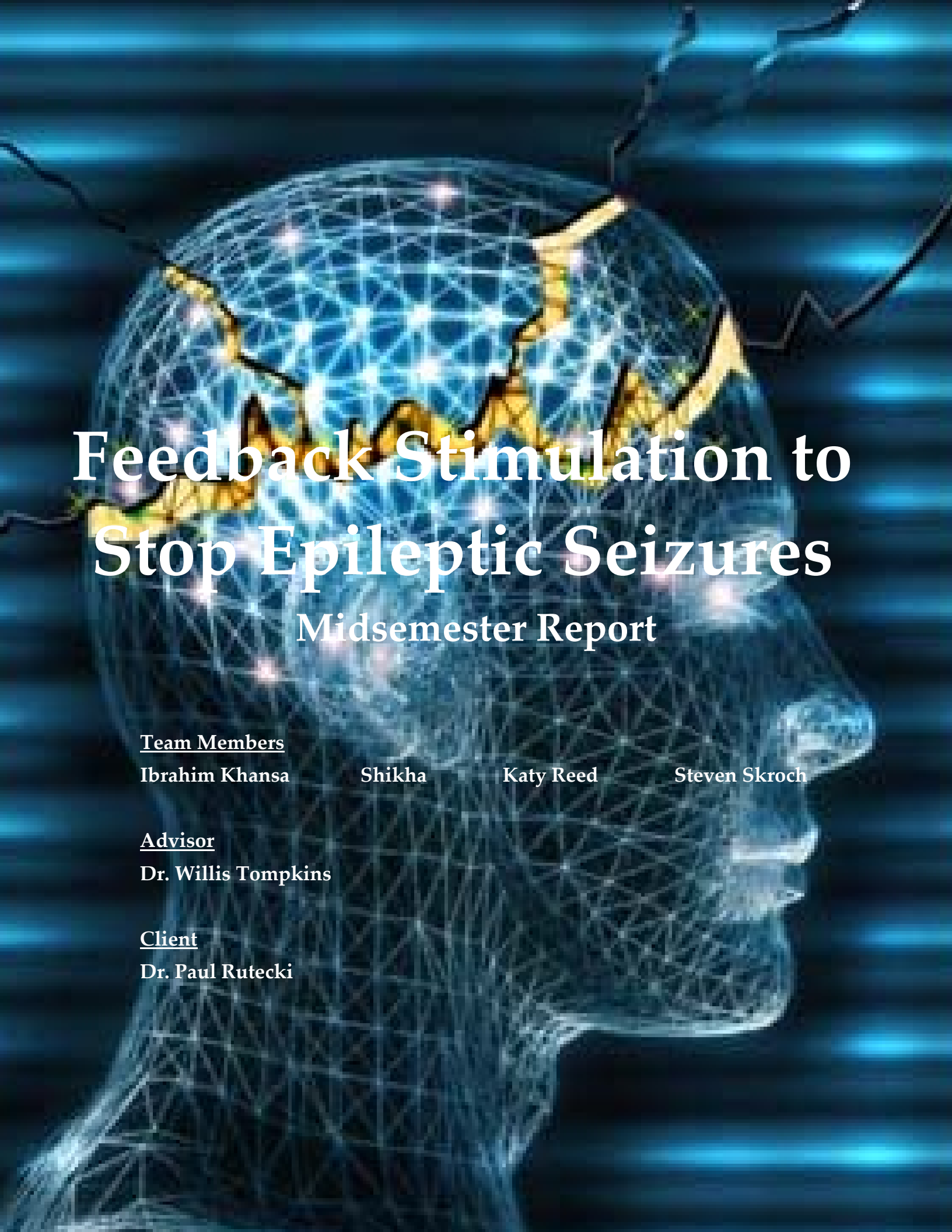

Feedback Stimulation to Stop Epileptic Seizures

Midsemester Report

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Client

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Abstract

A seizure-activated brain slice stimulator, analogous to a heart defibrillator, is proposed. The stimulator consists of a feedback-controlled algorithm built in LabVIEW, and is intended as a research aid for determining the ideal stimulus characteristics that can abort a seizure. The algorithm will be capable of multiple prediction, detection and stimulation modes, and will monitor its own performance by checking its ability to detect most seizures, while keeping the number of false-positive detection to a minimum. The stimulator is expected to be completed and installed in the client's lab within the next few months.

Background

I. Epilepsy and Effects

Stedman's Medical Dictionary defines epilepsy as "a chronic disorder characterized by sudden brain dysfunction due to excessive neuronal discharge, and usually associated with some alteration of consciousness" [1]. This "excessive neurological discharge" is more commonly referred to as a seizure. Seizures are temporary phenomena resulting from abnormal synchronization of electrical neuronal activity in the brain. The physical effects of a seizure range from partial or full body convulsions to momentary spells of impaired consciousness, and its duration ranges from a few seconds to possibly hours.

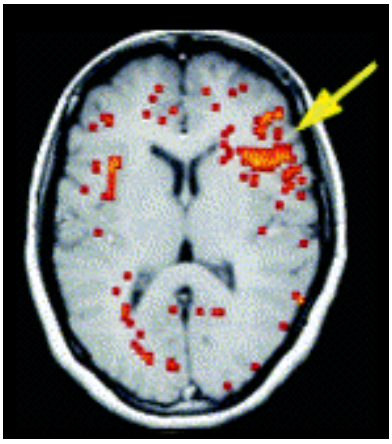

Figure 1: Brain scan of a person with frontal lobe epilepsy. The arrow points to the focus of seizure activity

Epilepsy can have several origins, such as head trauma, degenerative disease, low blood glucose levels, or genetic factors. A seizure may start at any point in the brain, and spread to other regions (figure 1). Certain seizures only happen at certain times, such as during sleep or during the menstrual cycle. Most seizures, however, show no recognizable temporal or causal pattern, and are therefore unpredictable.

Roughly one in a hundred people have epilepsy. Even though epilepsy does not follow any known pattern of genetic inheritance, the chances of expressing the disease increase four-fold in case a close

relative (mother, brother, child) also has it. Genetic factors are not major determinants in epilepsy caused by brain injuries after birth [2].

II. Current Treatments

The most common types of treatment are anti-seizure and anticonvulsant medications. Anticonvulsant medications work by interacting directly with the nervous system. They prevent or slow the pain caused by damaged nerves [3]. The current drug therapies are only effective for 70% of epilepsy sufferers. Currently there are about 20 seizure medications on the market. These drugs can not be used to stop a seizure in progress, only to prevent them. Often, multiple anti-epileptic drugs are used to keep the seizures under control. Furthermore, these drugs have a wide range of possible side effects including allergic reactions, vision problems, nausea, drowsiness, irritability, weight loss or gain, headache, insomnia, hair loss or growth, menstrual problems, depression, dizziness, gum overgrowth, acne, nervousness, mood changes, kidney stones, interaction with hormonal contraceptives, and birth defects (if used during pregnancy) [4].

Vagus Nerve Stimulation (VNS) is a treatment for seizures in which a “brain pacemaker” is used to deliver pre-programmed electrical impulses to the brain through the vagus nerve, a cranial nerve involved in the control of speaking, swallowing, and coughing [5, 6]. The device is implanted in the anterior chest wall and is connected to the left vagus

nerve by a wire. The stimulation settings are customized to each person's needs, but are most often 30 second pulses every 5½ minutes [1]. Stimulation of the vagus nerve may cause hoarseness, coughing or similar side effects. Microwaves and radios should also be avoided. Moreover, the device does not monitor or respond to the electrical activity of the brain, but stimulates rhythmically instead (open-loop neurostimulation[1]).

Another potential seizure treatment is focal cooling of the region of origin of the seizure [7]. In this technique, a thermoelectric probe reduces the temperature of a small area of the brain to around 20° C, reducing neural activity and stopping the seizure. This method is still experimental.

Client

Our client, Dr. Paul Rutecki, is investigating the possibility of using electrical stimulation to abort spontaneous seizures in slices of rat hippocampus (the technique is described in [8]). Stimulation is rhythmically administered to the slices, independently of their electrical activity (open-loop neurostimulation). A signal generator is used to create the stimulation, which consists of several square pulses at a frequency of 100–150 Hz. He hopes to be able to stimulate in response to predicting or

[1] Open-loop neurostimulation is done rhythmically, at set time intervals, not in response to a seizure.

detecting a seizures (responsive neurostimulation[2]), in order to maximize the efficiency of the stimulation.

Problem Statement

In order to abort epileptic seizures, or prevent their occurrence, electric shocks must be administered to the neurons where the seizure is originating. An algorithm, capable of measuring an electroencephalogram from slices of rat hippocampus, predict or detect a seizure, and send an electric stimulus to the neurons, is needed. The generation of the electric stimulus has to be effected in response to clear changes in the EEG that may preclude the occurrence of a seizure. The algorithm needs to check its own performance by operating in a feedback loop. This feedback loop will learn from its own mistakes.

Systems currently in use

Figure 2: The NeuroPace implantable RNS

The NeuroPace Responsive Neurostimulator (RNS) (US Patent No. 6,810,285) is a commercial EEG-based seizure detection and stimulation device. It is currently undergoing FDA clinical trials, and is still listed as an "investigational device", limited to

[2] Responsive neurostimulation is done in response to a seizure

scientific endeavors only **[9]**. The RNS system integrates the area under the positive parts of the EEG, and stimulates using two electrodes in case that area exceeds a threshold value. The pre-programmed threshold is determined experimentally on a per-patient basis. Right after device implantation, the device goes through a period of "learning", during which no stimulation is administered, but data are simply recorded and transmitted to a computer via a wireless link through the scalp. Typical ictal EEG areas for that patient are determines, and a threshold value is chosen.

Other brain stimulation devices, such as the Medtronic Activa or the NeuroCybernetic Prosthesis (NCP) from Cyberonics stimulate the brain to reduce seizure activity, but do not have any seizure detection abilities.

Design Requirements

There are three main design constraints, and one additional optional feature:

1) A high percentage of seizures must be predicted before they occur, or detected as soon as they occur.
2) Electric stimuli must be administered in response to seizure prediction/detection. This can be done either through the client's existing hardware, or through a new signal generator.

3) The algorithm must keep its own performance under check by operating in a feedback loop. In case of failure to abort a seizure, stimulation must be repeated until success.
4) (Optional) The algorithm can build a training set by keeping track of every failure to abort a seizure.

Our priorities in this project

In this project, we aim to satisfy the client's requirements as thoroughly as possible.

1) Versatility: The algorithm is intended as a research aid. Therefore, there should be as few rigid features as possible. It is essential to us that the client be able to adjust as many parameters as possible, as his research progresses, and as his knowledge of the optimal detection and stimulation methods advances.
2) Integration: The prototype needs to integrate nicely within the existing infrastructure at our client's laboratory. This includes the electrodes, amplifiers, computers, and other pieces of hardware.

Designs considered

The following is an account of all the design alternatives that have been considered so far. This section is structures by prototype component:

I. Seizure prediction

Stimulation has been shown to be most effective if administered early, before the onset of seizure [10]. Such early stimulation is only possible if the seizure can be predicted, by the observation of changes in the EEG. In some instances, such as the seizure in figure 3, preictal[3] pulsations may be detected. In most cases, however, no clear changes in amplitude or frequency are observable, as in figure 4.

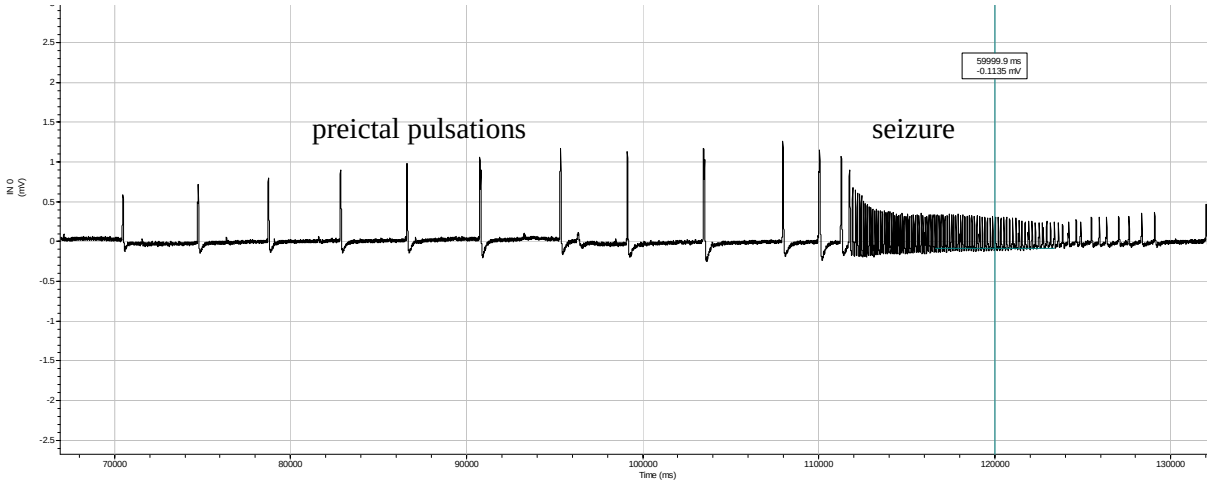

Figure 4: Some seizures are preceded by preictal pulsations. These can be used to predict a seizure.

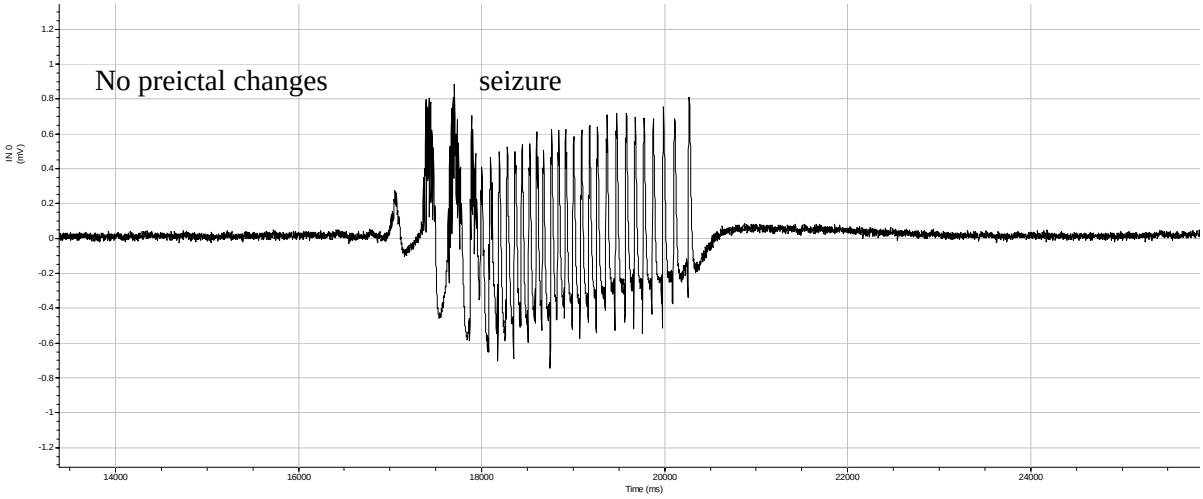

Figure 4: Most often, no changes in the EEG are visible before a seizure occurs.

[3] Preictal = Occurring just before a seizure

Since, most often, there are no clear changes in frequency or amplitude just before a seizure, nonlinear statistical methods must be used [11, 12]. The basis for such methods lies in the fact that preictal EEG stems from different cellular mechanisms than normal interictal[4] EEG. If those interictal and preictal modes can be compared, differences can be found and used to predict seizures. Two such comparison methods have been considered.

a. Analysis of Similarity

This method, described in [13], renders a similarity index which reflects the probability that two signals arise from the same underlying mechanisms. The index of similarity of two 30-second segments of interictal EEG will be close to 1, since those two segments probably arise from very similar cellular mechanisms. In contrast, the index of similarity between an interictal and a preictal segment will be much lower (around 0.7, according to [14]). These

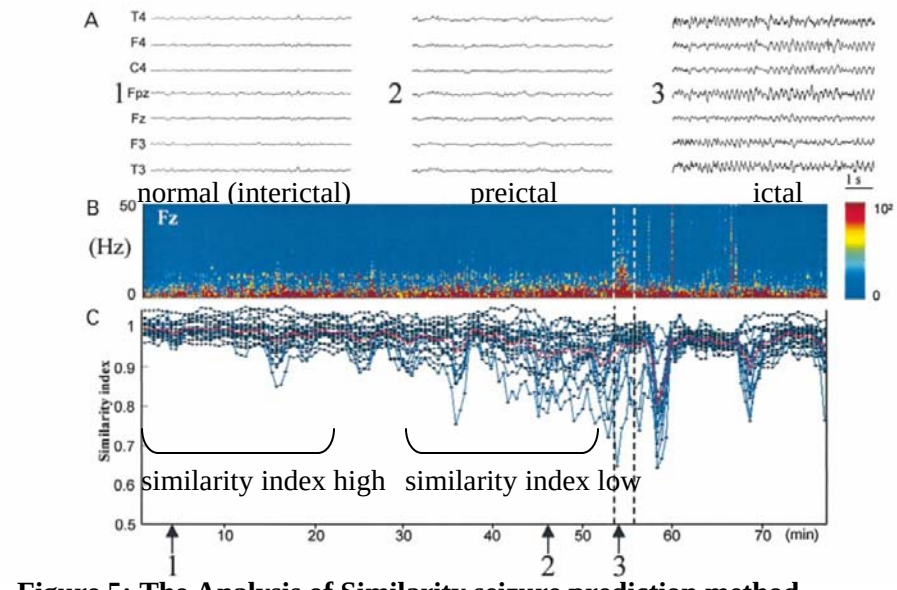

Figure 5: The Analysis of Similarity seizure prediction method

[4] Interictal = Normal, steady-state condition, away from any seizures

similarity measures can be made in real-time, and a similarity index below a certain threshold can be used as an indicator of an oncoming seizure (figure 5).

b. Correlation

A more concrete method would calculate the correlation between segments of EEG and a pre-recorded segment of interictal signal. The correlation between two random distributions x and y, with means $\bar{x}$ and $\bar{y}$, and with standard deviations σ_x and σ_y, is expressed as:

$$\rho_{x,y} = \frac{\overline{xy} - \bar{x} \times \bar{y}}{\sigma_x \sigma_y}$$

Correlations of 1 and -1 show perfect positive and negative dependences, respectively, while a correlation of 0 expresses perfect independence.

II. Seizure detection

Since some seizures cannot be easily predicted, a seizure detection algorithm also needs to be implemented. That algorithm would need to detect the seizure as soon as it starts. Several detection modalities are being considered:

a. Amplitude detection

Amplitude increase is the most obvious change in the EEG that occurs at the onset of seizure (figure 6).

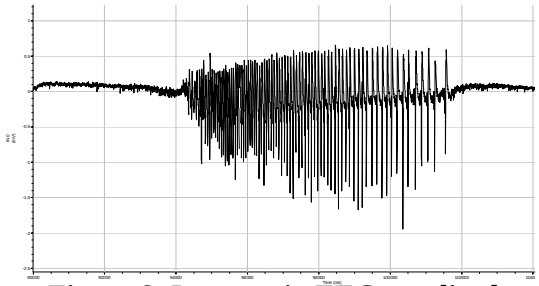

Figure 6: Increase in EEG amplitude at the onset of seizure

The cellular mechanisms responsible for ictal amplitude increase involve the constructive interaction of all the neurons firing in unison. Most seizure show a seizure amplitude of up to 1 mV (compared to less than 0.1 mV for a normal EEG). This makes amplitude change a particularly potent epilepsy detection modality.

Despite its ability to detect most seizures, amplitude-based detection can also give a significant number of false positives. In many instances, amplitude increases do not necessarily correspond to a seizure. The high-amplitude pulsations in figure 7, for instance, are normal, non-epileptic, unicellular pulsations that occur occasionally in the brain.

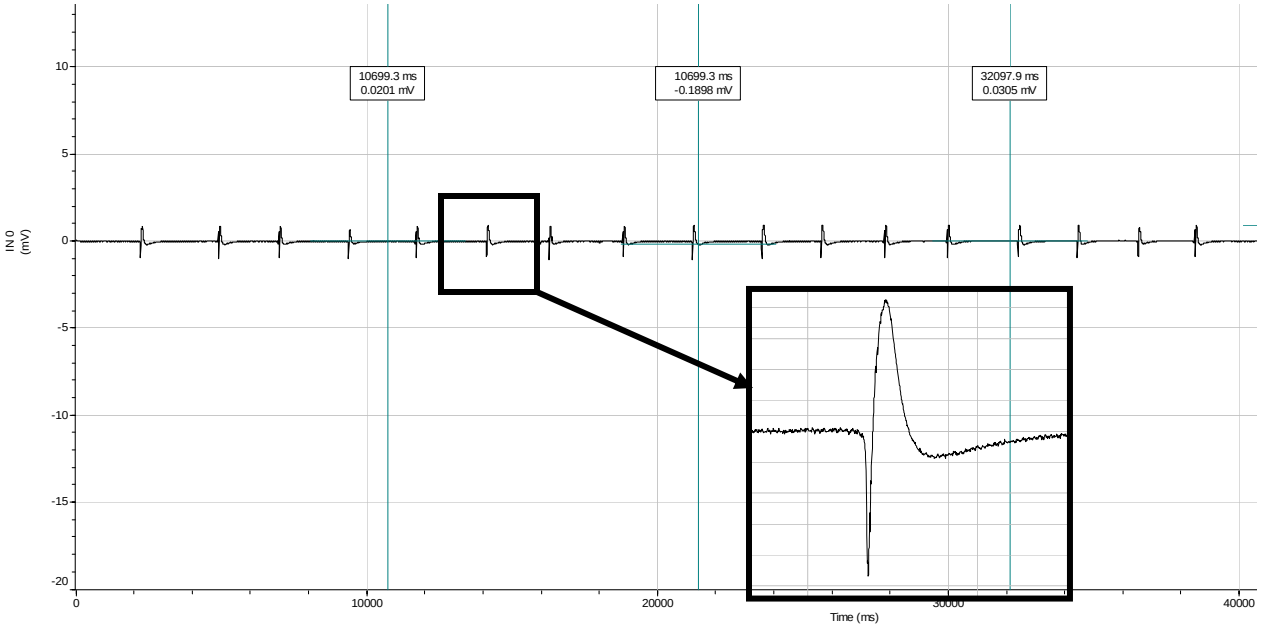

Figure 7: Normal, non-epileptic pulsations occur in some brain slices

b. Frequency detection

Seizures are often accompanied by an increase in EEG power at high frequencies [15, 16]. This frequency increase is particularly pronounced in the 10-100 Hz range (figure 8), and the power at these frequencies may increase by as much as a factor of 10^4. The cellular mechanisms responsible for the ictal frequency increase involve the increased frequency of generation of action potential of neurons, with action potentials occurring as soon as the refractory period of the previous cycle ends.

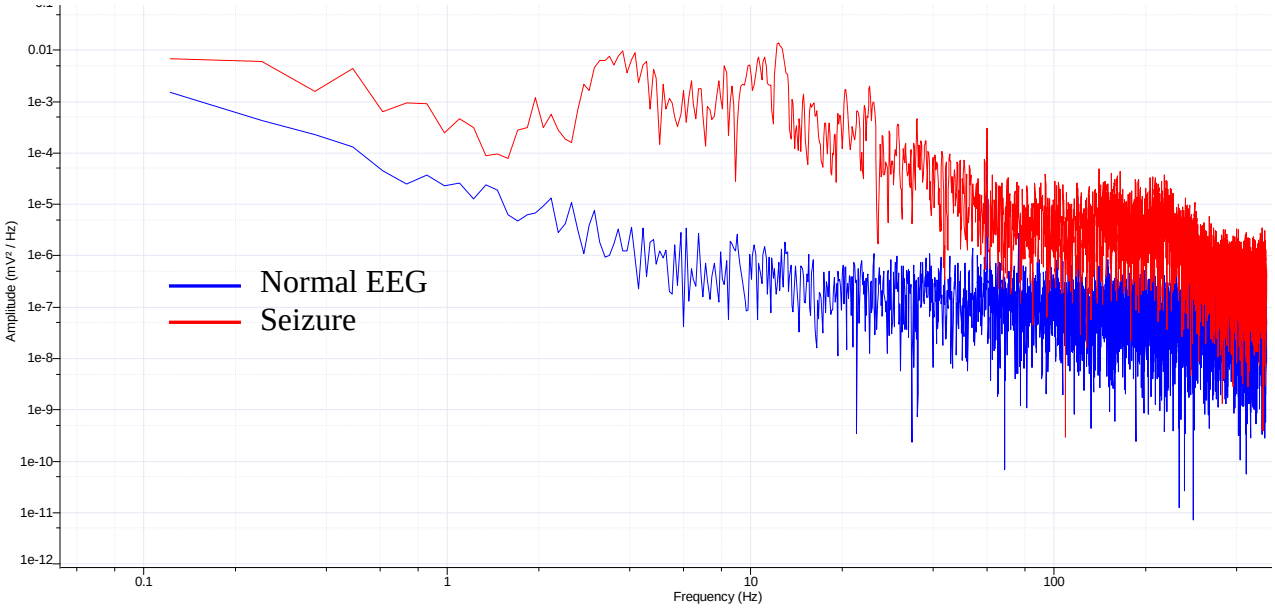

Figure 8: Power spectrum of the EEG before and during a seizure

c. Line length detection

Both amplitude and frequency seizure detection modalities are fairly potent. A method that combines both modalities consists of measuring the average line length per unit time, while the EEG is being acquired. Assigning the EEG to a function f, and taking the real-time derivative

df/dt, the line length of the EEG over a time span of Δt is given by (integral from t0 to t0+Δt of sqrt(1+(df/dt)^2).

Whether the amplitude or the frequency increase, an increase in the length of the EEG line per unit time will be obtained. The line length detection modality is thus particularly reliable.

III. Stimulation

The frequency of action potentials of cerebral neurons has an upper limit, due to the presence of a 2 ms refractory period after every action potential (figure 9). During an action potential, no new stimulation can occur. A normal EEG has a low amplitude, due to the fact that the action potentials of various neurons are out of phase, and thus interact destructively. A seizure, however, is characterized by high amplitude waves, which correspond to large neuron centers all firing synchronously (often described as a domino effect). The underlying mechanism of this sychronous electrical activity lies in the propagation of ions among nearby neurons through gap junctions.

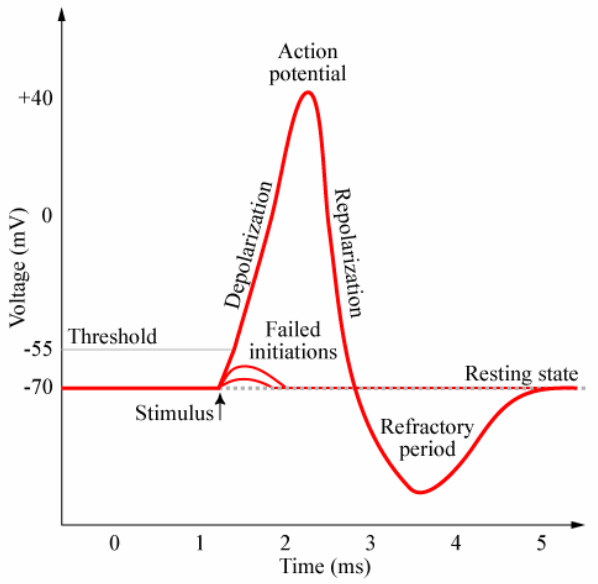

Figure 9: Action potential in a typical brain neuron

When this abnormal activity reaches the motor cortex of the brain, it

will cause visible convulsions. In other types of seizures, the parts of the brain pertaining to consciousness may be affected, causing a blackout.

Electrical stimulation aiming to stop seizure activity causes current to pass through an electrode, into a region of the brain, causing all the neurons in that region to go into excitation and then into refractory period simultaneously. Ideally, all the neurons can be fired before or just as the seizure activity hits. As a result, the refractory period cannot be recruited into the spreading seizure, and the seizure will not spread beyond this point[5].

When passing current through a metal electrode, metal ions will occasionally oxidize and electroplate off. An example of this would be the electroplating of copper: $Cu_{(solid)} \rightarrow Cu^{2+}_{(aq)} + 2e^-$. Over time, this accumulation of ions in the body can have harmful effects. In order to keep this from happening, a charge-balanced stimulation is used, where the total area under the stimulation voltage is zero. This is done to reverse the electroplating reaction, and reduce any metal ions oxidized in the first half of the stimulation. An alternative solution is to use glass electrodes, which are not prone to this problem.

A second potentially harmful effect is heating, since the electrode is very thin and thus has a high resistance. A high current going through the electrode will cause the surrounding tissue to heat up. The solution

[5] This technique is similar to the firefighting method called firebreaking. In order to stop large fires, a small line of fires is sometimes intentionally lit in an effort to consume all flammable material in the path of the large fire. These fires are put out, and the main fire will hit a wall of ash and stop there.

is to use very brief pulses, around 20 μs to 100 μs per pulse. This will allow time to cool down the electrode and surrounding tissue between excitations.

IV. Feedback loop and training set

In order to ensure maximum sensitivity and specificity of the prediction/detection algorithm, a feedback loop must be implemented. After stimulation, the algorithm needs to keep monitoring the EEG for any remnants of the seizure. If the no abnormal activity is detected two seconds after stimulation, then the stimulation was successful in aborting the seizure. Otherwise, stimulation is repeated in an attempt to abort the seizure.

Moreover, in case of failure to stop the seizure, the algorithm exports data to a training set. This set will consist of the EEG parameters detected just before the seizure started, including amplitude, frequency and line length characteristics. The algorithm will then optimize its own detection thresholds based on the data in the training set.

The presence of a training set implies that the detection parameters are in no way fixed, but rather customizable to each hippocampus slice. The researcher need not predetermine any of the detection parameters. Instead, the algorithm will set these parameters itself, based on the first few seizures it detects. This feature maximizes

the versatility of the algorithm, which satisfies one of our main priorities in this project.

Implementation alternatives

In order to implement the four signal treatments outlines in the previous section, the neuronal electrical potential needs to go through several stages: detection, digitization, real-time analysis (including seizure prediction and/or detection), triggering of the stimulation and training set compilation. Several combinations of software and hardware have been envisioned. All these options use common detection and stimulation electrodes. The following three options were found to be the most feasible.

I. Option 1

The client's existing ADC (Digidata 1322A) can be used to acquire the EEG into pClamp. Both of these elements are manufactures by Axon, and are thus compatible. They are, however, incompatible with most seizure detection modules that we may create. This necessitates the introduction of C++ scripts which can acquire data directly from pCLAMP, then analyze it to detect a seizure. Upon seizure detection, an external signal generator, consisting of a 555 timer circuit and connected to the stimulating electrode, is triggered. The 555 timer circuit outputs a square wave, whose frequency and duty cycle can be easily controlled.

Even though this option gives a very inexpensive design, the final product may be too cumbersome for the client. It is also expected that the versatility of the program may be compromised, as it would be hard to obtain complex signal analysis which the client can customize.

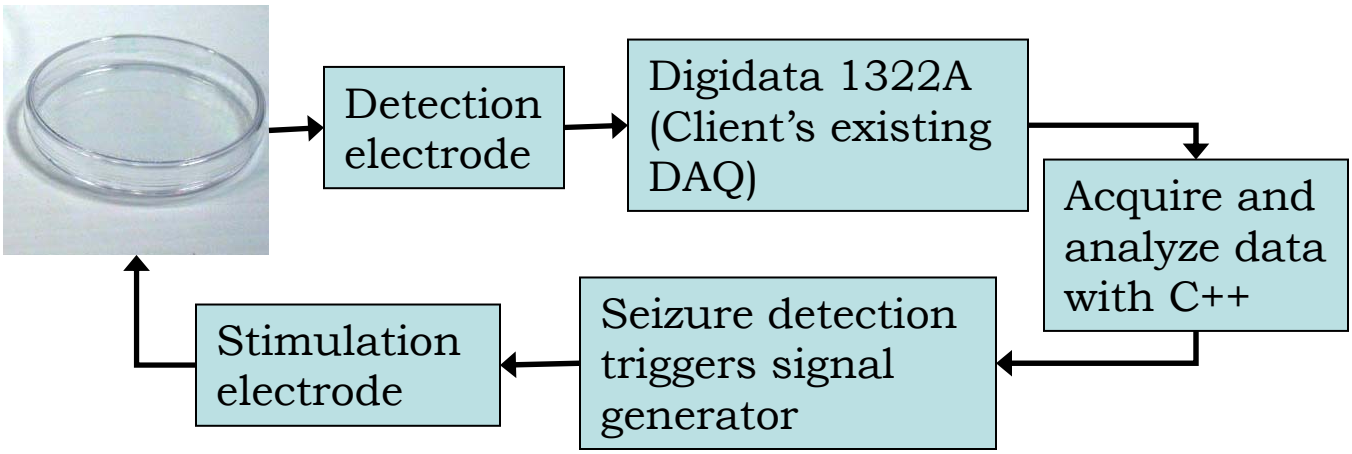

Figure 10: Schematic representation of our first design option

II. Option 2

To resolve the incompatibility between pClamp and our seizure detection modules, an intermediate step can be introduced: the data is exported from pClamp to a text file, in real-time. This text file can then be read by Matlab, and the data can be analyzed. The remaining parts of the design are the same as option 1.

The text export script was obtained from Axon. It has been tested and found to be reliable. It can export the data at a rate of 10 Hz, which is largely sufficient.

This option gives an inexpensive design, and is much easier to implement than option 1. It also allows several detection parameters to

be easily set by the researcher or by the training set, in order to optimize detection. However, the aggregation of several programs may be too cumbersome for the client, and increases the probability of unwanted compatibility problems.

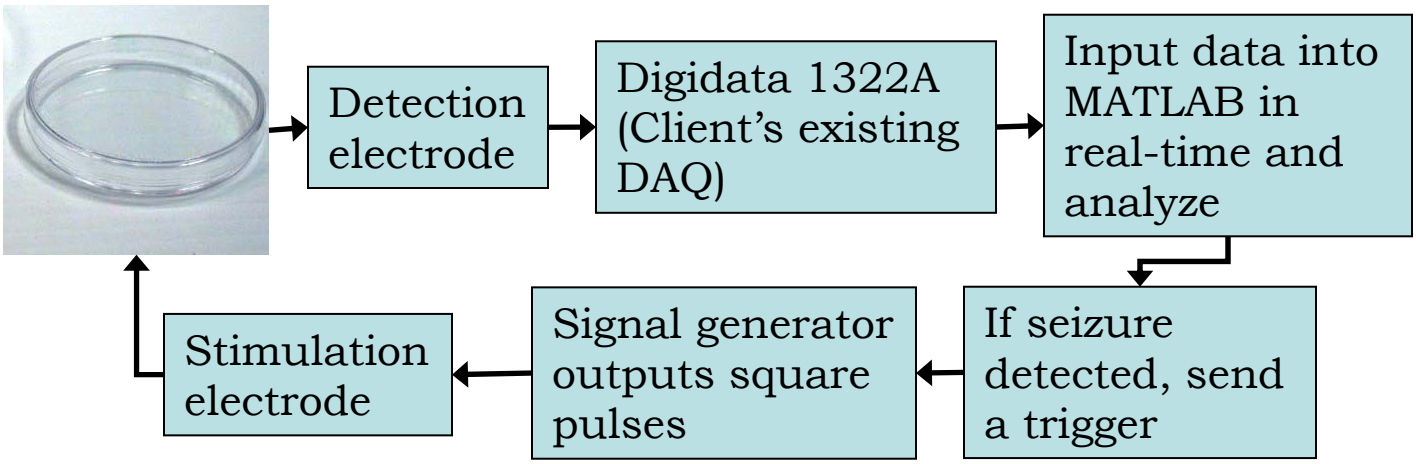

Figure 11: Schematic representation of our second design option

III. Chosen design

The chosen implementation combines simplicity, very fine control ability, and ease of use for the client. Several seizure prediction, detection and stimulation modules will be implemented with LabVIEW (National Instruments), and the client will have full control over all parameters, including which prediction/detection method to use and what kind of stimulation to administer (based on the needs of his research).

LabVIEW cannot be interfaced with the client's existing ADC (Digidata 1322A), since Axon does not provide any third party drivers. The client has agreed to purchase a PMD-1208ls, a versatile, inexpensive

and LabVIEW-compatible analog-to-digital converter, from Measurement Computing.

LabVIEW allows the easy integration of all the design components described in the “designs considered” section. Each of these components can be developed and tested separately, as Virtual Instruments. This option, therefore, provides maximal versatility, and we have found LabVIEW applications to be perfectly compatible with most of the client’s existing hardware (except the ADC).

No additional costs will be incurred by the client, since the application can be exported as an executable and installed on the client’s laboratory computer.

The EEG signal will be treated in several steps, which are summarized in the logical diagram of figure 12. At each step, the researcher will have control over the thresholds, and both sensitivity and specificity can be optimized. In seizure detection, false positives are tolerable, while false negatives are not. As a result, the researcher may choose the combination of parameters that provide the highest sensitivity for a moderate specificity.

As for the budget, the only cost that will be incurred by the client will be a new ADC. The PMD-1208ls costs about $100, which is much lower than our client’s budget limit of $10,000.

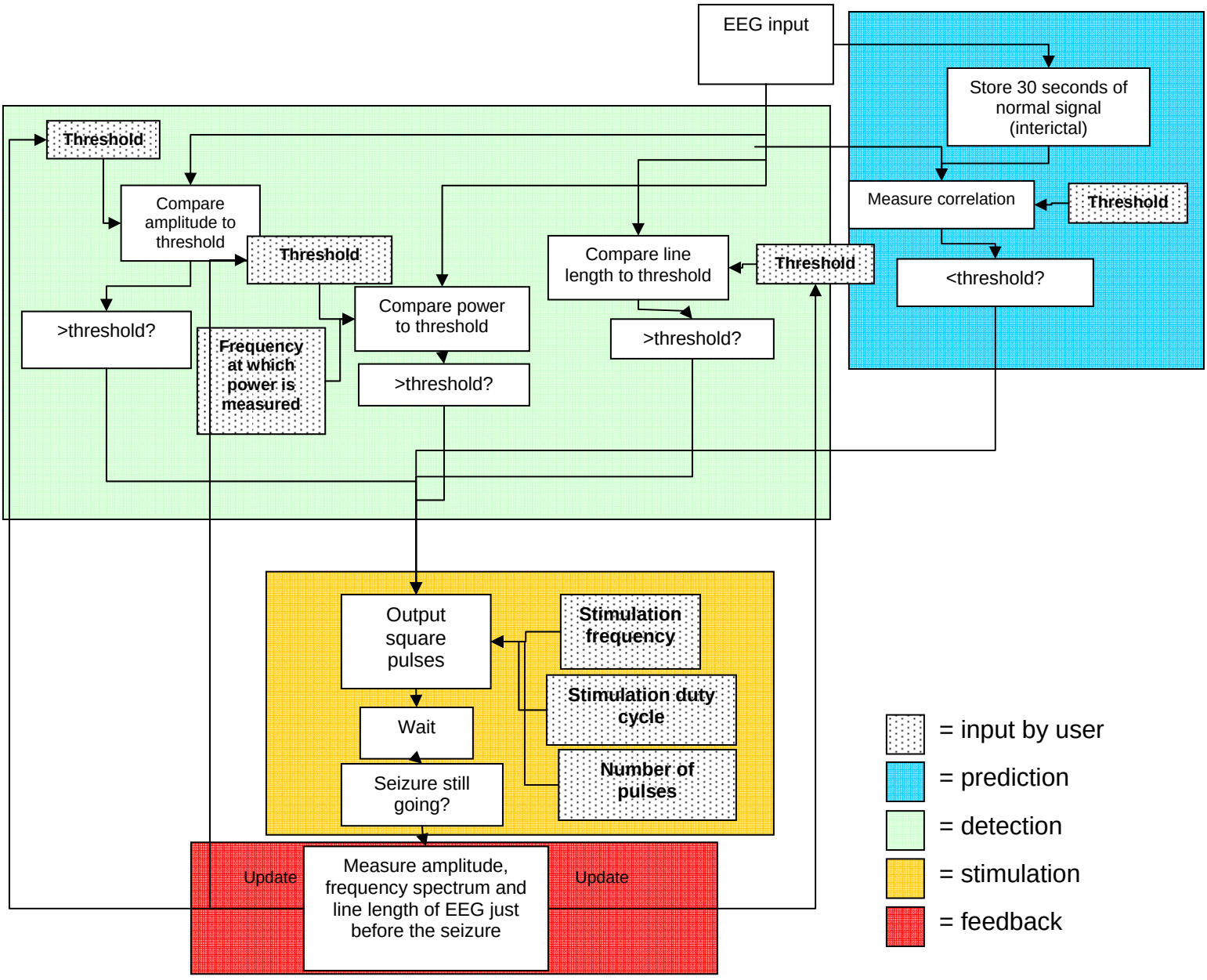

Figure 12: Simplified logical diagram for the functioning of our LabVIEW seizure detection algorithm

Future Work

We have successfully recorded data and detected seizures in live hippocampus slices, but no feedback loop has been established yet. Our first objective is to prove a simple feedback loop is possible. A multifaceted prediction/detection algorithm will be implemented. A

stimulation module will also be added.

The algorithm will place as many decisions as possible, such as detection modality and stimulation frequency, in the hands of the researcher.

If it is determined that the current ADC (PMD-1208ls) does not have an adequate data transfer frequency, a new ADC with the necessary capabilities will be acquired. Finally, a completed LabView program will be compiled into an executable (.exe program) for the client. This program will be installed on the client's lab computer, along with the DAQ.

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