

# Classifying and Localizing Epileptic Brain States Using Structural Features of Neuronal Sugihara Causation Networks

Kamal Kamalaldin\*, Rory Lewis†, Chad Mello†, Dorottya R. Cserpan‡,  
Somogyvari Zoltan‡, Peter Erdi\*‡, Zsolt Borhegyi§

\*Kalamazoo College, MI

†University of Colorado Colorado Springs

‡Wigner RCP, Budapest

§MTA-TKI , MTA-ELTE-NAP B-Opto-Neuropharmacology Group

## **Abstract**

ABSTRACT TO BE COMPLETED AT THE END OF THE DOCUMENT

## **Abstract**

## OLD ABSTRACT

Causality is a topic of philosophical and technical debate in scientific fields relating to multivariate systems. Sugihara Causality is a new model for describing causality. We investigate how this model can be applied to highly dimensional neuronal networks where epilepsy is induced. Different brain states will be classified using a neuroclustering algorithm. The time indecies of the clustered brain states will be used to discretize the original EEG signal into different epileptic seizures stages. A causality network will be created for each stage from the discretized EEG signal, and analysis on the network will be conducted to find predictive structural patterns in epileptic seizures.

## I. OUTLINE

Here is my proposed outline for the SIP:

- Abstract: Summarize the introduction, methods, results, and conclusion
- Introduction: Introduce the focus of this SIP and the purpose for which it has been conducted.
- Background: A gentle reminder to myself as much as the audience that the domain presented henceforth is not a common one, so a well placed background seems necessary to allow accessibility to all readers.
- Epilepsy: Provide a somewhat comprehensive history of the discovery, diagnosis, treatment of, and recovery from epilepsy. Stress why treating it remains so elusive and highly risky.
- Machine Learning: This is probably the most computer-sciency aspect of the SIP. Describe the three main branches of ML, where they are used, and the success rate of several techniques in each.
  - Supervised Learning
  - Unsupervised Learning
  - Reinforcement Learning
- Causality and the Sugihara Model: Give a brief overview of the field and study of causality (Granger, Judea Pearl). Describe and explain the Sugihara model and the reasons for why it was chosen. Give examples of where it was used successfully.
- Methods and Experiments:
- Results
- Discussion
- Conclusion

## II. INTRODUCTION

This SIP will be on the topic of Machine Learning (ML) its usage in the biological and medical fields. My thesis will be more specifically that the origin site of epilepsy in the brain can be approximately located using ML.

Machine Learning is the science of training a machine to recognize certain patterns in the given data. There are 3 main subcategories of ML, namely supervised learning, unsupervised learning, and reinforcement learning. While all of these categories have been used in the biological field, my own work has been done in supervised and unsupervised learning. The data of my work is comprised of voltage signals collected through electroencephalogram (EEG) electrodes inserted into specific regions of the brain. As the brain alters in state, the voltage fluctuates, and these fluctuations are recorded by this electrode. Due to the nature of epilepsy, only one electrode is typically required to identify the stages of an epileptic seizure. However, our thesis is that recording of multiple EEG electrodes in the brain could help not only identify epilepsy but also localize its origin in the brain.

### III. MACHINE LEARNING

#### A. History of Machine Learning

The first sight of ML is attributed to Arthur Samuel who, in 1952, wrote the first learning computer checkers game. This game learned by playing against itself and against other human players in a supervised setting [1]. After multiple enhancements throughout the years, this program was able to beat novice checker players, demonstrating the potential power of ML. The same basic principles used by Samuel's program more than 60 years ago are still being used (with more optimized algorithms on greatly more powerful computers) today at Deep Brain, beating humans at more and more board games (See alpha Go).

While Dr. Sameul was working on his checkers game at IBM, a major development was happening at College of Medicine at the University of Illinois. There, Warren McCulloch and Walter Pitts proposed the first mathematical model of what they believed to be the structural unit of the brain: the neuron. In their paper *A Logical Calculus of The Ideas Immanent IN Nervous Activity* published in 1943, they described the brain as a network of neurons in which each neuron had excitatory and inhibitory input and with each of these inputs came a weight to imply its importance [2]. Each neruon in the brain had a certain threshold which represented its reluctance to "fire." If the weighted sum of all its excitatory and inhibitory inputs was greater than the threshold, then the neuron would fire. Otherwise, it would not. This was coined as the "all or none" behavior.

Mathematically, the model describes a set of inputs  $X = x_0, x_1, \dots, x_n$ , a corresponding set of weights  $W = w_0, w_1, \dots, w_n$ , and a threshold  $\theta$  the output of the neuron is described as the function  $f(x)$

$$f(X, W) = \begin{cases} 1 & \text{if } \sum_{i=0}^n x_i w_i \geq \theta, \\ 0 & \text{Otherwise.} \end{cases}$$

#### MUST INCLUDE GRAPH OF STEP FUNCTION

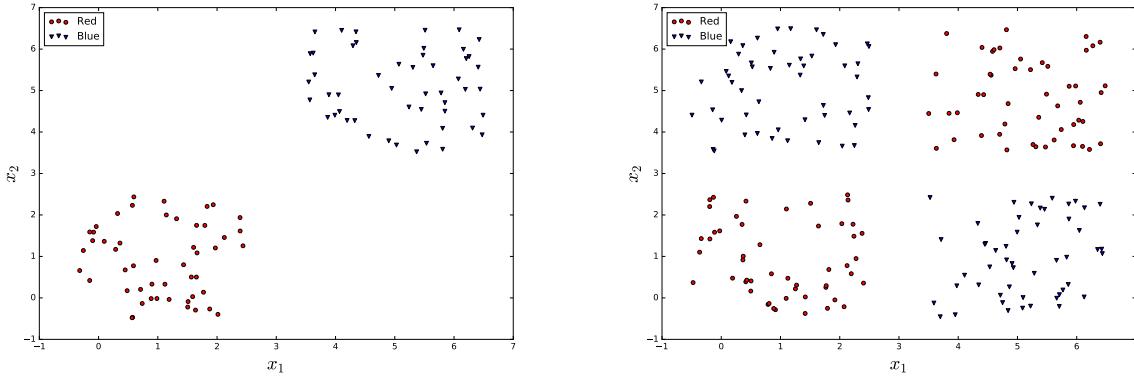
For the neuroscience field, the McCollough-Pitts model was a mathematical breakthrough that many have been waiting for to accurately model neurosn and the brain. However, the importance of the McCollough-Pitts model to the machine learning field was in that it laid the ground work one of the most important building blocks of today's Artificial Neural Networks: The Perceptron. In 1958 and at the Cornell Aeronautical Laboratory in Buffalo, New York, Frank Rosenblatt introduced this mathematical model that was very similary to the McCollough-Pitts neuron, but

had one major difference which was that it had a learning rule that allowed it to adjust the weights of the neurons that feed it. This allowed the perceptron to accept new input as a series of node inputs and adjust the weights of each of these nodes in such a way that allowed the output of the neuron to be consistent with the true label of the input [3]. This was the first sight of an algorithm that can find classification solutions for linearly separable problems (See section III-B1). TO BE CONTINUED

## B. Supervised Learning

Supervised learning can be generally thought of as function approximation where, given a set of inputs and expected outputs, a function from the input to the output is approximated by using a set of learning rules. The input and output of the approximate function depends on the input and output specified by the question posed by the data. Supervised learning can be broken down into two main branches: label classification and regression prediction.

1) *Label classification*: The simplest form of label classification is often referred to as binary classification, in which the classifier (machine learning algorithm) has to discriminate between two classes. For example, a simple binary classification problem would be to discriminate between sets of points on a Cartesian plane (Fig. 1).



**Fig. 1:** Two sets of data, one of which is linearly separable (Left) and the other is non linearly separable (Right). Linear separability means that a line can be found that can perfectly segregate the two classes into two sections. A diagonal, horizontal, or vertical line between the blue and red points can be drawn on the left that achieves that goal. However, on the right there is no one line that can be used to separate the red from blue points. This problem of finding a line of separation between two linearly separable data sets can be solved by using a binary classifier, the earliest example of which is the perceptron.

The perceptron was the first machine learning algorithm designed to solve binary classification in linearly separable conditions. Perceptrons were designed to mimic the McCollough-Pitts neuron model which relied on three main components: inputs, weights, and an activation function. In addition to these components, the perceptron had a learning rule that allowed it to learn when to and not to fire. Listing all the components of a perceptron:

- **Inputs:** A dataset of  $n$  dimensional points. Each input point  $x$  consists of  $n$  features such that each input point can be described as  $(x_1, x_2, \dots, x_n)$ .
- **Weights:**  $n$  weights described as  $w_1, w_2, \dots, w_n$ . These weights are randomly initialized.

- **Activation function:** a function on which the neuron decides to fire or not fire. The first one was the threshold (or step) function where the neuron fires if the weighted sum of inputs and weights is larger than threshold  $\theta$ , and doesn't fire otherwise.
- **Learning Rule:** A rule by which the weights change, described below.

A perceptron can be trained by passing to it each data point from the dataset. In our example (Fig. 1), each data point would have a two-dimensional input consisting of the  $x_1$  and  $x_2$  values. Since we are working with two dimensions, the perceptron would have two weights  $w_1$  and  $w_2$ . Every time the perceptron encounters a data point it tries to make a prediction by calculating the weighted sum of the inputs  $S$  as  $\sum_{i=1}^n w_i x_i$ . If  $S \geq \theta$  then the neuron fires, meaning it predicts the category to be  $+1$ . If  $S < \theta$ , the neuron doesn't fire, predicting the category to be  $-1$ . Given this determination, the perceptron evaluates its predicted output with the actual output of the data point, then manipulating its weights, completing the learning process of the perceptron on that data point.

The learning process for input  $x$ , given a true label  $\gamma$  and a threshold  $\theta$  is summarized by the following updates:

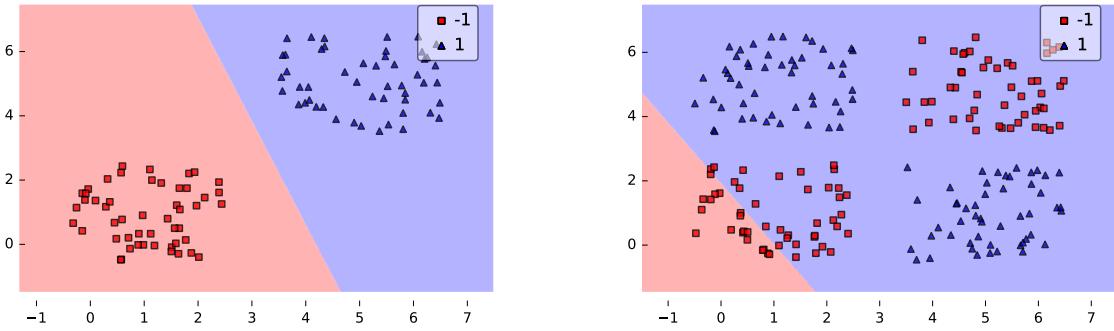
$$S = \sum_{i=1}^n w_i x_i > 0 \quad (1)$$

$$\kappa = \begin{cases} +1 & \text{if } S > \theta \\ -1 & \text{otherwise} \end{cases} \quad (2)$$

$$w_{new} = w_{old} + (\kappa - \gamma)x. \quad (3)$$

As can be seen from above, the perceptron learns by changing its weights, as this causes the same input to give a different  $S$  which in turn could give a different predicted value  $\kappa$ . Following this learning rule, it can be proven that the perceptron model converges in finite time to a set of weights that result in a perfect classification for all data points in the dataset. A simple implementation of the perceptron was used to solve the sample datasets presented earlier (Fig 2).

The perceptron model did exceptionally well in solving such binary problems when it was introduced, but its lack of versatility when facing non linearly separable datasets resulted in an echoing cry of concern as to how realistic of a learner it could be. In fact, the scathing criticism that the perceptron model received lead to a 10-year hiatus in research on perceptrons [4]. Researchers who worked on the perceptron and neural network fields published under the

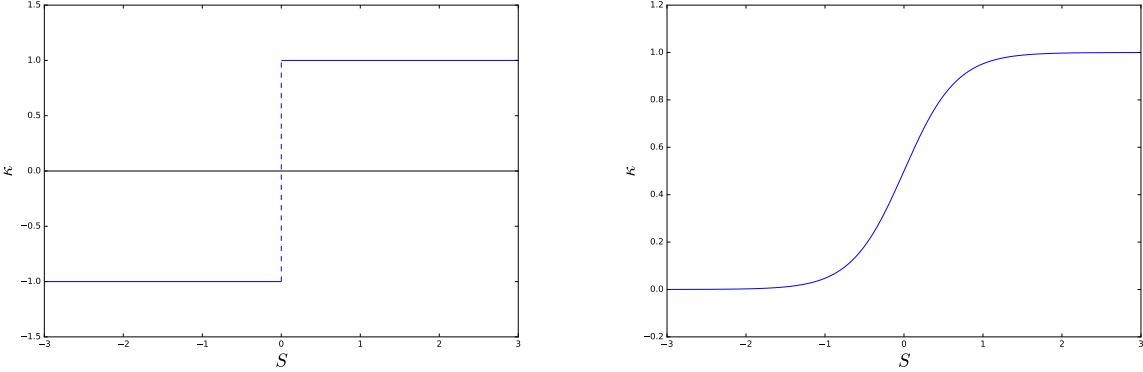


**Fig. 2:** The perceptron model can be used to solve binary classification in linearly separable datasets as in the left image. After training, all points below the shown line of separation would be classified as -1, and all points above the line would be classified as +1. Seemingly, this behavior would correctly extrapolate to unseen data points from a similar distribution. In the case of non linearly separable datasets, the perceptron keeps adjusting its weights but never reaches a solution which correctly classifies all data inputs, meaning the model quits after a set limit of iterations through the dataset. This results in a having a line that clearly does not separate the two classes (Right).

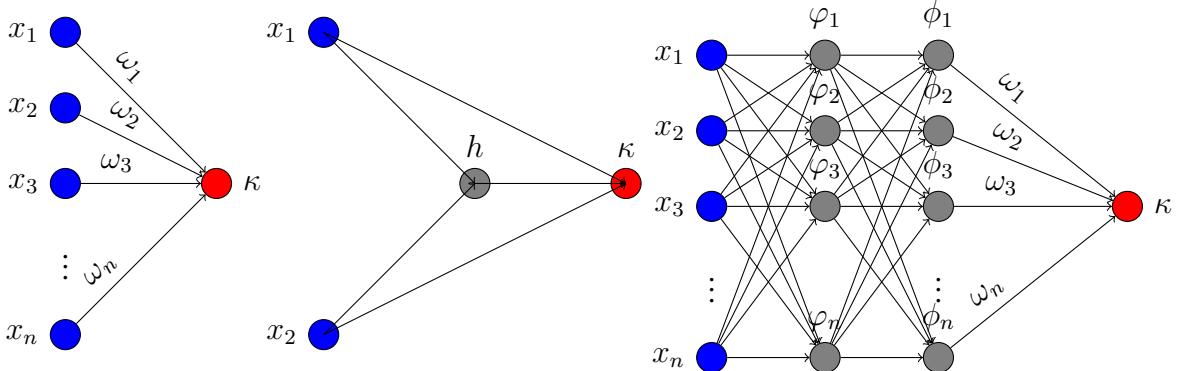
umbrellas of "adaptive signal processing", "pattern recognition", and "biological modeling" [5]. Slowly but surely, some loyalists to the neural machine learning perspective worked on enhancements to the perceptron model, leading to breakthroughs that skewed public opinion back in favor of what researchers now call neural networks: a group of perceptrons that are linked together to perform learning on datasets that one perceptron alone couldn't learn.

The first breakthrough came when scientists put several neurons together in different topologies (Fig 4), calling them a neural network. In a neural network, layers can be defined as a collection of nodes that are fed data from a previous layer, perform a calculation on this data, and pass it to another layer or as a final result. Although the neural network could approximate more functions, there was no clear way to tune the learning rule from one layer to another. This is when two important ideas came about: first, a realization that choosing a different, continuous activation function (as opposed to the discrete step function) could mean that a derivative could be taken (Fig. 3); second, a method by which the chain rule (from calculus) can be employed on the these derivatives that allows error calculations to be passed down from layer to layer reliably, a method called Back Propagation (Fig. 5). Together, these breakthroughs caused a resurgence in the field of neural networks which used perceptrons as their building block. When the activation function changed from a step function, the field moved away from the perceptron naming convention, and used the term *learning units* instead (Fig. 3, 4). The name change is also because the learning rule changes with the change of the activation function, which moves

the learning unit further away from the initial conceptualization of the perceptron model.



**Fig. 3:** Different activation functions can be applied to the perceptron model. The simplest and earliest activation function is the step function (Left) which outputs either a +1 or -1. A disadvantage of the step function is that small changes in the weighted sum ( $S$ ) could cause a large change in the output ( $\kappa$ ). This is solved by the sigmoid activation function (right) which gives a output (between 0 and +1) that is proportional to  $\S$  within a given range. When a perceptron implements a sigmoid activation unit, it is referred to as a sigmoid learning unit.



**Fig. 4:** Perceptrons linked in networks with different topologies. Blue represents input notes, gray represents hidden nodes, and red represents output nodes. The left network contains only one layer, the input layer, with its associated weights that feed into the output layer. This network essentially simulates a computation that is equivalent to the perceptron model. The center network contains a hidden layer composed of simply 1 node. This network can solve the XOR problem, and is able to solve the linearly inseparable dataset in Fig 1. The more nodes added to the hidden layer and the more hidden layers there are, the more communication happens between the nodes in the previous layer, and therefore the higher the abstraction. The network on the right is a more dense network with two hidden layers and many more hidden nodes.

A common continuous activation function for learning units is the sigmoid learning unit. Instead of the stepwise function in equation 2, the output function becomes

$$\kappa = \sigma(S) = \frac{1}{1 + e^{-S}} \quad (4)$$

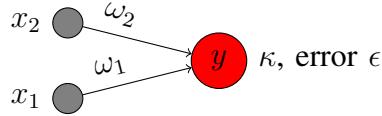
which is bounded by 0 and 1. This function is popular because its derivative is rather simple to compute and leads directly into the theory of back propagation. When the sigmoid function is

used, the learning rule becomes a minimization of an error term using gradient descent. For a data point with target classification  $\lambda$  and predicted classification  $\kappa$ , the error term is described as

$$\epsilon = (\lambda - \kappa)^2$$

and is called MSE and is derived in III-B2. Gradient descent is an iterative approach to finding the maximum or minimum of a continuous function by using its derivative (Fig. ??).

For example, if a learning unit in a predicts an output of  $\kappa$  with an error  $\epsilon$  and it has two learning units feeding it



and keeping in mind that  $\kappa$  is  $\sigma(S) = \frac{1}{1+e^{-S}} = \frac{1}{1+e^{-\sum_{i=1}^n w_i x_i}}$  then the error can be expressed as

$$\epsilon = (\lambda - \kappa)^2 = (\lambda - \sigma(S))^2$$

or in our example

$$\epsilon = \left( \lambda - \frac{1}{1 + e^{-w_1 x_1 - w_2 x_2}} \right)^2$$

Using gradient descent, minimizing  $\epsilon$  with respect to node  $x_1$  requires us to change  $w_1$  by the negative of its gradient. This gradient is

$$\frac{\partial MSE}{\partial w_1} = \frac{\partial(\lambda - \sigma(S))^2}{\partial w_1} = \frac{\partial \sigma(S)}{\partial w_i} 2(\lambda - \sigma(S)) \quad (5)$$

because  $\sigma(S)$  is the only function of  $w_i$ . This is where having an activation function that can be easily differentiated is advantageous. For the sigma function, the derivative evaluates to

$$\frac{\partial \sigma(S)}{\partial w_i} = \frac{\partial \frac{1}{1+e^{-\sum_{j=1}^n w_j x_j}}}{\partial w_i} = \frac{x_i e^{-\sum_{j=1}^n w_j x_j}}{\left(1 + e^{-\sum_{j=1}^n w_j x_j}\right)^2} = \sigma(S)' \quad (6)$$

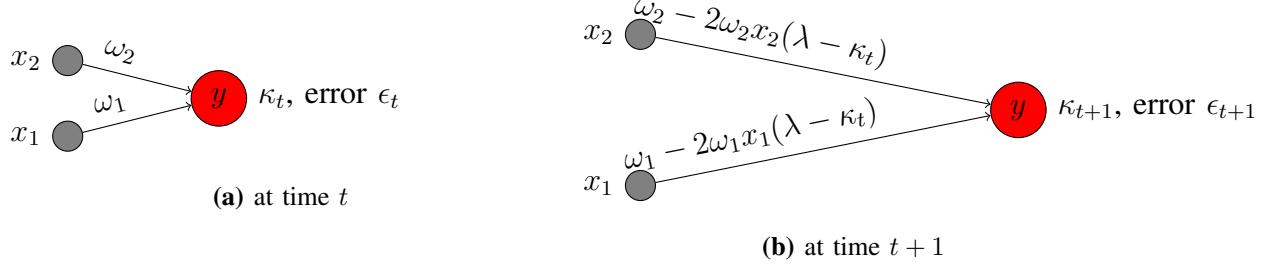
The last step is carried for notational simplicity. Combining equations 5 and 6, we find that the weight of the  $i$ th node  $w_i$  must be changed by the negative of the gradient

$$2\sigma(S)'(\lambda - \sigma(S))$$

which leads to a weight update rule of

$$w_{i_{t+1}} = w_{i_t} - 2\sigma(S)'(\lambda - \sigma(S)) \quad (7)$$

In this way, the error that is produced at the top layer, where the final classification decision is contrasted with the desired decision, trickles down to all lower layers, with each node changing its weights according to the error of the upper node. Back propagation is worked out example above in Figure 5.



**Fig. 5:** Back propagation works by minimizing the error function using gradient descent. In this case, the error function is the MSE, and its partial derivative with respect to each weight from the  $i$ th node in the previous layer is  $2w_i x_i (\lambda - \kappa_t)$  where  $\lambda$  is the desired outcome and  $\kappa_t$  is the predicted outcome at iteration  $t$ . In each iteration, applying gradient descent results in a move towards the opposite of the gradient, meaning partial derivative of the error with respect to that weight is negated from the weight (right). This method is guaranteed to converge, however slowly, over well defined continuous activation functions, an example of which is the sigmoid function (Fig. 3).

In this subset of supervised learning, the input and output are both categorical data, as opposed to numbers in a range. The canonical example of categorial data for supervised learning is swimming pool opening based on weather conditions. In this example, there are several weather-related features such as *Outlook*, *Temperature*, *Humidity*, and *Windy*. The *Outlook* feature could contain categories such as sunny, overcast, or rainy; the *Temperature* feature could include categories such as hot or cold; the windy category could include false or true. All these features contain values from finite set of possibilities.

Table III-B1 shows possible data points of such a dataset. From this small sample, a general rule for playing like

If outlook = sunny  $\wedge$  humidity = high

If outlook = rainy  $\wedge$  windy = true

can be formulated. Although this might be a good rule to follow, it might not generalize well to the rest of the dataset, and inspecting the entire dataset by eye becomes unfeasable

beyong 20 datapoints. A common approach to solving this problem is called a Decision Tree. In this algorithm, the datapoints are iteratively separated by the feature that splits the data most evenly. For example, NEED TO INCLUDE FORMULA FOR INFORMATION GAIN AND CATEGORY SEPARATION FOR DECISION TREES.

Outlook	Temperature	Humidity	Windy	Play
Sunny	Hot	High	false	no
Sunny	Hot	High	true	no
Overcast	Hot	High	false	yes
Rainy	Mild	High	false	yes
Rainy	Cool	Normal	false	yes

For example, if the input takes the form of images that contain a number and the output (labels of the images) is a number from 0 to 9, then the function would produce a mapping from a set of image properties to the set of numbers 0 to 9. Conversely, if the input is a set of numbers each representing a cost

2) *Regression Prediction:* For cases when the desired output of a function is a number on a meaningful range, label classification is not possible. This is because a supervised label classification problem deals with *choosing* the best label out of a given set, and not generating a label out of the given data. This is where regression prediction comes into play. For functions whose output is a continuous range of numbers, one can not possibly assign a label to each possible output. And even if each output is assignable, there is rarely a dataset big enough to cover possible mappings to each such label.

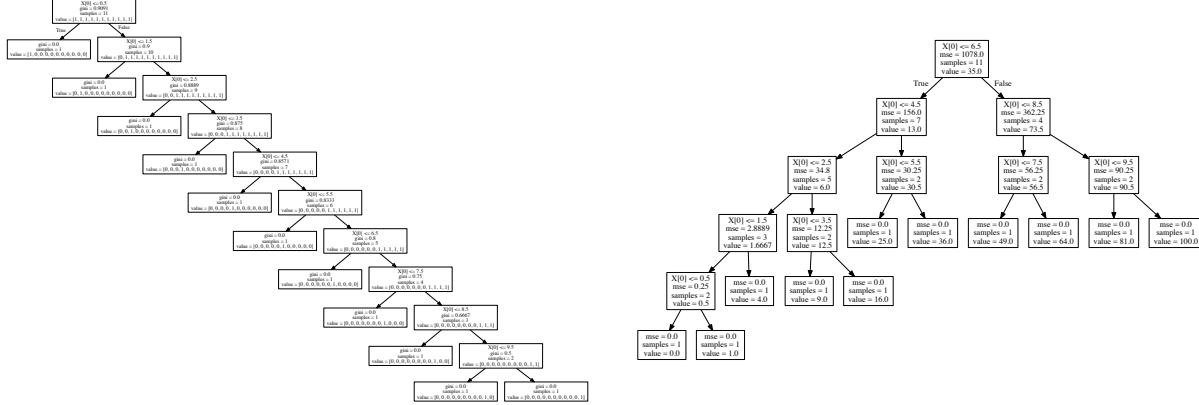
For example, given an input set of 1, 2, 3, 4, 5, 6, 7 and an output set 1, 4, 9, 14, 25, 36, 49, a good—and almost any—supervised learning algorithm would approximate the function  $f(x^2)$ . However, such a function would have rely on regression learning, and not label classification. To show this, let's delve into a thinking exercise. Say we make a training set for the function  $f(x) = x^2$  consisting of input that is all the integers from one to one million and output that is the square of all these input numbers. If we are to use label classification, then we would train the algorithm to map each number to its square label. The first problem arrises on the first step of learning, especially in the Decision Tree technique. Because each input is looked at as a categorial input, an input of one (1) will be converted to a string. Sicne each data point has its own label, the information gain will be maximized and the entropy loss will be minimized

when the input is split into one million branches on the first level of the tree. At that point, the function mapping is resolved by simply going through one level. However, this leads to the second problem, which arises when feeding in new test data that the classifier was not trained on. Because the classifier only has access to labels that it trained on, any number other than an integer from one to million will have to map to an already known label from the squares of the integers from one to one million. For example, an input of 1.76 will map to either 1 ( $1^2 = 1$ ) or 4 ( $2^2 = 4$ ), meaning this incurs an accuracy cost. This cost might not be a big problem for the purposes of the algorithm, but the real problem arises when we try to predict the mapping of a number outside the range of our training dataset: numbers below 0 and those above one million. The nearest value for all numbers below 0 is 1, so all the numbers below 0 will be mapped to the label of 0, while all the numbers above one million will be mapped to the label of one million (Fig 6).

From this small experiment, the need for a different approach to supervised learning is obvious. Such a technique would need to generalize the mapping not to categorial labels and their limited space, but to an unlimited range of numbers. This method would solve a more conventional mathematical problem of function approximation. Another way to think about the problem is curve fitting: given input and output sets, the curve of the approximated function should pass—or be proximal—the points given in the sets. As the approximated curve moves further and further away from the given points, the distance between the points and the curve increases, which we can use as a measurement of error (Fig. 7). The sum of this error can be expressed as

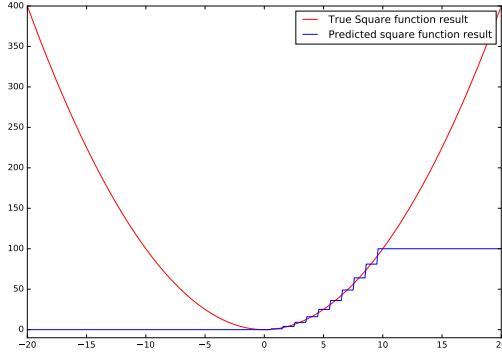
$$\text{Error} = \sum_{i=1}^n (y_i - f(x_i)),$$

where for the  $i$ th data point  $y_i$  represents the actual  $y$  value and  $f(x_i)$  represents the approximation of the regression line at  $x_i$ . Minimizing this error term ensures that our resulting function is the closest line fit to our data points. However, notice that in our error function, positive and negative errors will cancel out, leading to the assumption that "two wrongs make a right". To avoid this, we can either take the absolute value of the error, or the square. For mathematical convenience, the squared error is preferred. This results in the method of Least Squared Error (LSE) as given by

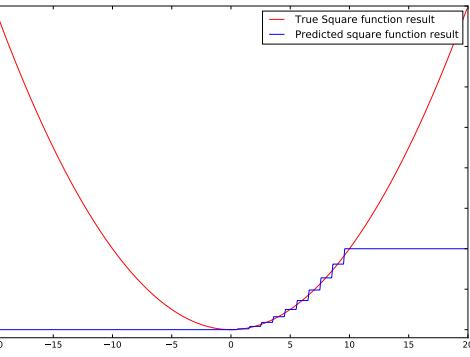


(a) Classification Decision Tree

(b) Regression Decision Tree



(c) Classification Decision Test Results



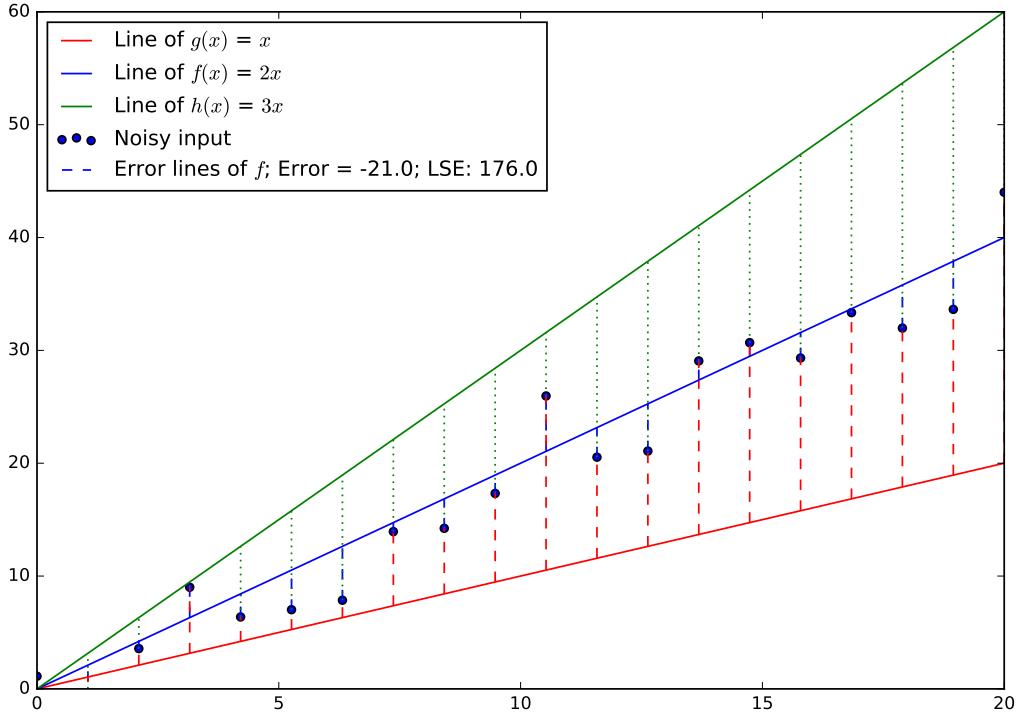
(d) Regression Decision Test Results

**Fig. 6:** Although a regression tree and a label classification tree have a different decision path with the same training data, they exhibit similar erroneous behaviour when tested on input that ranges outside the training sample. The trees were trained on a dataset of simple square functions, where the inputs were numbers from 0 to 10 and output is the square of each number. Both decision trees show a jagged approximation of the square function between 0 and 10, which indicates some level of learning. However, the trees show very poor generalization outside the learning range. When tested on input that is below 0, the trees match to the closest label in the decision boundary, which is "0". A similar decision is made for input that is greater than 10, where the trees matches all numbers greater than 10 to the label of 10 ("100").

$$LSE = \sum_{i=0}^n (y_i - f(x_i))^2 = \sum_{i=0}^n (y_i - b_0 - b_1 x_i)^2 \quad (8)$$

From this equation it can be shown that

$$b_1 = \frac{\sum_{i=1}^n y_i x_i - \frac{\sum_{i=1}^n y_i \sum_{i=1}^n x_i}{n}}{\sum_{i=1}^n x_i^2 - \frac{(\sum_{i=1}^n x_i)^2}{n}} \quad (9)$$



**Fig. 7:** Different lines of fit and their errors (dashed and dotted lines) with respect to the noisy input data. Because  $g(x)$  and  $h(x)$  have larger error lines than  $f(x)$ ,  $f(x)$  is the best fit for the data out of the three drawn lines. Note that for  $f(x)$ , the negative and positive errors cancel out, leading to a sum of error of  $-21$ . This is allayed by summing the square of the error instead, which results in a minimizable equation that evaluates to  $176$ .

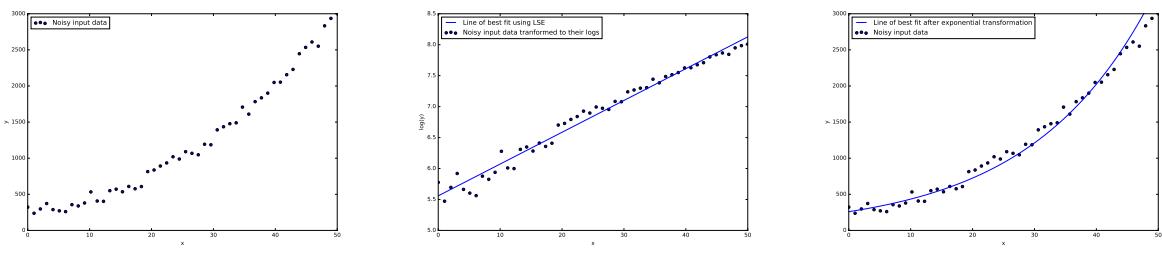
and

$$b_0 = \bar{y} - b_1 \bar{x}$$

where  $\bar{y}$  and  $\bar{x}$  are the respective means of all  $y$  and  $x$  values [6]. This formula guarantees a line of best fit that minimizes squared errors for linear data points. For cases when the data points do not display a linear behavior, they can be transformed into a space where they become more linear, linear regression applied, and the regression functions transformed back into the original space (Fig 8).

TO BE CONTINUED WITH PERCEPTRON MODEL AND NEURAL NETWORKS

TO BE CONTINUED WITH SVM (SUPPORT VECTOR MACHINES)



**Fig. 8:** Finding line of least squared error for data with an exponential trend. First, the datapoints (Left) are transformed to their logs (Center). Then a line of best fit is found through linear regression (Center). The line is then transformed back to the original space by applying the exponential function (Right).

*C. Unsupervised Learning*

*D. Reinforcement Learning*

## IV. EPILEPSY

### A. Definition

The medical field defines a seizure as a sudden burst of electricity in the brain that causes a disturbance in its electrical activity. An epileptic seizure is more strictly defined as a "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain." Until recently, epilepsy has been defined as a brain disorder where the patient suffers from two unprovoked epileptic seizures in a span greater than 24 hours. In 2014, the definition of epilepsy has been revised to encompasses patients who display any of the following symptoms:

- At least two unprovoked (or reflex) seizures occurring in a span greater than 24 hours.
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
- Diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals who either had an age- dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last 10 years and off antiseizure medicines for at least the last 5 years.

The new definition was designed to allow physicians more freedom in diagnosing cases of epilepsy and take drastic measures in special circumstances where the first occurrence of an epileptic seizure can be greatly suggestive of a problem, necessitating an urgent procedure. It also allows patients to 'outgrow' epilepsy in cases where the condition is age dependent or has not manifested for a prolonged period of time, indicating the condition no longer affects the patient. Most importantly, the new definition classifies epilepsy as a *disease* rather than a disorder, an action that hopes to spread awareness regarding the "lasting derangement of normal function" that epilepsy can entail on a patient [7].

There are two main types of epileptic seizures: general seizures and partial seizures. The distinction between the two is where they originate and how greatly they spread in the brain. In general seizures, an electric discharge spreads to both hemispheres of the brain causing the electrical dysfunction that results in the seizure. Similarly, partial (of Focal) seizures are caused by an electric discharge, but this charge spreads only to certain areas of the brain in which it causes a dysfunction leading to the seizure syndrome cite.

## *B. Syndrome*

Epilepsy patients can experience a wide range of physical syndromes, not all of which are observable to a bystander. Some observable syndromes are

- drooling; inability to swallow; difficulty talking.
- repeated non-purposeful movements; rigid or tense muscles; tremors, twitching or jerking.
- pale or flushed skin color; seating; biting of tongue.

Some non-physical signs that the patients report feeling are

- loss of awareness; forgetfulness; distraction; daydreaming
- loss or obscurity of vision, hearing, and sensation
- body feels different, or out of body feeling

## *C. Epilepsy in Numbers and Life*

In the United States alone there are 150,000 new cases of epilepsy a year, or about 48 cases for every 100,000 people. In total, there are about 2.2 million cases of epilepsy in the United States, averaging close to 7 cases for every 1000 people. The disease onset is most common in young children and older adults [8].

A recent review [9] showed that epilepsy "creates a substantial burden on households" through either loss of productivity or out of pocket costs. While the review noted that the burden could be offset by health insurance, the upfront costs associated with treatment are significant. In Italy, the annual cost per patient is \$1,736, while in Spain it was \$2,813, not accounting for a \$2,924 surgery consultation fee. While these costs represent health system costs in socialized medical care societies, and are therefore shared over a larger population, the case is less forgiving in countries where individual insurance is the norm. In the US, out of pocket cost for a hospital stay is \$1,018. The review also considered indirect costs by associating productivity and employment status changes. While employment status did not differ after the diagnosis, productivity losses accounted for an annual average of \$2,037 in Spain, and \$2,146 per 3 months in Germany. The review concluded that the highest costs of epilepsy treatment come from surgery. A different study [10] showed that hospital charges for epilepsy patients has increased by 137 .9% between 1993 and 2008, rising from \$10,050 to %23,909 while the average length of stay decreased from 5.9 to 3.9 days.

Epilepsy also affects patients' lives in other ways. Patients become restricted to their homes due to a fear of having a seizure during their child's recital, work, or even grocery shopping.

Even if the fear of embarrassment subdues, patients take a risk when performing activities that put them in a position in which they can endanger them and the people around them. For example, deciding to ride a bike becomes a more challenging preposition since the patient could suffer from a seizure and endure serious injuries while biking. More importantly, driving is an increasingly risky activity with seizure prone patients. Driving laws make it difficult for patients to live an ordinary individual life with driving restrictions on patients who suffer from seizures. Each state in the United States has its own laws regarding the requirements that patients must meet in order to be allowed to drive on the road. In most cases the patients physician is involved in the decision on whether or not they should be allowed to drive.

#### *D. Treatment*

No real cure for the dysfunction of electrical activity in the brain has been developed, therefore epilepsy has no real cure as of yet. Most treatments attempt to mitigate the symptoms (seizure) by using a combination of strategies including the reduction of brain activity through medication, removal dysfunctional parts of the brain, and changing the chemistry of the body through restrictive diets. The following gives a summary of each of these strategies and the ways in which they work.

1) *Medication:* Medication is the first and most common treatment prescribed by doctors for epilepsy cases. Medications differ for different cases of epilepsy, and there is no *one* specific medication that is commonly prescribed. Such medications, commonly called AED (Anti-Epileptic Drugs) can completely control seizures in 7 our of 10 patients. AEDs work by suppressing seizures that are caused by epilepsy, and do not cure or address the true underlying causes of epilepsy. Epilepsy medication is known to only be effective if taken regularly. AEDs commonly induce side effects in patients, some serious like mental slowness, hepatotoxicity, dizziness, and drowsiness, and some minor ones like skin rashes and weight gain [11]. AEDs treatments usually continue until the patient is proven to no longer suffer from epileptic seizures.

2) *Surgery:* Surgery is usually performed on patients who suffer from partial epilepsy and on whom medication has not been affective. However, decisions to have surgery are being made sooner as some correlation has been shown between how early the surgery is performed and its success rate [12]. Epilepsy surgeries are split into two main categories: resection and disconnection surgeries. Resection surgeries entails removing the part of the brain that causes electric dysfunction and therefore seizures, sometimes resulting in a complete 'cure' from epilepsy. Such

a procedure can have the immediate side effect of losing brain functions or memories like being able to play the Piano or the memory of a child's first word. On the other hand, the goal of disconnection surgeries is to cut nervous pathways that are thought to cause epilepsy in the specific patient. Disconnection surgery is often undertaken if seizure is caused by a vital part of the brain and does not provide a 'cure' from epilepsy but rather a relief for the patient. Even more than typical surgeries, brain surgery can be highly risky and physicians advice it as a final resort. This risk draws a sharp contrast to the convenience of medication, since most AEDs can be administered easily and require only an adherence to the drug schedule. Therefore, medication is recommended before any surgical approach is considered.

*3) Diet:* Dietary restrictions such as fasting have been used to mitigate the onset of epilepsy since biblical times [13], and recent developments in the nutrition perspective on epilepsy have resulted in the resurgence of what is now known as the ketogenic diet. This diet consists of high fat and low carbohydrate items and focuses on mimicking the body's reaction to fasting by using fatty acids as a main source of fuel for the body. The diet works remarkably well on infants who have a mutation that affects the transport of Glucose (a main body fuel source): with the ketogenic diet helps prevent microcephaly, mental retardation, spasticity, and ataxia as a consequence of relative brain hypoglycemia (lack of glucose). This bolsters the evidence that the ketogenic diet regulates the body to use fatty acids as an alternative fuel for the brain. The ketogenic diet was also shown to help Alzheimer Disease patients, though that might have to do with eating less carbohydrates than eating more fatty acids [14].

COUD POSSIBLE ADD MORE ABOUT ALTERNATIVE MEDICINE (<http://www.epilepsy.com/learn/treatment/seizures-and-epilepsy/complementary-health-approaches>)

## V. SUGIHARA CAUSALITY

## VI. PROBLEM DEFINITION

Given multiple spiking signals from a set of interconnected neuronal regions, can the CCM model identify structural patterns in causal relationships between those regions? Can the patterns and properties of the causality graph resulting from the CCM model be clustered into brain states that represent different stages of epilepsy in the brain? In other words, can a machine learning algorithm be applied to the causal network properties, the model of which could be able to correctly classify epileptic brain states.

## VII. METHODS

### A. Data Collection

EEG data was collected from an 4x8 endodermal electrode array (31 channels, one channel malfunctioned, Fig. 9, 10). During the experiment epileptic seizures were evoked using 4-aminopyridine and EEG data was recorded from the electrode array. The spiking voltage of each recorded electrode is used as a signal and is referred to as a channel.

### B. Data Preprocessing

Kernal Current Source Density (kCSD) method was used on the grid of channels to account for possible electrical interference with the direct measurement [15]. The measured potentials produced by kCSD arise as the linear combination of the transmembrane currents, which is a more direct and localized quantity to measure the neural activity. Therefore current source density distribution was calculated by the kCSD method and used for the analysis.

Afterwards, in order to reduce the data size that is operated on, we lumped channels from the same regions together by averaging them (Fig. 11). In addition to reducing dimensionality, this process also puts emphasis of causality on functional brain regions instead of a local cluster of neurons.

## VIII. RESEARCH PAPER INTRODUCTION (OLD)

The concepts of abstract correspondence, correlation and interpreting causation has been discussed in philosophical literature at least as early as Berkley's and Locke's arguments on human perception [16] [17]. Until now, the debate focused on what constitutes a causative effect and how such an effect might be discerned. From philosophy, the debate has moved to

empirical science, where different models of causality have been proposed, none of which has been declared the true standard. A particular causality model, Granger Causality (GC), has been widely used in application in the econometric fields [18], and has been the de facto model when causality is concerned. However, while GC behaves best in linear, stochastic systems, it carries its own limitations. Even with extensions to non-linear systems, GC has generally not been seen capable of inferring causality in deterministic systems where feedback loops and nonlinearity are a defining feature. New models of causality have been introduced to attempt to rectify these limitations. Dynamic Bayesian Networks and, more recently, the Convergent Cross Mapping (CCM) are some such models.

The CCM model relies convergence of distance of nearest neighbors in the shadow manifold of pairs of variables [19]. A shadow manifold of variable  $\omega$  is an  $E$  dimensional reconstruction of  $E$  delayed signals of  $\omega$ . Each of these signals is delayed by a scalar multiple of  $E\tau$  such that shadow the manifold of  $\omega$ ,  $M_\omega$  is described as

$$M_\omega = f\left(\omega(t), \omega(t - \tau), \omega(t - 2\tau), \dots, \omega(t - (E - 1)\tau)\right)$$

. Applying Takens' embedding theorem, it can be shown that each shadow manifold of a variable is a projection of the dynamic system's manifold,  $M$ , that preserves the topology of  $M$  [20], [21], [22]. For example, in a dynamic system like the Lorenz Attractor where the dynamics of each variable is affected by the other variables in the system, it can be said that each variable subscribes to the overall dynamic of the system. Therefore, the state of one variable could be used to infer the state of another variable if they are dynamically linked.

Using this feature of dynamic systems, the CCM model infers causality from the convergence of prediction of one variable's state based on another's as  $L$  increases, where  $L$  is the length of data points considered in the prediction. This implies that  $L$  needs to be sufficiently large to allow an observation of convergence. This convergence is the test used to determine Sugihara Causality, named after its author who describes it as a required but not complete definition of causality [19]. This approach is the first step towards more general and applicable causality models since GC. Since the introduction of CCM, it has been shown to be successfully predictive in biological [23], [24], [19], [25], [26] and cosmological [27] applications while showing weaknesses in others [28].

Extensions to and amalgamations of the CCM model are beginning to surface in literature. Clark *et al.* proposed an extension to CCM that relies on measuring the smoothness of the

mapping (also called flow) function  $\phi$ , thereby reducing the  $L$  length requirement[29]. Wismller *et al.* proposed a Mutual Connectivity Analysis framework for the "analysis and visualization of non-linear functionalconnectivity in the human brain from resting state functional MRI" [30] which relies heavily on CCM. Tajima *et al.* use the fundamental idea of state space reconstruction to find two measures. The first is *Complexity* which is the best embedding dimension for a certain signal (embedding dimension at which the cross mapping is saturated). The second is *directionality*, the difference in cross map skill or embeddedness between two a pair of signals. With those two measures, they show that the brain exhibits different complexities during conscious and unconscious states. Here, we explore the application of CCM in estimating the causality between neuronal regions by constructing a network of pairwise causality. We then analyse features of such networks during normal and epileptic seizure periods. We attempt to localize the origin of seizures as well as predict their occurrence by using the properties of causal networks.

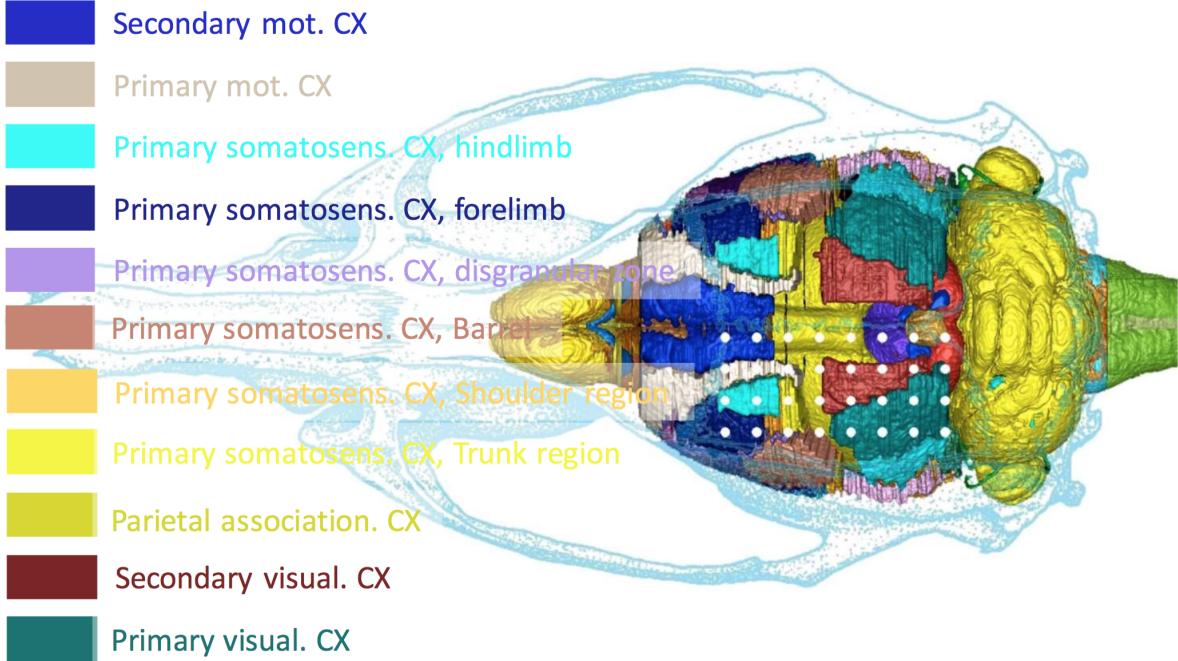
### A. Experiments

Using the preprocessed data, a pairwise analysis of the signals will be carried using CCM. For each pair of regions, two directions of causality will be considered. Since there were 12 regions,  $12 * 11 = 132$  unique causality relationships were analyzed. The causality measures were recorded on sliding windows of time segments. The time segment lengths were chosen through a heuristic that focused on attaining multiple causality measures within a second. Once the causality measures were attained for each time segment, a combination of heuristic and statistical measures were used to analyze the significance of the causality measures (see section VIII-B).

From the causality measures, a graph was constructed for each time segment (Fig. 16).

### B. Significant Causality Measures

Since every CCM computation returns a real number in the range  $[0, 1]$  that represents a relative causality measure, 132 causality measures for each time segment will be returned. Therefore, an important question to consider is how exactly should a causality measure be defined to be significant. Although Sugihara *et al.* [19] and Nes *et al.* [26] carry out a significance test based on altering the signals by random shuffling and Fourier transformation on Phase shift [33], this

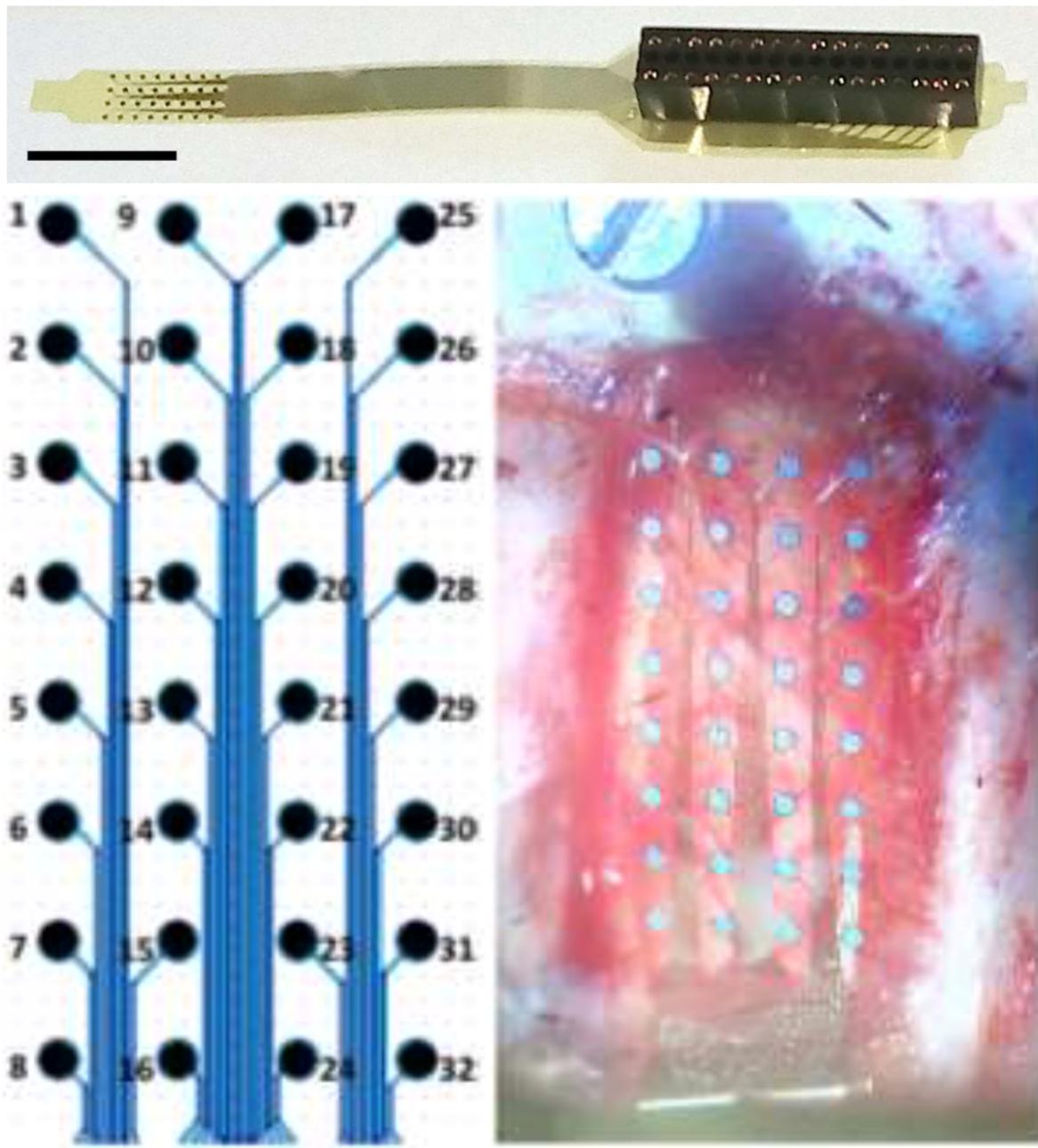


**Fig. 9:** A composite drawing showing the brain in the scull. The 3D reconstruction of the brain has been made using the maps of the Paxinos atlas, and the localization of cortical areas are indicated by different colors. White points indicate the position of the recording sites of the membrane electrode. Names for the cortical areas are also shown (based on Hjornevik *et al.* and Paxinos *et al.* [31] [32]).

method has not been implemented on EEG data when applying the CCM model. Therefore, we do not rely on it completely, and take into account several heuristic conditions.

1) *Most Causal Relationship Method*: In this method, a simplistic approach is taken whereby for each region only the highest incoming  $\rho$  is considered. While this approach is reductionist by definition, and most likely does not reflect the true causal relationship in the brain, it achieves simplicity in the network, and affords us the possibility of examining which regions could be the most causal in the network. Such regions would have a large out degree which would imply it being a center of causality in the network.

Another important property of this measure is that it could alleviate the problem of downstream causality sensitivity. As shown by Ye *et al.* [34], the CCM algorithm can detect downstream causality, which means that if  $\alpha$  causes  $\beta$  and  $\beta$  causes  $\kappa$ , then if  $\rho_{\alpha \rightarrow \beta}$  is a significant causality measure from  $\alpha$  to  $\beta$ , there can also be a causality measure  $\rho_{\alpha \rightarrow \kappa}$  detected to be significant such that the indirect causality is less than the direct causality  $\rho_{\alpha \rightarrow \kappa} < \rho_{\alpha \rightarrow \beta}$ . This can be an undesired consequence of the model, since we are interested only in the direct relationships, and not necessarily the indirect ones. Indirect relationships could be extrapolated from direct ones.



**Fig. 10:** Photograph of a membrane electrode shows the construction on the top, the numbering (bottom right) and the surgical implantation (bottom left) is also shown. Electrode 1 malfunctioned during recording.

If we assume that all downstream causality measures are evaluated to be less than their direct counterparts, then we expect that taking the most causal relationship would rid of all the indirect relationships that could otherwise be detected, with the expense of also ridding of other direct relationships.



**Fig. 11:** The distribution and lumping of the brain regions in the brain. A total of 12 region channels were constructed from the initial 31 local channels. The schematic is based on rat brain atlas mapping.

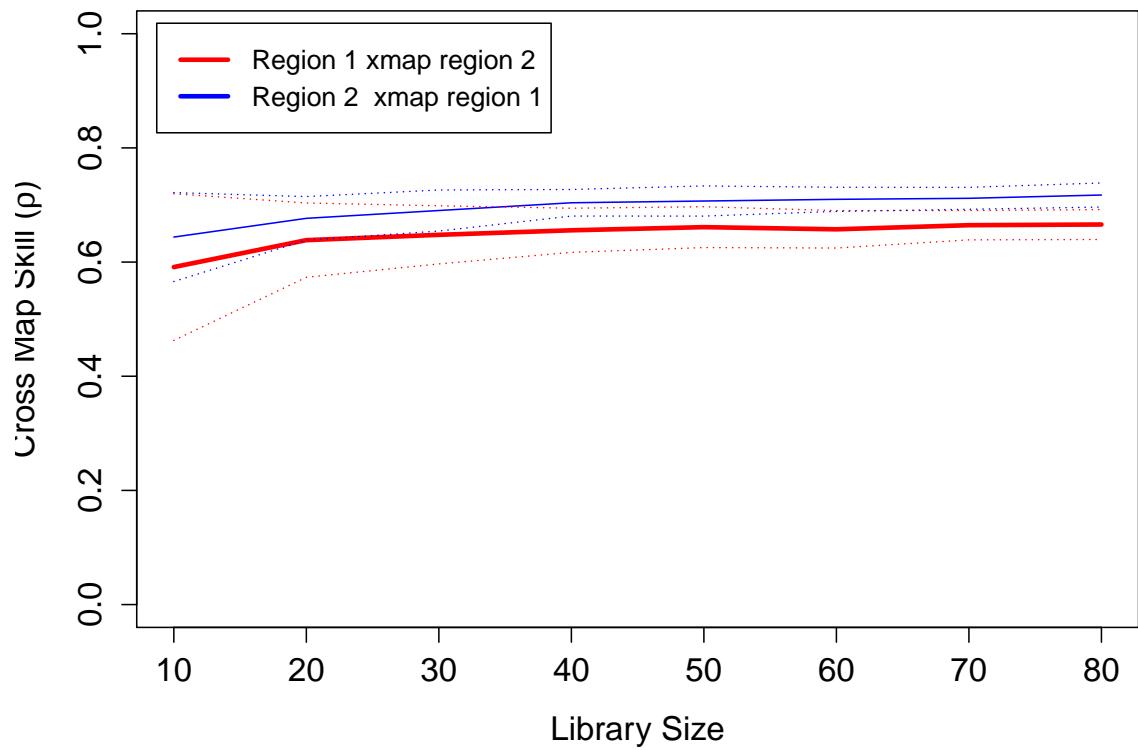
2) *Threshold Method:* In this method, only causality measure over a certain threshold  $\rho_{th}$  will be counted as significant. As this is a heuristic measure, the data must first be examined to clarify what is meant by a significant  $\rho_{th}$ . With this heuristic comes unavoidable human bias towards refusing generated data. Since the true causality relationships are not yet uncovered, almost any threshold is certain to be wrong. For example, if the brain was highly connected and regions are highly causal to one another, a neuroscientist who disregards such a possibility would be inclined to choose a high  $\rho_{th}$  as to filter many of the causal relationships that could in fact be present. Alternatively, if the brain regions were minimally causal to one another and a neuroscientist disregards that possibility, they would be inclined to choose a low  $\rho_{th}$  as to allow for more causal relationships for the model. However biased this method is, if implemented correctly it could provide a list of the most causal relationships to each region, while excluding most indirect relationships.

3) *Fourier Transform and Random shuffling Method:* For a more mathematically grounded significance measure, we also use a bootstrap test where a signal for both channels in a pair is created from the original signal, and the causality measure is significant if it is above a specified  $\alpha$  threshold. Another statistical method used to calculate significance is randomizing the data based on bootstrapping the frequency distribution of the signal calculated from the signal's Fourier

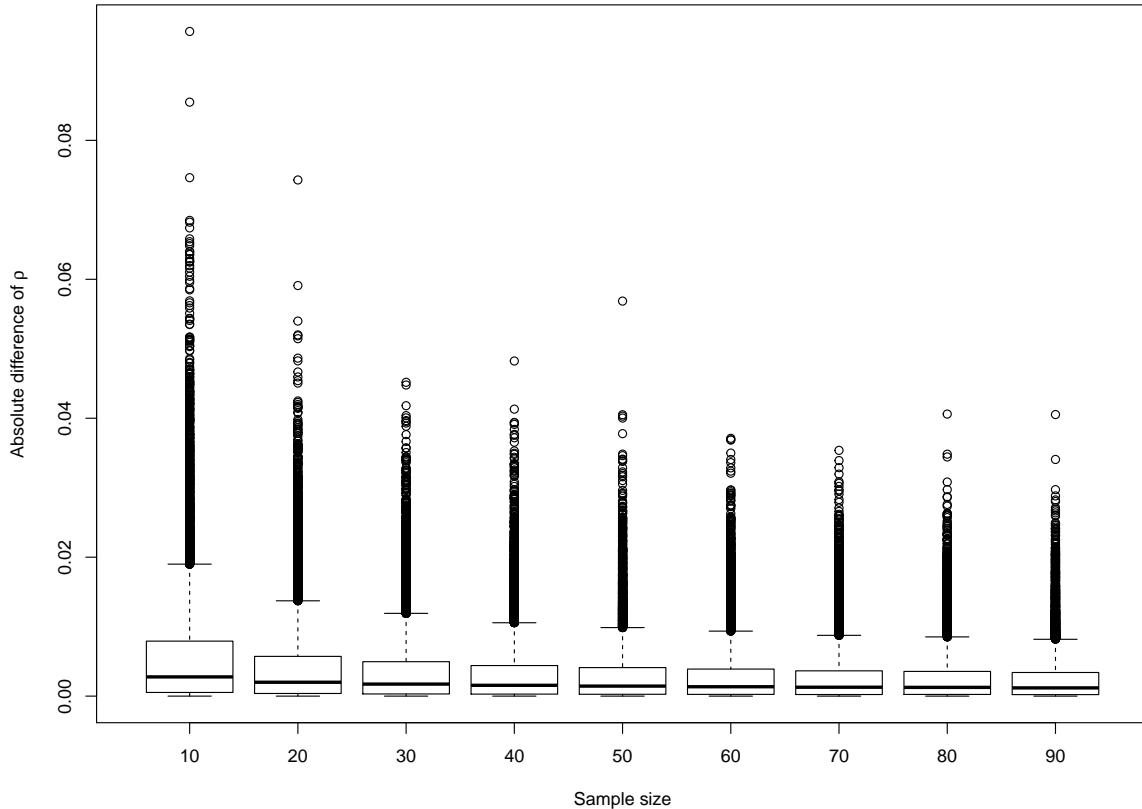
transform as used by Nes *et al.* [26][22].

## IX. RESULTS

By running the CCM algorithm through every pair of channels, we collected 132 causality measures (Fig. 12). To increase the efficiency of our calculations, we also observed the variance of the causality strengths as we decreased the sample size for each calculation (Fig. 13). Most of the causality measures appear to be of high values, suggesting high connectivity between brain regions (Fig. 12). Furthermore, we also notice that many of the pair causality measures appear to be similar within the pair (Fig. 15). For example, when looking at regions 1 and 2 within the first 200 ms, they appear to be equally causal to one another (Fig. 12).



**Fig. 12:** A sample graph plotting the convergent cross mapping skill ( $\rho$ ) between region 1 and 2 during the first 200 ms of the experiment. The skill mapping channel 1 to channel 2 is very similar to the one mapping channel 2 to channel 1. This might infer either bidirectional causality or unidirectional forcing. A similar pattern (close  $\rho$  value between pairs) was found for most of the pairs. Cross mapping was done with random library samples.

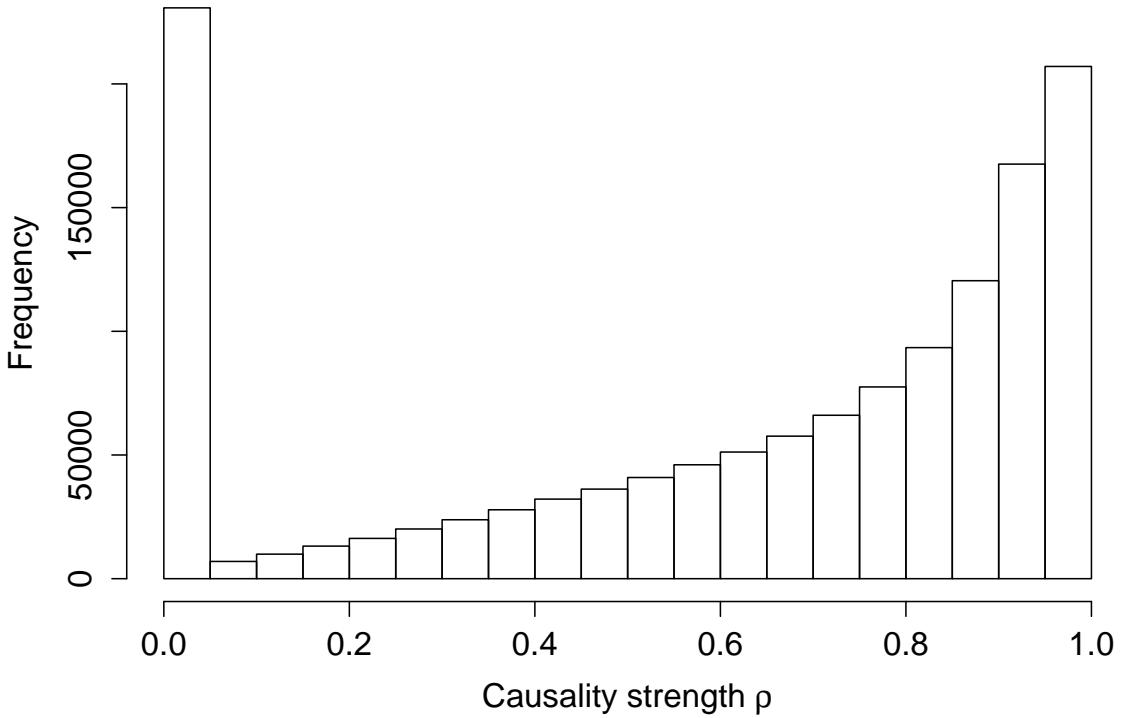


**Fig. 13:** Difference of rho scores between shown sample size and 100 samples. Decreasing sample size from the default 100 when calculating Sugihara Causality does not have a drastic affect on the acquired result. This shows that the data and method used are robust. Using this analysis, we conduct all further tests on a sample size of 20. Data shown is from the first 5 seconds of the experiment, using a library size of 80. Sliding windows of 200 ms were used, with a sliding step of 50 ms.

## X. DISCUSSION

Initial analysis shows that the causality network is very dense with highly weighted edges. The high density of the graph could have been a side effect of Sugihara's model ability to detect downstream causality. If that is the case, then many of the causal connections detected are in fact residuals of upstream interactions in the network.

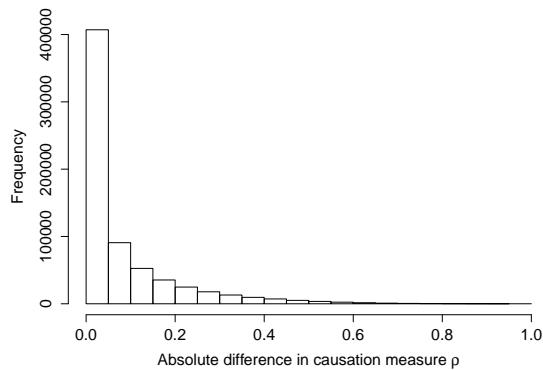
Downstream causality measures can be detected by observing both the magnitude of the cross map skill as well as the time lag that produces the greatest cross map skill (Fig. 3 in [34]). Following the assumption that downstream causality decreases in magnitude as it travels downstream in the network, we can use this to traverse the graph and rid of any paths that decreases in causality as it goes downstream.



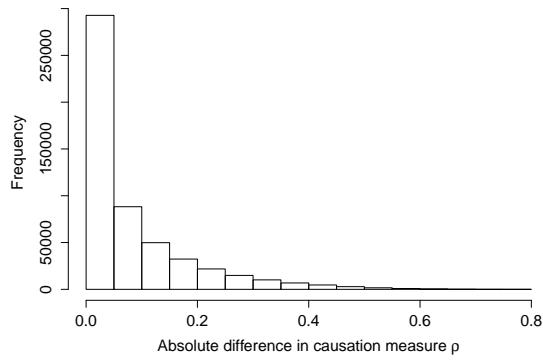
**Fig. 14:** The distribution of CCM skill ( $\rho$ ) during the entire experiment. Many relationships appear to be causal in the brain, with equally as many being non-causal throughout the experiment. Causality was calculated from signals of lumped regions after calculating the CSD. Cross mapping was done on every pair of regions with library size of 80, and each pair has two causality directions. Sliding windows of 200 ms were used, with a sliding step of 50 ms.

Concerning the high possibility of the presence of unidirectional forcing, Ye *et al.* showed unidirectional forcing can be untangled by inspecting the greatest time lag of the two that produces the highest causality measure (Fig. 2 in [34]). In order to allay the problem of unidirectional forcing, the best lag of each pair is considered. This is a tricky problem because there is no clear range for which to test the lag. This is because the time delay for neuronal activity is yet studied, and how that translates to EEG data could be tricky. We reserve the use of this method due to its computational complexity which would add to the already high time complexity of the analysis.

The theoretical implications of this model could present a novel representation of information flow in the brain and determining causality within the brain. If the graph output of this method is reliable, it could help outline information flow within the brain, much like one would observe



**(a)** Absolute difference of  $\rho$  between all pairs



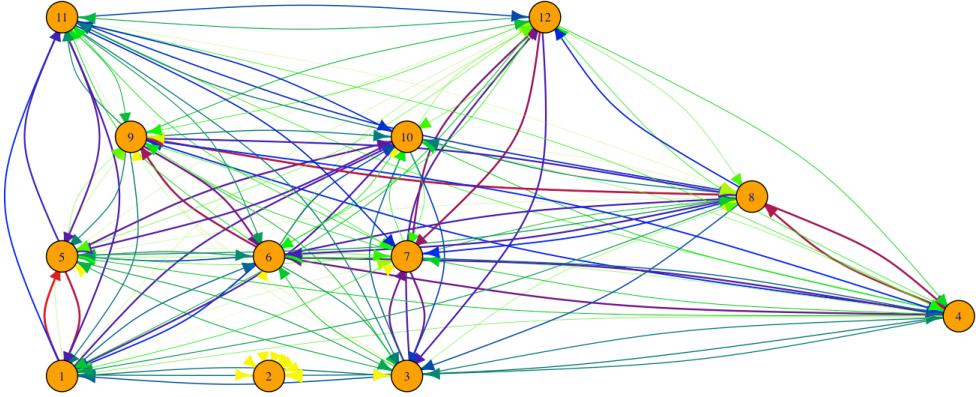
**(b)** Absolute difference of  $\rho$  between pair both of which  
is at least 0.2

**Fig. 15:** Difference of causality values within a pair is small, even when accounting for non-existing relationships where both causalities are below 0.2. This similarity between directions of causality in a pair could imply a bidirectional relationship between most regions, or could alternatively imply a unidirectional forcing (synchrony) phenomenon. Sliding windows of 200 ms were used, with a sliding step of 50 ms. A library size of 80 was used.

in a magnetic wave flowing through an fMRI recording.

## XI. FUTURE WORK

Future work will focus on verifying this model through controlled experiments. Such experiments could be in the form of stimulating a part of the brain (e.g. shining strong light on the eye to excite the visual cortex) and observing the model's behavior. One would expect a high value of out degrees from the specific region during such an experiment, as it attempts to convey a considerable portion of information to the rest of the brain. Moreover, a clear proof should be presented as to what the most reliable time window and step size ought to be when



**Fig. 16:** Sample graph constructed from calculating the sugihara causality between brain regions through CCM. Lumped brain regions correspond to the gray circular mapping in Fig. 11. Edge colors represent the strength of the causal relationship. From weakest to strongest: Yellow, Green, Blue, Red.

producing the causality graphs. Such a task can be done by measuring graph similarity of the same time segment as the time window gets shortened incrementally.

Continuing our efforts, we would like to integrate the neuroclustering algorithm developed by Lewis and Mello into this work [35]. This would allow us to discretize the EEG data into frames of epileptic seizure stages. Once these stages are identified and compartmentalized, the kCSD method will be applied to account for experimental design errors. A pairwise causality network will then be constructed using the Sugihara causality model, and the origin of the epilepsy will be localized during the initiation of the seizure.

Furthermore, the feature set of the neuroclustering algorithm could be augmented with the information of edge weights of the pairwise causation graph. The effect of such an integration could be tested to see if it improves classification metrics. Similarly, the neuroclustering algorithm

could be used to label seizures in neural data which then our pairwise causality algorithm could be tested against to see if the clustering of edge weights clusters epilepsy segments separately.

## XII. CONCLUSION

The paper shows promising initial results using the Sugihara CCM model to construct causality graphs between brain regions. We find that the brain network for this experiment is highly causal with a range of time windows. This, however, could be due in part to experimental design limitations, where the electrodes were 1 mm apart which might have caused electrical interference. To limit this phenomenon we used kCSD to preprocess the data. Initial results show a time varying graph in which information flow can be tracked. At the moment, more analysis is required to make conclusions on the capabilities of the pairwise causality graph model. Some of most incurring difficulties to overcome are the running complexity of the kCSD preprocessing and CCM algorithm required for the analysis of the amount of pairs in a large network, and the mathematical representation of information flow within the time-dependent graph. We plan on using the Neuroclustering algorithm to discretize the EEG data into epileptic seizures, extract causal network features from the stages, and train a k-means learning algorithm on the created feature set. The implications of these findings could relate more generally to discoverability of causality in modeling scalable natural phenomena. Real world applications manifest in localization of epilepsy in the brain. Furthermore, if the technique of distinguishing causal networks in systems and clustering their properties is successful, it could be a clear indication that the Sugihara causality model is able to detect causation in extremely complex systems comparable to the human brain.

## ACKNOWLEDGMENT

Special thanks goes to Dr. Somogivari and Dorottya R. from Wigner RCP, Budapest for providing the neuronal data used in this paper. Furthermore, Dr. Peter Erdi is thanked for his patient guidance of this research topic which was instrumental for the production of this paper.

## REFERENCES

- [1] E. B. E. B. Online., “Artificial intelligence (ai),” 2016 25 Sep.
- [2] W. S. McCulloch and W. Pitts, “A logical calculus of the ideas immanent in nervous activity,” *The bulletin of mathematical biophysics*, vol. 5, no. 4, pp. 115–133, 1943.

- [3] "Some specific models of artificial neural nets," <http://ecee.colorado.edu/ecen4831/lectures/NNet2.html>, accessed: 2016-10-16.
- [4] M. Minsky and S. Papert, "Perceptrons." 1969.
- [5] N. Yadav, A. Yadav, and M. Kumar, *History of Neural Networks*. Dordrecht: Springer Netherlands, 2015, pp. 13–15.
- [6] D. J. Finney, "A note on the history of regression," *Journal of Applied Statistics*, vol. 23, no. 5, pp. 555–558, 1996.
- [7] R. S. Fisher, C. Acevedo, A. Arzimanoglou, A. Bogacz, J. H. Cross, C. E. Elger, J. Engel, L. Forsgren, J. A. French, M. Glynn, D. C. Hesdorffer, B. Lee, G. W. Mather, S. L. Mosh, E. Perucca, I. E. Scheffer, T. Tomson, M. Watanabe, and S. Wiebe, "Ilae official report: A practical clinical definition of epilepsy," *Epilepsia*, vol. 55, no. 4, pp. 475–482, 2014. [Online]. Available: <http://dx.doi.org/10.1111/epi.12550>
- [8] P. Shafer and J. I. Sirven. (2010) Epilepsy statistics. [Online]. Available: <http://www.epilepsy.com/learn/epilepsy-statistics>
- [9] K. Allers, B. M. Essue, M. L. Hackett, J. Muhunthan, C. S. Anderson, K. Pickles, F. Scheibe, and S. Jan, "The economic impact of epilepsy: a systematic review," *BMC Neurology*, vol. 15, no. 1, p. 245, 2015. [Online]. Available: <http://dx.doi.org/10.1186/s12883-015-0494-y>
- [10] A. C. Vivas, A. A. Baaj, S. R. Benbadis, and F. L. Vale, "The health care burden of patients with epilepsy in the united states: an analysis of a nationwide database over 15 years," *Neurosurgical focus*, vol. 32, no. 3, p. E1, 2012.
- [11] K. S. Walia, E. A. Khan, D. H. Ko, S. S. Raza, and Y. N. Khan, "Side effects of antiepileptics a review," *Pain Practice*, vol. 4, no. 3, pp. 194–203, 2004. [Online]. Available: <http://dx.doi.org/10.1111/j.1533-2500.2004.04304.x>
- [12] P. Shafer and J. Sirven. (2013) Enew terms and concepts for seizures and epilepsy. [Online]. Available: <http://www.epilepsy.com/learn/types-seizures/new-terms-and-concepts-seizures-and-epilepsy>
- [13] E. E. Bailey, H. H. Pfeifer, and E. A. Thiele, "The use of diet in the treatment of epilepsy," *Epilepsy & Behavior*, vol. 6, no. 1, pp. 4–8, 2005.
- [14] K. W. Barañano and A. L. Hartman, "The ketogenic diet: uses in epilepsy and other neurologic illnesses," *Current treatment options in neurology*, vol. 10, no. 6, pp. 410–419, 2008.
- [15] J. Potworowski, W. Jakuczun, S. Łski, and D. Wójcik, "Kernel current source density method," *Neural computation*, vol. 24, no. 2, pp. 541–575, 2012.
- [16] J. Locke, *An essay concerning human understanding*, 1841.
- [17] G. Berkeley, *A treatise concerning the principles of human knowledge*. Philadelphia: JB Lippincott & Company, 1874.
- [18] C. W. J. Granger, "Investigating causal relations by econometric models and cross-spectral methods," *Econometrica*, vol. 37, no. 3, pp. 424–438, 1969.
- [19] G. Sugihara, R. May, H. Ye, C.-h. Hsieh, E. Deyle, M. Fogarty, and S. Munch, "Detecting causality in complex ecosystems," *science*, vol. 338, no. 6106, pp. 496–500, 2012.
- [20] G. S. Paul A. Dixon, Maria J. Milicich, "Episodic fluctuations in larval supply," *Science*, vol. 283, no. 5407, pp. 1528–1530, 1999.
- [21] E. R. Deyle and G. Sugihara, "Generalized theorems for nonlinear state space reconstruction," *PLoS One*, vol. 6, no. 3, p. e18295, 2011.
- [22] F. Takens, *Detecting strange attractors in turbulence*. Springer, 1981.
- [23] E. R. Deyle, M. Fogarty, C.-h. Hsieh, L. Kaufman, A. D. MacCall, S. B. Munch, C. T. Perretti, H. Ye, and G. Sugihara, "Predicting climate effects on pacific sardine," *Proceedings of the National Academy of Sciences*, vol. 110, no. 16, pp. 6430–6435, 2013.
- [24] X. Wang, S. Piao, P. Ciais, P. Friedlingstein, R. B. Myneni, P. Cox, M. Heimann, J. Miller, S. Peng, T. Wang, H. Yang, and A. Chen, "A two-fold increase of carbon cycle sensitivity to tropical temperature variations," *Nature*, vol. 506, no. 7487, pp. 212–215, 02 2014.

- [25] J. C. McBride, X. Zhao, N. B. Munro, G. A. Jicha, F. A. Schmitt, R. J. Kryscio, C. D. Smith, and Y. Jiang, "Sugihara causality analysis of scalp eeg for detection of early alzheimer's disease," *NeuroImage: Clinical*, vol. 7, pp. 258–265, 2015.
- [26] E. H. van Nes, M. Scheffer, V. Brovkin, T. M. Lenton, H. Ye, E. Deyle, and G. Sugihara, "Causal feedbacks in climate change," *Nature Climate Change*, vol. 5, no. 5, pp. 445–448, 2015.
- [27] A. A. Tsonis, E. R. Deyle, R. M. May, G. Sugihara, K. Swanson, J. D. Verbeten, and G. Wang, "Dynamical evidence for causality between galactic cosmic rays and interannual variation in global temperature," *Proceedings of the National Academy of Sciences*, vol. 112, no. 11, pp. 3253–3256, 2015.
- [28] J. M. McCracken and R. S. Weigel, "Convergent cross-mapping and pairwise asymmetric inference," *Physical Review E*, vol. 90, no. 6, p. 062903, 2014.
- [29] A. T. Clark, H. Ye, F. Isbell, E. R. Deyle, J. Cowles, G. D. Tilman, and G. Sugihara, "Spatial convergent cross mapping to detect causal relationships from short time series," *Ecology*, vol. 96, no. 5, pp. 1174–1181, 2015.
- [30] A. Wismüller, X. Wang, A. M. DSouza, and M. B. Nagarajan, "A framework for exploring non-linear functional connectivity and causality in the human brain: Mutual connectivity analysis (mca) of resting-state functional mri with convergent cross-mapping and non-metric clustering," *arXiv preprint arXiv:1407.3809*, 2014.
- [31] T. Hjornevik, T. B. Leergaard, D. Darine, O. Moldestad, A. M. Dale, F. Willoch, and J. G. Bjaalie, "Three-dimensional atlas system for mouse and rat brain imaging data," *Frontiers in neuroinformatics*, vol. 1, p. 4, 2007.
- [32] G. Paxinos, C. Watson, P. Carrise, M. Kirkcaldie, and K. Ashwell, "Chemoarchitectonic atlas of the rat brain," 2009.
- [33] W. Ebisuzaki, "A method to estimate the statistical significance of a correlation when the data are serially correlated," *Journal of Climate*, vol. 10, no. 9, pp. 2147–2153, 1997.
- [34] H. Ye, E. R. Deyle, L. J. Gilarranz, and G. Sugihara, "Distinguishing time-delayed causal interactions using convergent cross mapping," *Scientific reports*, vol. 5, 2015.
- [35] H. Ali, Y. Shi, D. Khazanchi, M. Lees, G. D. van Albada, J. Dongarra, P. M. Sloot, J. Dongarra, R. Lewis, C. A. Mello, and A. M. White, "Proceedings of the international conference on computational science, iccs 2012 tracking epileptogenesis progressions with layered fuzzy k-means and k-medoid clustering," *Procedia Computer Science*, vol. 9, pp. 432 – 438, 2012.