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A phase-locked loop epilepsy network emulator

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ABSTRACT

Most seizure forecasting employs statistical learning techniques that lack a representation of the network interactions that give rise to seizures. We present an epilepsy network emulator (ENE) that uses a network of interconnected phase-locked loops (PLLs) to model synchronous, circuit-level oscillations between electrocorticography (ECoG) electrodes. Using ECoG data from a canine-epilepsy model (Davis et al., 2011 [6]) and a physiological entropy measure (approximate entropy or ApEn, Pincus 1995 [21]), we demonstrate that the entropy of the emulator phases increases dramatically during ictal periods across all ECoG recording sites and across all animals in the sample. Further, this increase precedes the observable voltage spikes that characterize seizure activity in the ECoG data. These results suggest that the ENE is sensitive to phase-domain information in the neural circuits measured by ECoG and that an increase in the entropy of this measure coincides with increasing likelihood of seizure activity. Understanding this unpredictable phase-domain electrical activity present in ECoG recordings may provide a target for seizure detection and feedback control.

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1. Introduction

Recent combinations of machine-learning based statistical classifiers [16], advanced information metrics [21], and publicly available electrocorticography (ECoG) data from patients and animal models [6,5] have begun to successfully identify biomarkers that predict seizures. However, specificity remains a challenge especially with regard to false positives [18,2].

While more data, better recording techniques, and more advanced classification algorithms will undoubtedly improve seizure prediction, these approaches lack a representation of the underlying neurophysiology that contributes to epileptic pathology. Theoretical and empirical work on epilepsy suggests that runaway network-level interactions produce the cascade of uncontrolled, high frequency oscillations (HFOs) that produce the voltage discharges that characterize seizures [27,13,25]. This mirrors emerging work on non-pathological brain activity that highlights the importance of coordinated oscillations for information flow between different neural processors [9,10,7]. Information routing in neural networks is often modeled with oscillatory phase dynamics between different neural populations. These phase-sensitive neural networks are frequently used to model phenomena such as recognition memory [11,15], wherein oscillations are used to bind together different memory components by locking different sub-processors to a target memory state. We reason that these same techniques could be used to emulate the circuit-level dynamics between neural populations that contribute to epileptiform activity, thereby identifying the circuit-level oscillatory cascade that precedes HFOs and seizures. Previous neural network models of epilepsy [17] have had success in generating seizure-like activity, and have called attention to the intrinsic difficulty of seizure prediction due to the underlying chaotic dynamics of seizure generation [1].

In the current work, we present an epilepsy network emulator (ENE), designed to be sensitive to unpredictable, non-linear fluctuations in the phase of neural communication. The ENE is a phase-locked loop neural-network (a PLL is a non-linear control loop that synchronizes the phase of the output signal to the phase of the input, see [8]) to model coordination between the recorded voltages from multiple ECoG sites in a canine epilepsy model [6]. In the current study, we lock the network directly to recorded ECoG voltages gathered during ictal and interictal periods and employ an entropy measure (approximate entropy, or ApEn, a measure of the entropy of patterns in physiological data, see [22]), to monitor how the entropy of the interactions between different

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ECoG sites changes over the course of seizure activity. As emulated interactions become less predictable (i.e., when ApEn of the ENE's phase-domain information increases), we can identify periods of time where the ENE is more likely to produce HFOs and produce voltage discharges. By comparing how the emulator's behavior is related to changes in recorded ECoG voltages we can identify how coordinated interactions between ECoG electrodes are related to ictal activity.

2. Methods

Phase locked loop trajectories: A PLL contains a voltage-controlled oscillator (VCO), a low-pass filter, and a phase detector (Fig. 1). It detects the phase-difference between a periodic input signal and the VCO, and adjusts the VCO to "lock" to the phase of its input.

If the input frequency and the internal frequency are different, or if the output of the PLL is perturbed (such as by the weights of PLL neural network), then there exists no steady-state solution [11,19], and the PLL cannot synchronously lock to the input. Instead there will be a class of solutions, and the PLL will find a low-energy limit cycle trajectory that orbits within this class. This limit-cycle trajectory is characterized by either (1) synchronizing with the harmonics of the different frequencies, (2) periodic synchronization to each frequency (such that the network is synchronized "on average"), or (3) chaotic behavior [15].

Because PLLs use voltages as inputs, they can map directly onto EEG (electroencephalography), ECoG, and LFP (local field potential) recordings. We map the raw, measured voltages one-to-one from an ECoG electrode to a PLL in our network. The network then attempts to synchronize with oscillatory phase or frequency information implicit in the changing ECoG voltages. The PLL network thus models network dynamics across electrode sites by locking to phase-frequency interactions present between electrodes.

Epilepsy data: We used canine epilepsy data [6] made public as part of the American Epilepsy Society Seizure Prediction Challenge. (https://www.ieeg.org/). This data consisted of intercranial EEG data from four dogs with naturally occurring epilepsy collected via a chronic implantable monitoring system over several months. EEG was sampled from 16 electrodes at 400 Hz, referenced to group average, and binned into 1 s samples labeled "interictal" or "ictal." In all cases, we use the raw voltages from these samples as inputs to our emulator and characterize the phase-trajectories of the PLLs in response to the different classes of data.

PLL epilepsy network emulator: We used a PLL neural network to emulate the cortical dynamics that contribute to eplieptiform activity in the canine model. Our network consisted of 16 PLLs, one for each recording electrode, connected via a symmetric weight matrix with uniform weights of 0.5 (Fig. 1). Each PLL's VCO had an internal frequency of 1 Hz. All used a third-order type 2 Chebyshev low pass-filter with $\tau = 0.4$ Hz, and a window size of 0.25 s. All implementations used a multiplicative phase detector. The dynamical system embodied by this network is characterized by

$$\dot{\vartheta}_i = \Omega + V(\vartheta_i)\sum_{j=1}^{n} s_{ij} V(\vartheta_j - \pi/2), \tag{1}$$

where ϑ_i is the phase of the ith PLL, Ω is the free-running frequency of the VCO, and $V(x)$ and $V(x-\pi/2)$ are $\sin(x)$ and $\cos(x)$ respectively.

Each PLL in this network was locked to voltages from one electrode in a single dog's chronic recording array. We observed the model's phase trajectories over a period of 8π (4 s). This network was fully implemented in python using the SciPy package (Jones, Oliphant, Peterson et al. 2001-, Open Source Scientific Tools for Python) and the PyEEG package [3] with data visualizations using PyQtGraph. In all cases, the two variables of interest are PLL phase (ϑ), and ECoG voltage (V). We plot these over time, and characterize the complexity of these trajectories using a measure of entropy.

Approximate entropy: Approximate entropy (ApEn) is a measure of the unpredictability of the fluctuations within a set of time-series data that was developed for computing the amount of information present in finite samples of physiological data [21]. ApEn has previously been used as a metric for predicting seizure activity from EEG and ECoG data [28,14]. ApEn is a measure of the likelihood that similar patterns in time-series data will be followed by dissimilar patterns. A low ApEn means that patterns in a time-series are likely to be repeated, a high ApEn means that patterns

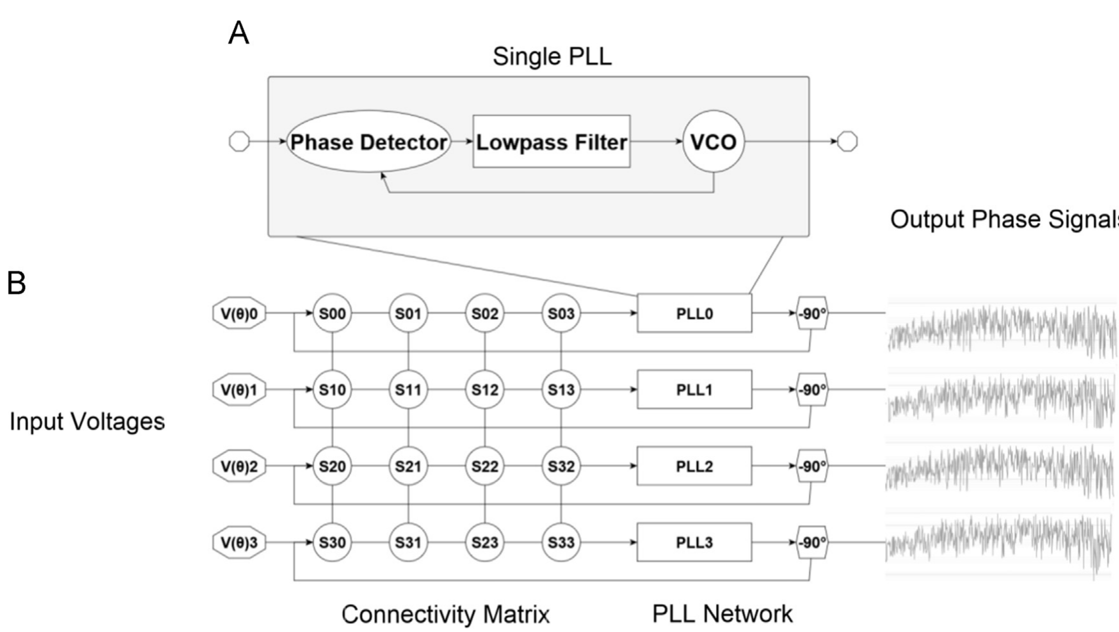

Fig. 1. Diagram of the PLL neural network emulator.