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Patient-specific bivariate-synchrony-based seizure prediction for short prediction horizons

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Summary This paper evaluates the patient-specific seizure prediction performance of pre-ictal changes in bivariate-synchrony between pairs of intracranial electroencephalographic (iEEG) signals within 15 min of a seizure in patients with pharmacoresistant focal epilepsy. Prediction horizons under 15 min reduce the durations of warning times and should provide adequate time for a seizure control device to intervene. Long-term continuous iEEG was obtained from 6 patients. The seizure prediction performance was evaluated for all possible channel pairs and for different prediction methods to find the best performing channel pairs and methods for both pre-ictal decreases and increases in synchrony. The different prediction methods involved changes in window duration, signal filtering, thresholding approach, and prediction horizon durations. Performance for each patient, for all seizures, was first compared with an analytical-Poisson-based random predictor. The performance of the top 5% of channel pairs for each patient closely matched the top 5% of analytical-Poisson-based random predictor performance indicating that patient-specific, bivariate-synchrony-based seizure prediction could be random in general (under the assumption that channel-pair prediction times are statistically independent). Analysis of the spatial patterns of performance showed no clear relationship to the seizure onset zone. For each patient the best channel pair showed better performance than Poisson-based random prediction for a selected subset of prediction thresholds. Given the caveats of comparing with this form of random prediction, alarm time surrogates were employed to assess statistical significance of a four-fold out-of-sample cross-validation analysis applied to the best channel-pairs. The cross-validation analysis obtained reasonable testing performance for most patients when performance was compared to random prediction based

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on alarm time surrogates. The most significant case was a patient whose testing set sensitivity and false positive rate were 0.67 ± 0.09 and $3.04 \pm 0.29\,h^{-1}$, respectively, for decreases in synchrony, an intervention time of 15 min and a seizure onset period of 5 min. For each testing set for this patient, performance was better than that obtained by random prediction at the significance level of 0.05 (average sensitivity of 0.47 ± 0.05). Moreover, there were 9 seizures in each testing set which gives greater power to this cross-validation result, although the cross-validation was performed on the best channel pair selected by within-sample optimization for all seizures of the patient. Further validation with larger datasets from individual patients is needed. Improvements in prediction performance should be achievable through investigations of multivariate synchrony combined with non-linear classification methods.

Introduction

Epileptic seizures are manifested by hyper-synchronous rapid neural activity (McCormick and Contreras, 2001; Avanzini and Franceschetti, 2003). This synchrony occurs primarily between the membrane potentials of neurons or their spike trains, but depending on the brain networks within which the seizure occurs, this synchrony at the neuronal scale can give rise to emergent field potentials that can also synchronize across different brain regions. Given the difficulty of experimentally analysing seizure-related synchrony at the neuronal scale in humans, intracranial electroencephalography (iEEG), which involves course sampling of mesoscopic field potentials across the brain, has been the tool of choice for analysing seizure-related synchrony (Arnhold et al., 1999; Lai et al., 2007; Kiss et al., 2008; Sabesan et al., 2009).

A primary application for the analysis of seizure-related synchrony has been epileptic seizure prediction (Litt and Lehnertz, 2002; Chávez et al., 2003; Lehnertz et al., 2003; Mormann et al., 2003a,b; Jouny et al., 2005; Mormann et al., 2005; Schelter et al., 2006b; Osterhage et al., 2007; Schad et al., 2008; Mirowski et al., 2009). It is thought that as brain activity moves along a trajectory towards a synchronized seizure state, there will be noticeable changes in synchrony in iEEG recordings that can be used to predict the seizure state. Automated seizure prediction algorithms can be useful for giving a patient a warning before an oncoming seizure, or for activating a deep brain stimulator to prevent or abort seizures — see Litt and Lehnertz (2002), Lehnertz et al. (2003), Mormann et al. (2007) and Hughes (2008) for reviews.

Mormann et al. (2003a,b, 2005) were one of the first groups to analyse the bivariate-synchrony of iEEG signals for the purposes of seizure prediction. Mormann et al. (2003b) performed an analysis of synchrony on data taken from 10 temporal lobe epilepsy patients by tracking mean phase coherence (MPC) and maximum linear cross-correlation between iEEG channel pairs. For both measures of synchrony, they observed pre-ictal decreases in synchrony for 12 out of 14 seizures. Mormann et al. (2003a) also performed a similar analysis on data from 18 focal epilepsy patients and they observed decreases in synchrony prior to 26 out of 32 seizures. Mormann et al. (2005) investigated the predictability of seizures by comparing pre-ictal and interictal distributions for 5 patients. For relevant phase synchrony measures it was found that statistically significant prediction performance could be obtained with prediction horizons of 240 and 5 min for a constant baseline and dynamic baseline, respectively. Chávez et al. (2003) analysed synchrony-based seizure prediction using phase synchrony and non-linear regression analysis in 2 patients with focal epilepsy. For the 10—25 Hz frequency band it was observed that decreases in synchrony occurred within 30 min before seizures in both patients. Jouny et al. (2005) observed no pre-ictal changes when they tracked a univariate autoregressive measure of synchrony in 2 patients. Schelter et al. (2006b) also used MPC for the purposes of prediction and obtained sensitivities (i.e. the proportion of seizures correctly predicted) in the range of 0.4—1 for a maximum false prediction rate (FPR — the number of false predictions per hour) of $0.15\,h^{-1}$. However, performance was only better than a random predictor for 2 out of the 4 patients and for certain prediction thresholds. Similar conditional results were obtained by Winterhalder et al. (2006) and Schelter et al. (2007). Using a synchrony measure based on multivariate coincidence detection of iEEG signals, Schad et al. (2008) obtained sensitivity of 0.5 with a maximum FPR of $0.15\,h^{-1}$ for 26 seizures recorded from 6 patients. This performance was better than that of a random predictor for certain thresholds. Mirowski et al. (2009) combined non-linear classifiers with phase-synchrony measures for 21 patients with dis-continuous data and found perfect prediction performance for 71% of the patients.

This paper addresses five major aspects of proper evaluation of bivariate-synchrony-based seizure prediction applied to individuals (Mormann et al., 2005) by (1) analysing synchrony between all iEEG channel pairs to find the channel pairs that provide the best synchrony-based seizure prediction performance for a given patient; (2) performing the analysis on long-term continuous iEEG data, instead of discontinuous chunks of data; (3) analysing the different times over which pre-ictal changes in synchrony could take place; (4) determining whether or not increases, as opposed to decreases, in synchrony are also relevant to seizure prediction; and (5) comparing the performance of a synchrony-based predictor with a random predictor. The following paragraphs summarise each of these aspects.

Chávez et al. (2003) observed focal decreases in synchrony preceding seizures in 2 patients. This focal decrease in synchrony is to some degree contrary to the results of Mormann et al. (2003a,b) who observed that pre-ictal desynchronization was not necessarily confined to the focus, but could instead be observed in more distant, even contralateral areas of the brain. These seemingly conflicting results highlight one of the problems of bivariate-synchrony analysis for seizure prediction; namely, it is difficult to analyse the