more patients an effective treatment that could replace resective surgery and give patients that are not candidates for surgery an alternative [28].

### B. INNOVATION

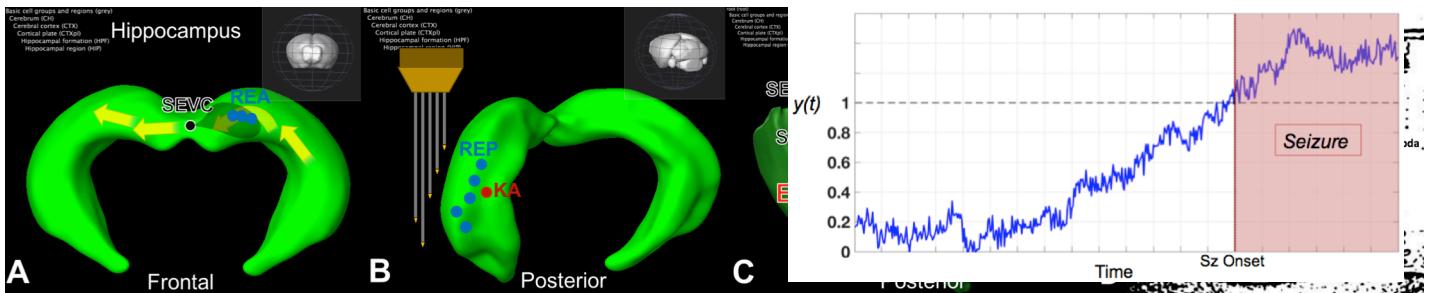
Effective closed-loop treatment requires suppression of seizure initiation mechanisms to impede the seizure from reaching onset before the appearance of disabling clinical symptoms [18]. Given the complexity of seizure dynamics and the variability of seizure-onset patterns across patients, the understanding of underlying neurophysiological mechanisms that drive epileptic networks is necessary for closed-loop therapy to be effective [17]. Furthermore, characterization of the dynamical properties of the epileptic network is required in order to understand its behavior under the effects of electrical stimulation as the seizure onset approaches.

Recent development of control engineering tools for epilepsy treatment [21-27] has encouraged the idea of using closed-loop systems to suppress seizure progression through electrical stimulation, but lack rigorous models that explain the temporal-spatial dynamics of the epileptic network. The closed-loop strategies that have been proposed are actually “responsive switches” and have not produced reliable results. These are actually responsive strategies that *wait* until a seizure is detected (via a seizure detection algorithm) and then stimulate with a *fixed* pattern to suppress the seizure. Consequently, these approaches suffer from many false alarms (detection algorithms lack specificity) and ad-hoc stimulation that does not change with feedback from EEG activity. Furthermore, stimulation may be delivered at a time when the seizure is much harder to prevent or suppress because of the epileptic network’s unstable behavior.

Here we propose an innovative approach to develop an intelligently adapting responsive stimulator that tracks the progression of seizure genesis mechanisms (*before* electrographic seizure onset) and is able to steer the spatio-temporal dynamics of the epileptic network away from reaching seizure onset altogether. The closed-loop feedback controller will dynamically tune stimulation parameters to hinder seizure initiation according to measurements of neurophysiological activity, making it patient-specific. Additionally, the development of such a system would provide critical insight into neurophysiological mechanisms involved in ictogenesis and epileptogenesis, as well as controllability of epileptic networks through multisite feedback-based stimulation. This, may lead to new approaches to improve treatment strategies for epilepsy patients [28].

### C. APPROACH

We plan to construct a closed-loop controller for seizures that steers the network away from seizure initiation at all times. To design and validate this closed-loop neuromodulation system, we will perform *in vivo* experiments that will provide us with valuable neurophysiological data required to meet our goals. Experiments will be based on a well-characterized *in vivo* chronic rat model of focally induced temporal lobe seizures [2]. Epilepsy will be induced in two groups of 20 rats. In each group, rats with higher frequency of seizures will be implanted



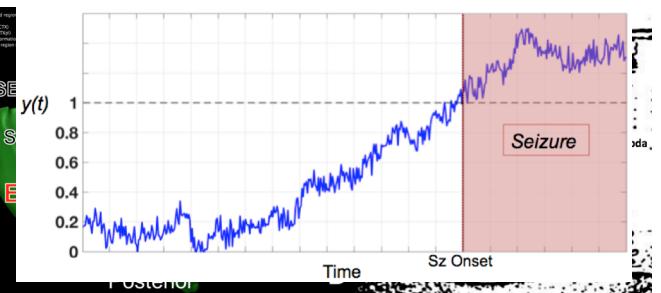
**Figure 1:** A-C show a three-dimensional representation of the hippocampal formation and Entorhinal Cortex [40]. A) Frontal hippocampal view, blue points mark the anterior recording MEA (REA). The stimulation site of the ventral hippocampal commissure is shown in black (SEVC). B) Shows in red the chemoconvulsant injection site in the CA3 region of the hippocampus to induce status epilepticus (SE) and the subsequent development of SRS. Induced SE arises within the first half hour of KA injection, and lasts several hours. Then after a few days, SRS start to appear and increases in frequency over the course of the disease. This approach models human temporal lobe epilepsy, as it resembles the development of focal-onset, secondarily generalized SRS with a progression of severity over the course of induced epilepsy [3]. Furthermore, it replicates the dynamics of mesial temporal lobe seizures in humans, which is the most common surgical case [14,34,42]. Additionally, this model was selected because it induces slowly evolving seizures, allowing us to monitor the temporal dynamics of epileptic network behavior as it reaches seizure initiation. We will monitor neural activity by recording LFPs from the CA1 region of the hippocampus using MEAs.

The chronic model consists of the application of kainate acid (KA), a neurotoxin analog of glutamate. A local injection of 0.4 µg of KA is administered into the CA3 region of the hippocampus to induce status epilepticus (SE) and the subsequent development of SRS. Induced SE arises within the first half hour of KA injection, and lasts several hours. Then after a few days, SRS start to appear and increases in frequency over the course of the disease. This approach models human temporal lobe epilepsy, as it resembles the development of focal-onset, secondarily generalized SRS with a progression of severity over the course of induced epilepsy [3]. Furthermore, it replicates the dynamics of mesial temporal lobe seizures in humans, which is the most common surgical case [14,34,42]. Additionally, this model was selected because it induces slowly evolving seizures, allowing us to monitor the temporal dynamics of epileptic network behavior as it reaches seizure initiation. We will monitor neural activity by recording LFPs from the CA1 region of the hippocampus using MEAs.

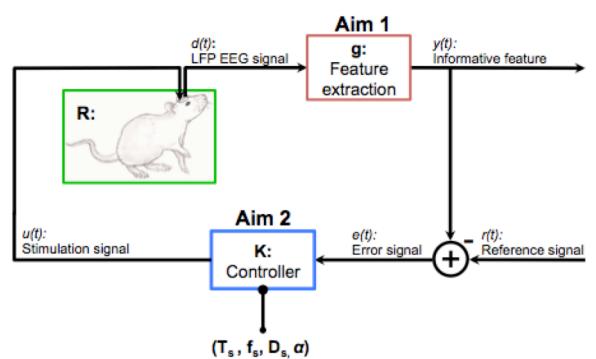
Approximately eight weeks after KA injection, rats will be video monitored for a period of 24 hours to quantify seizure frequency and severity. Rats that show a higher seizure frequency (i.e. more than three seizures in 24 hours) will be implanted with chronic recording and stimulation MEAs as shown in Fig. 1D. Our innovative recording–stimulation strategy entails 5 craniotomies. Two craniotomies will be used to record from the anterior (REA), and posterior (REP) portions of the hippocampus. The other three craniotomies will be used for stimulation: 1) ventral hippocampal commissure (SEVC), 2) dorsal portion of the perforant pathway (SEDP), and 3) ventral portion of the perforant pathway (SEVP).

The simultaneous recording of anterior and posterior portions of the hippocampus will enable us to track the propagation of epileptic activity throughout the ipsilateral hippocampus and towards the contralateral hippocampus. Multi-site stimulation of the previously mentioned white tracts will enable us to selectively stimulate different portions of the hippocampus, an innovative strategy that will empower our closed-loop feedback controller to drive the network away from seizure initiation.

Our specific aims represent two sets of experiments necessary to gain scientific insight into preictal dynamics and develop the proposed closed-loop controller shown in Fig. 2. For **Aim 1**, we will record LFPs from our animal model to observe the evolution of network dynamics as the seizure onset approaches. Offline analysis of the data collected will be done to design a computational algorithm ( $\mathbf{g}$ ) that transforms the LFP signal into a set of informative features of network behavior during seizure initiation. For **Aim 2a**, we will construct the controller,  $\mathbf{K}$ , by studying the changes produced in LFPs under different stimulation settings at different neurological states leading to seizure onset. Specifically, we will



**Figure 2:** Expected informative feature behavior. The outcome for the behavior of the rat shown, where a unit value is reached at seizure onset, and greater values represent ictal activity.



**Figure 3:** Closed-loop system block diagram for seizure control.  $d(t)$  is the LFP signal,  $y(t)$  is the informative feature scalar or vector,  $r(t)$  is the reference value,  $e(t)$  the error signal to minimize,  $u(t)$  is the electrical stimulation signal with parameters parameters:  $T_s$ ,  $f_s$ ,  $D_s$  and  $a$ .  $\mathbf{g}$  is the feature estimator,  $\mathbf{K}$  is the controller that computes the change in stimulation parameters as a function  $y(t)$  and generates the control input  $u(t)$ .

perform a grid search over electrical stimulation parameters (i.e. signal period ( $T_s$ ), frequency ( $f_s$ ), duty cycle ( $D_s$ ) and signal gain ( $\alpha$ )) to determine which type of stimulus is able to better delay seizure initiation and characterize the relationship between type of electrical stimulation and the dynamic response observed in the epileptic network through the informative feature behavior. This will result in a controller ( $K$ ), that dynamically computes the change in stimulation parameters to drive the informative features, ( $y$ ), to a desired reference value associated with low-risk of seizure initiation. For **Aim 2b**, we will test the performance of the closed-loop controller in preventing preictal activity from reaching seizure onset in a long-term setting.

**Sample Sizes:** An experimental proposal of 70 rats will be submitted to the Technion's Animal Care and Use Committee (ACUC). This number was estimated taking into account, training (20), a control group (20) and experimental errors (20) such as mortality and failure to induce epilepsy and/or bad quality recording as well as statistical significance needed for each of the two sets of experiments. Epilepsy will be induced in two groups of 20 rats each, 10 male and 10 female per group. The first group will be used for Aims 1,2a, and the second for Aim 2b. Although we cannot perform formal statistical analysis as we do not know the variability of the experiments (and variability and statistical power is different for paired and unpaired experiments). However, based on our previous experience and data from the literature, a 10 rodent group can detect a 20% difference in paired experiments (same rat different stimulation conditions) and a 35% change in unpaired experiments.

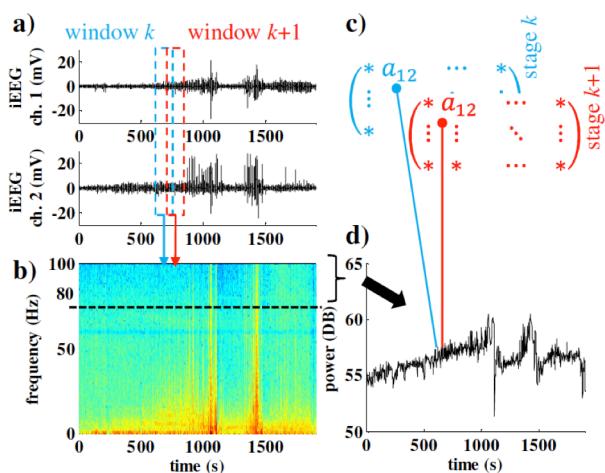
### **Aim 1: Identify features of network behavior sensitive to neural activity that leads to seizure initiation.**

**Rationale.** Our *in vivo* rat models produce a recurring pattern for seizure genesis that has been characterized as a multiple-state mechanism [9,33,34]. Recent studies have shown that between chemoconvulsant application and seizure initiation, there is a gradual increase in firing rates of individual neurons [33,34], this is a constant observation in both acute and chronic models [1,2,3,33,34]. Additionally, it was also shown that interneuronal synchronization decreases initially and re-emerges as the seizure onset approaches, eventually reaching a hypersynchronized state [35]. The early desynchronization in development of seizures suggests that there must be a functional dissociation of the epileptic network from normal network activity, and that seizures could be a network-driven phenomenon. We thus hypothesize that network-based statistics derived from matrix theory can be used to extract informative features of network behavior leading to seizure initiation.

**Methodology.** Induction of epilepsy will be performed on the first group of rats using our chronic epilepsy model as described above and in [2]. Recording of hippocampal seizures will be performed after 3 months of KA injection to ensure a high incidence of seizures. LFPs will be recorded through MEAs, and digitalized and acquired by our ME-16 amplifier (MCS, Germany) for posterior offline analysis. While it is not possible to perform power analysis, our choice of 20 rats is based on recent studies of this model system. (While not expected, we will look for sex-specific trends in this and subsequent experiments; such trends if found may necessitate additional animals to increase statistical power).

**Analysis.** Multivariate analysis of the LFP signal will be performed using a sliding window approach to compute the maximum singular value of the connectivity matrix. To achieve this, each LFP signal will be treated as a node in a graph, where any two nodes are considered connected (i.e., an edge exists between them) if there exist statistical dependencies between nodes in a given time window  $t$ . The connectivity (topology) of the graph is then described by the connectivity matrix,  $A(t)$ , which is defined as the matrix whose elements are the cross power spectrum between each pair of LFP signals in a chosen frequency band (i.e., theta, alpha, etc.). The function derived in this aim ( $g$  from Fig. 2) computes an informative feature from  $A(t)$  by sliding the window to generate  $y(t)$ , which modulates during seizure genesis. Initially, we will compute the maximum singular value of  $A(t)$  such that  $y(t) = \sigma_{max}(A(t))$ . The maximum singular value,  $\sigma_{max}(A(t))$ , is a coarse summary of the network connectivity. If all nodes are equally connected, then  $\sigma_{max}(A(t))$  is "large" compared to  $\sigma_{min}(A(t))$ , and if the network is disconnected, then  $\sigma_{max}(A(t))$  is "small" compared to  $\sigma_{min}(A(t))$ . Here,  $\sigma_{min}(A(t))$  is the minimum singular value of  $A(t)$ .

**Preliminary Data:** Fig. 4 shows data from our previous study where the proposed approach was implemented for two male Sprague-Dawley rats with a local application of a chemoconvulsant (pentylenetetrazol) to the anterior thalamus [35]. The high-gamma frequency band (80-100 Hz) cross power spectrogram was used to compute the connectivity matrix  $A$  over a five-second sliding window of LFPs every second, which results in a sequence of matrices  $A(t)$ , one per second  $t$ . From each connectivity matrix, we computed the maximum singular value,  $\sigma_{max}(A(t))$  at each second as our informative feature to track the time-varying complexity in epileptic network behavior as it reaches seizure initiation [29,35]. The maximum singular value of the connectivity matrix comprises an informative feature of network behavior as it shows a gradually increasing trend starting several minutes before the seizure onset until seizure termination, where it abruptly decreases. By using  $\sigma_{max}(A(t))$  as our informative feature, we can evaluate the state of present neurological activity in the



**Figure 4.** (Left) a) 2 EEG signals; b) cross power spectrum of 2 signals; c) representation of cross power in connectivity matrix; d) maximum singular value computed over time from sequence of connectivity matrices. (Right) a) 2 raw EEG signals; b) max singular value over time.

epileptic network as well as identifying a threshold that when crossed seizure evolution is imminent. This information will be employed by the closed-loop controller to tune its stimulation parameters according to the neurological state in order to prevent it from reaching the identified threshold.

**Alternatives.** Other possible alternatives to derive informative features of network behavior sensitive to seizure onset activity include the extraction of phase-lock values from the LFP signal [43]. Alternatively a set of multiple features can be used with a machine-learning algorithm to classify states leading to seizure initiation [44]. Previous studies have characterized several features including entropy, complexity and spectral features for early seizure onset detection [45]. The extraction of complexity features such as Higuchi fractal dimension and Lempel-Ziv complexity could prove valuable for tracking network behavior of the epileptic network [45].

**Outcomes.** The derivation of  $\mathbf{g}$ , will yield an informative feature that has a repetitive behavior throughout seizure evolution. We plan to derive  $\mathbf{g}$ , such that  $y(t)$  has values between 0 and 1 for all interictal activity. At seizure onset  $y(t)$  will reach a unit value and keep increasing until seizure termination, as illustrated in Fig. 3.

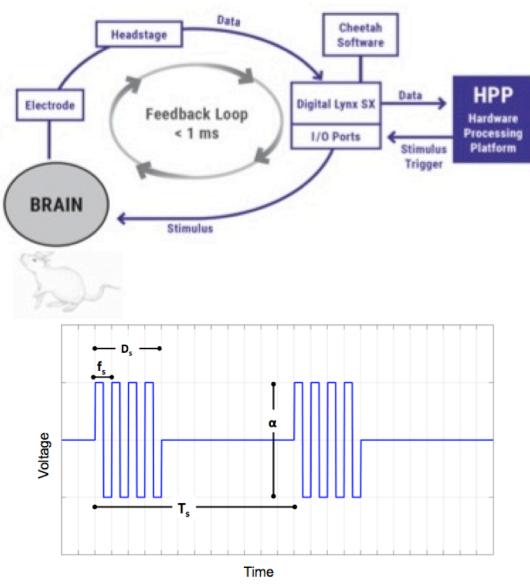
### Aim 2: Design and validate closed-loop feedback controller to prevent seizure initiation.

**Rationale.** Electrical stimulation has proven to be capable of modulating brain activity. Moreover, electrical stimulation has shown to be capable of: shortening seizure duration [25], decreasing seizure frequency [20], modulating network excitability and seizure modification [46,48], and suppressing seizures after their electrographical onset [9,21,46,47]. We thus hypothesize that electrical stimulation can suppress epileptogenic activity and delay seizure onset. Furthermore, it has been shown that seizure genesis mechanisms progressively change the temporal dynamics and behavior of the epileptic network reaching a hypersynchronized state [34]. Therefore, it is reasonable to assume that in order to suppress seizures, a dynamical stimulus must be applied in accordance to present neuronal activity.

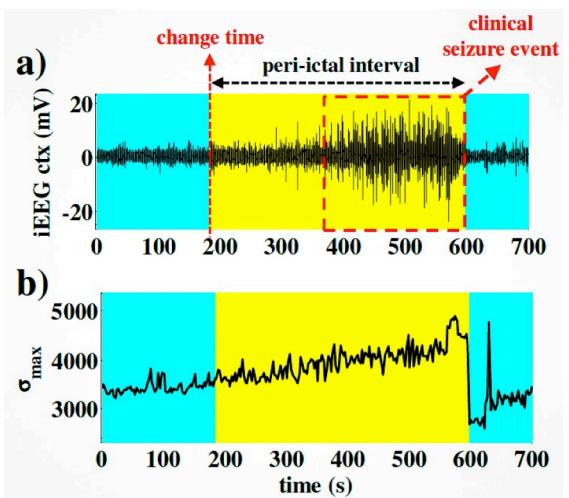
Closed-loop stimulation systems present a novel technique that has proven to have positive results to drive neurological activity and suppress seizures [21-26,46]. We hypothesize that control theory can be used to design a feedback controller that dynamically constructs the best set of parameters to drive neurological behavior away from seizure initiation mechanisms and prevent seizure onset.

### Aim 2A: Closed-Loop System Identification of Stimulus-Response Dynamics

**Methodology.** Closed-loop experiments in the first group of rats will be carried out after 6 months of intrahippocampal KA injection to perform a grid search of stimulation parameters (Fig. 5). We will use our chronic animal model to deliver electrical stimulation to the dorsal-anterior hippocampus through the



**Figure 5.** (Top) Hardware implementation diagram. (Bottom) Biphasic electrical stimulus. Time series of the electric stimulation signal, parameters are: period ( $T_s$ ), frequency ( $f_s$ ), duty cycle ( $D_s$ ) and signal gain ( $\alpha$ ).



ventral hippocampal commissure, and to dorsal and ventral portions of the posterior hippocampus through the perforant pathway . This will be done using different parameters at different times to observe the changes induced in our informative feature. In Fig. 5, we illustrate the stimulation signal that will be used and the parameters to vary. Multiple stimulation frequencies will be explored given the fact that positive results have been shown using different stimulation frequencies to suppress seizures. It has been shown that frequency above 40 Hz, leads to polysynaptic inhibition decreasing network excitability [48]. While another study showed that high frequency (500 Hz and 1000 Hz) stimulation is more effective at shortening seizure durations [25]. Finally, low-frequency electrical fields have also been locally applied to successfully suppress ictal activity [22,46]. However, the most efficient approach would be to modulate the stimulation frequency, duty cycle, and signal gain according to ongoing neural activity as it has been shown that the phase component of the epileptic network is of great importance to design a stimulation protocol that desynchronizes it effectively [49].

Implementation and Hardware: We will record multi-unit activity through MEAs, the LFP signal acquired will be then digitalized and acquired by our Digital Lynx 4SX. The Digital Lynx 4SX will be paired with the Hardware Processing Platform (HPP), by Neuralynx, which is capable of doing sub-milisecond real-time processing of data and then execute a stimulus trigger using the Digital Lynx 4SX analog and digital outputs. This is possible given that the HPP is integrated by a Xilinx Zynq XC7Z030 FPGA. Traditionally a Field Programmable Gate Array (FPGA) is a programmable logic and memory device. It is very high density so it can support complex logic designs (custom processors, digital filters, etc.). The FPGA used on the HPP also contains a CPU. The combination of the FPGA logic and CPU allows the intensive tasks to be handled by the FPGA logic and the control/communication to be handled by the CPU. This results in a very fast and efficient architecture for *processing* large amounts of data simultaneously (perfect for real time processing of many acquisition channels). Through the integration of the Digital Lynx 4SX and the HPP, we can build a state of the art real-time closed-loop feedback controller.

Analysis of Parametric Search Data. We will do real-time tracking of the informative feature,  $y(t)$ , while we deliver different electrical stimuli at different times before the epileptic network reaches seizure onset to analyze which stimulation parameters best delay the seizure onset. This will be done through a grid search of the electrical stimulus parameters, in order to characterize the stimulation effects in neural activity, i.e. between the input (stimulation) and output (features). This is possible since for each trial we know which stimulation parameter is varied, and which electrical stimulus,  $u(t)$ , is delivered. Moreover we also know the feature extraction algorithm ( $g$ ). We then define the control signal  $u(t)$ , as:

$$u(t) = \alpha(e) \cdot s(t; T_s(e), f_s(e), D_s(e)) \quad (1)$$

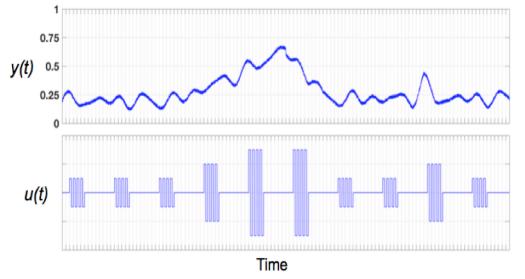
Where  $s(t)$  is a stimulation signal with parameters that change as a function of  $e(t) = y(t) - r(t)$ , as illustrated in Fig. 6. Once we find the optimal stimulation parameters to delay the seizure onset, we will build a computer controlled feedback system that uses the error signal as a basis for feedback. This will result in the design of a dynamic feedback controller ( $K$ ) that drives the epileptic network away from reaching seizure initiation ( $y(t) < 1$ ). Specifically, optimization of our controller will be done such that minimum energy is delivered to the epileptic network as follows:

$$\min_{s,\alpha} \|e(t)\|_2 \quad s.t. \quad \|u(t)\|_2 < \gamma \quad \forall t \quad (2)$$

Note that the optimization will be done over quantized values of  $e(t)$ . That is, for each quantized set of values for  $e(t)$ , there will be an associated optimal set of parameters  $\alpha$  and  $T_s, f_s, D_s$ .  $\gamma$  is our energy tolerance level.

Alternatives. Stimulation of a single target may not be sufficient to control seizures. In some patients, seizures emerge from the interaction of multiple nodes within a network. Therefore, stimulation of more than one node in the network simultaneously may be required to improve seizure control. One approach to simultaneously modulate multiples nodes within a seizure network is to stimulate nuclei or fiber tracts that have widespread modulatory effects [28] or to deliver multiple coordinated stimuli at different sites to desynchronize the epileptic network [47]. Also, it has been shown that low-frequency electric fields can be used to entrain field postsynaptic potential discharges during seizures to a certain frequency [27]. These entrained seizures, can then be more easily suppressed through phase-locked stimulation or coordinated reset to antagonize the frequency the seizures were entrained to [47,49,50].

Outcomes. The different analyzed stimulation protocols and derivation of the controller will provide us with valuable new insight



**Figure 6:** Outcome expectations. Shows the expected behavior between the output,  $y(t)$ , and the electrical stimulation signal,  $u(t)$ .

into preictal dynamics and identify which electrical stimulus parameters are most effective in hindering the epileptic network from reaching seizure onset. We expect that by delivering the appropriate electrical stimulus after 4-AP administration for certain values of our informative feature, seizure initiation mechanisms will be blocked. Furthermore, we expect that the optimal controller will effectively modulate neural activity and drive the epileptic network away from a high-risk neurological state of seizure initiation. As illustrated in Fig. 6, we expect that the controller will dynamically deliver electrical stimuli according to the neurological state described by the informative feature in order to stabilize the epileptic network.

### **Aim 2b: Validate of our closed-loop feedback controller with a chronic epilepsy model**

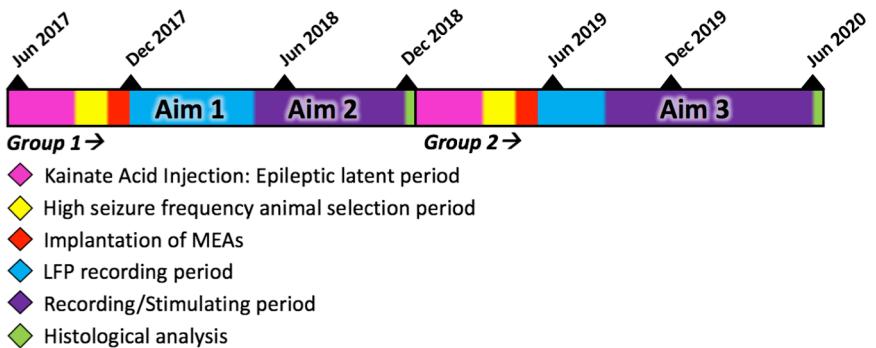
This set of experiments will be performed to design and test the feedback controller. We will perform closed-loop experiments to design tune a model-based control system, based on the model identified in Aim 2a. The control goal will be to stabilize the epileptic network to a desired reference value ( $r(t)$  in Fig.2) at which the controller will try to minimize the error in relation to the real-time measurement of the informative features using minimal energy consumption. **It is important to note that most of the aforementioned studies aim to suppress ictal activity once the electrographical onset of the seizure is detected. In this study, we plan to deliver electrical stimulation continuously in order to prevent the epileptic network from reaching seizure initiation by tracking the informative features derived in Aim 1.** The design and validation of our algorithm on the same chronic epilepsy model will give us an idea on the applicability of our approach to treat temporal lobe epilepsy in humans [1,3].

**Methodology.** Induction of epilepsy will be performed on the second group of rats as described above and in [2]. After 6 months of KA injection, closed-loop experiments will be carried out to validate our closed-loop feedback controller. A set of 10 chronic models will be used as a control group that will not receive any treatment (sham surgery). Animals will be implanted with MEAs in the CA1 region of the anterior and posterior hippocampus approximately 3 months after KA application to the CA3 region of the posterior hippocampus. Following SE, animals will be video-monitored for the appearance of SRS. Then we will implement our closed-loop algorithm and record LFP for a period of two weeks in our test group. Specifically, in these experiments we will compare the frequency, duration and severity of seizures during our closed-loop stimulation to a control sham stimulation group, where the stimulus intensity of our closed-loop system will be set to 0. This will be done at different stages of the disease, to further evaluate the performance under different severities of the disease.

**Analysis.** Offline statistical analysis will be performed to evaluate the effectiveness of the developed algorithm at different stages of disease severity of our chronic epilepsy model. In particular, seizure frequency and duration will be measured and compared between the test and control groups. Rats will be video-monitored every 2 weeks for a period of 24 hours to track different stages of the disease in pairs of animals, to further evaluate the performance under different severities of the disease. Severity of seizures will be evaluated according to the modified Racine scale [4]

**Outcomes.** Results from these experiments will allow us to evaluate the robustness and efficacy of our closed-loop controller for a rat model of temporal lobe epilepsy. Our chronic epilepsy model is considered to resemble human temporal lobe epilepsy, as it has a focal-onset, secondarily generalized SRS and a progression of severity over the course of induced epilepsy [3]. Therefore the results will determine if our algorithm is a convincing technique for the closed-loop control of temporal lobe epilepsy in humans. This could provide an alternative to resective surgery for epilepsy patients.

**Timeline:** Dr. Schiller and Dr. Assaf have performed similar animal experiments several times; Dr. Sarma has extensive experience analyzing EEG data and is trained in systems and control theory; and Dr. Cowan, also trained in systems and control theory, has successfully implemented closed-loop control systems in fish and rats. Specifically his lab deployed a closed-loop system that changes optic flow cues, based on the real-time-decoded output of unsorted spiking activity in the hippocampus, as the rat navigates in virtual reality.



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