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The Road to Practical Epileptic Seizure Prediction Part-1

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Abstract

Researchers have been working on models of brain function for over 40 years, and while progress has been made in understanding and predicting the onset of epileptic seizures, a practical system remains elusive. Deconstructed and simplified models of the brain have failed time and again to capture the complex and nonlinear dynamics which arise at the system level during a seizure. Currently, the development and success of machine learning techniques in other fields, proliferation of affordable computing power and storage, and the open sharing of clinical datasets are all combining to attract and engage an interdisciplinary community of interested researchers. If this community pools their resources and talents, applies a rigorous discipline of validating their results, and works to improve the quality and diversity of patient time series data, it is extremely likely they will be able to translate the power of these techniques over to the field of neuroscience, producing breakthroughs in understanding and treating epilepsy and other neurological disorders.

Keywords: *Epilepsy; Machine Learning; Modeling; Algorithms; Prediction; Seizure*

Abbreviations: ECG: Electrocardiogram; EEG: Electroencephalogram;EMG: Electromygraphy; FAIR: Facebook AI Research group; GPU: Graphics Processing Unit;

Introduction

Epilepsy, one of the most common neurological diseases, affects over 50 million people worldwide. Epilepsy is a dynamic, non-linear disease characterized by numerous types of seizures, syndromes, and presentations. Because one of the most debilitating characteristics of epileptic seizures is their inherent unpredictability, the ability to reliably predict their onset would have a significant impact on overall morbidity. Arguably, a seizure prediction system would even improve mortality, as patients could mitigate their risk from potentially hazardous situations (e.g., driving, operating equipment) and increase their ability to influence the onset of seizures by applying therapeutics.

Tremendous progress in neuroscience over the past two decades has broadened the therapeutic armamentarium for epilepsy by increasing the number of pharmacological agents and devices available to clinicians and patients. However, at least 30% of all epilepsy cases remain refractory to current therapeutic modalities, contributing to the significant morbidity and mortality associated with this disease. Hence, the chronic and variable nature of epilepsy and lack of effective treatments create a therapeutic area of high unmet medical need.

For the past 40 years in life sciences and medicine, there has been a considerable interest in developing prediction algorithms using the power of mathematical and computational modeling to integrate a large quantity of biological and medical data. In epileptology in particular, researchers have sought to use statistical models and computer algorithms to predict the onset of epileptic seizures from EEG data [1]. However, nearly all published seizure prediction studies have been retrospective. In other words, despite the existence of many published seizure prediction algorithms, no Class 1 evidence of clinical usefulness (prospective, blinded, and randomized) exists.

That this remains an open area of research is a testament to the difficulty of the problem. In essence, an epileptic seizure is an abnormal firing pattern generated by a collection of neurons in the brain. In severe cases or cases where anti-seizure medications are not effective, the epileptogenic region may be surgically removed via a focal resection procedure.

For patients living with epilepsy, the ability to reliably determine when a seizure is about to occur would dramatically improve their quality of life, restoring a sense of predictability to an otherwise arbitrary and emotionally debilitating disease. Ideally, such a system would ingest patient data in real-time, either from inpatient monitoring systems or outpatient wearable devices. Using a model trained on population data, and refined on the patient's own history, the system could then make educated guesses as to when a seizure was imminent.

A reliable seizure prediction system could be integrated into a wearable device which would warn a patient of an imminent seizure, hopefully giving them enough time to make adequate preparation (such as pulling over if driving). As our understanding of the mechanisms underlying epilepsy grows, such a system could be used in a closed-loop seizure-prevention system where the detector triggers the release of antiepileptic drugs [2], or the activation of a brain stimulation device [3,4] to modulate neural activity back to normal function.

Because a seizure emerges from the dynamic interactions of a network of many neurons, a system-level approach is required. Most recently, people have attempted to use machine learning techniques to tackle this problem, with mixed success [5,6]. In the following, we describe the general features of machine learning as applied to the field of epilepsy, highlighting the associated challenges and opportunities.

Machine learning has become a widely-accepted approach to classification problems in other fields, such as the identification of fraudulent credit card transactions, recognition of handwritten characters, and detection of anomalies from aerospace sensor data. It is also gaining increased acceptance in the medical community due to an explosion in available patient data, with genomics as a prime example of where this is happening. Unprecedented computing power, combined with affordable storage, makes it feasible to apply sophisticated computational approaches to the healthcare field. Whereas traditionally, computers have been used to process data and extract summary statistics, we see them increasingly used as tools for discovery, not just for automation.

Materials and Methods

There are many broad definitions of the term "machine learning," but for our purposes we will focus on supervised binary classification algorithms. We will illustrate this approach through an example.

Consider a data set consisting of one hour of EEG data for each of 100 patients. One question we could ask is: "Which patients experienced a seizure during this hour?" To train a computer system to answer this question, we would first need a specialist to go through the data sets and label the data sets with a "yes" or "no" indicating whether that particular patient experienced a seizure. Training the system on labeled data, where the answer is known, is what makes the method supervised. The fact that there are only two classifications (seizure/non-seizure) makes the system binary. For this example, we could attempt to simply distill the specialist's approach down to a set of rules to be programmed into a computer, thus automating the classification of EEG data by rote application of these rules. This automation approach rapidly becomes very complex, as we must codify years of experience interpreting EEG data, as well as capture any nuances such as the specialist's knowledge of the particulars of the individual patient being evaluated. Such an approach breaks down entirely when we start to ask more complex questions such as, "When were we 90% sure a seizure was occurring?" or more interestingly: "How likely is it that a seizure will occur in the next ten minutes, and how sure are we of that likelihood?"

Rather than automating the application of a fixed set of rules to classify data, machine learning designs the system to learn how to distinguish categories using a set of features extracted from training data. These features could be as common as spiking rates or spectral peaks, or more exotic options such as Lyapunov exponents and similarity measures [7]. The machine learning approach attempts to determine, using the labeled set of training data, which collection of features are relevant, and how they can be combined—often in nonlinear ways—to best classify the data. As more labeled data becomes available, it can be used to improve the system through additional training. Model complexity (and the related risk of overfitting) is reduced by the practice of regularization, where elaborate models are penalized more heavily than simpler models during the training process, resulting in a desired balance between predictive power and complexity.

Another intriguing aspect of the machine learning approach is that a patient can become their own experimental control. The model can be trained on long-duration recordings of a patient, thus enabling better seizure detection based on personalized knowledge of that patient's own normal vs. abnormal brain function. The quality of such a system for epilepsy can be quantified by three metrics [6]: sensitivity, specificity, and latency. Specificity refers to the number of seizures correctly flagged, specificity refers to the amount of non-seizure data correctly passed, and latency refers to the lag between when a seizure is flagged by the system and the actual onset of that event as determined by the labeling specialist.

A potential obstacle in the construction of a system that is both sensitive and specific is that the nature of EEG may be a fundamental limiting factor [8]. EEG readings aggregate the electrical activity of large (centimeter-scale) areas, tend to be sensitive to only the superficial layers of the cortex, and suffer from distortions due to the propagation of the electrical signal through the physiological pathways from the site of generation to the detecting electrode. This difficulty may be mitigated by the incorporation of non-EEG data into the model [6], such as electrocardiogram (ECG), electromyography (EMG), and/or eye-tracking data.

It is important to highlight that these machine learning systems represent a very different paradigm from traditional parametric modeling or simulation techniques. In particular, they represent a departure from the traditional approach of building up a model from a set of building blocks in an attempt to represent the behavior of the system as a whole. Although we have good models of individual neurons, there remains tremendous variation in neural morphology and connectivity, and significant nonlinear dynamic complexity in even a limited set of neurons in an epileptic network. Because seizures are an emergent phenomenon of a complex system, reductionist techniques prove to be of limited utility, and we are encouraged to move away from the concept of recreating the epileptic brain as a simulation or set of rules. Rather, machine learning examines the features of signals coming from the actual epileptic brains themselves. The approach seeks to classify and anticipate the behavior of the brain based on what it is doing, not based on a separate simplified representation.

In contrast to a machine learning approach, an example of parametric modeling would be to describe a system using a straight line or bell curve. Each of those models has only two parameters: the slope and intercept in the case of the line, or the mean and variance in the case of the bell curve. If we wanted to calibrate such a model to our data, we would not need very many measurements to determine the two parameter values reliably. Increasing our data would incrementally improve the quality of our parameter estimates.

Similarly, a simulation differs from machine learning because it specifies a set of rules by which a system evolves, either deterministically or probabilistically, and the computer simply iterates through those rules to update the state of the system from its past and present configurations. In this case, data is used to tune the parameters of the simulation and to validate that the system has adequate predictive power. Again some data may be sufficient to have confidence that the model is behaving well, and additional data simply increases that confidence.

In contrast, we have no parametric or simulation model for epilepsy. While some network-based system models are being developed for schizophrenia [9,10], there does not yet exist a predictive model for epilepsy. Structural variations from brain to brain also limit the usefulness of generalized simulation. We have very limited prior information on which to construct our model, rather, we must rely on the data itself to point the way. This implies we need large amounts of data to have reasonable confidence that the system is both sensitive as well as specific. We are not trying to constrain the unknown values of predefined parameters; we are trying to quantify features of the data itself, and tease out the combination of features which presage a seizure. This underscores the importance of not just the quality of the data, but also the quantity of the data, and how that data is processed to draw inferences.

A common pitfall in machine learning is to evaluate the system on the same data used to train it. In the example earlier, we could imagine calibrating a model to perform very well on the data for the 100 patients by introducing a large number of parameters and complicated transformations. When we consider data from a new set of patients the system has not seen before, it would likely fail to be predictive. This failure to generalize is known as overfitting, and is a consequence of evaluating the performance of a system on its own training data. Rather, one should perform cross-validation, where the system is trained on part of the data, and evaluated on the remaining held-out data. For example, having information on 100 patients, we could train on 80 patients, and see how well the system performs on the remaining 20 patients it has not yet seen. Cross-validation consists of the rigorous application of this approach: repeatedly holding out different subsets of data, training the system, and evaluating its resulting performance.

The ultimate success and widespread adoption of these techniques will not be due to the algorithms, nor to the computers on which they run, but will be driven by the open and collaborative trends currently taking place in research centers around the world. These organizations are making large datasets of raw clinical data available for free, and many are also publishing the features and training algorithms they are using. This liberation of data not only allows the independent reproduction and testing of claims, but also encourages a much broader community of data scientists to build on that work. This open, decentralized approach to scientific problem solving brings tremendous intellectual resources to bear on these difficult problems.

This shift from the proprietary to the open is taking place in industry as well. Some of the largest recognized contributors to the application of machine learning methods to life sciences such as Google and IBM have opened up their tools (Tensor Flow and System ML, respectively) for people to use, maintain, and extend. Facebook's AI research group (FAIR) has contributed open source packages for Torch, and Nvidia provides free training and access to machine learning libraries optimized for their GPU accelerator hardware.

Much work remains to be done, however. Having a large quantity of data is not enough; one must also ensure the integrity of the data. Training sets must be labeled correctly by specialists to be useful, and once models are trained, they must be rigorously evaluated using a robust cross-validation system. Once a viable model is identified and trained, it must be deployed to the end user, which implies an entire ecosystem of software distribution. Whether the system is hosted on cloud servers or embedded into a medical device, careful thought must go into the software architecture, and thorough verification testing must be performed.

Conclusion

The development of a clinically-useful seizure prediction algorithm for epilepsy remains both desired and elusive. The emergent and system-level character of seizures makes it extremely difficult to construct a model which accurately captures the relevant behavior. The machine learning approach uses the features of the data itself to classify the signal, improving as more training data becomes available, and specializing to a patient's own particular brain activity signatures. A major trend in this area is the open sharing of not just patient data by research institutions, but also the tools and techniques of machine learning by major innovating companies. This opens up the arena to a much broader community of researchers, and has accelerated the translation of these powerful machine learning techniques over to healthcare. We consider it to be extremely likely that as these techniques continue to be adopted in neuroscience, they will generate spectacular breakthroughs in the understanding and treatment of epilepsy and other neurological disorders.

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Conflict of Interest

No perceived conflicts of interest for this publication.

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