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Characterising the dynamics of EEG waveforms as the path through parameter space of a neural mass model: Application to epilepsy seizure evolution

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ABSTRACT

In this paper we propose that the dynamic evolution of EEG activity during epileptic seizures may be characterised as a path through parameter space of a neural mass model, reflecting gradual changes in underlying physiological mechanisms. Previous theoretical studies have shown how boundaries in parameter space of the model (so-called bifurcations) correspond to transitions in EEG waveforms between apparently normal, spike and wave and subsequently poly-spike and wave activity. In the present manuscript, we develop a multi-objective genetic algorithm that can estimate parameters of an underlying model from clinical data recordings. A standard approach to this problem is to transform both clinical data and model output into the frequency domain and then choose parameters that minimise the difference in their respective power spectra. Instead in the present manuscript, we estimate parameters in the time domain, their choice being determined according to the best fit obtained between the model output and specific features of the observed EEG waveform. This results in an approximate path through the bifurcation plane of the model obtained from clinical data. We present comparisons of such paths through parameter space from separate seizures from an individual subject, as well as between different subjects. Differences in the path reflect subtleties of variation in the dynamics of EEG, which at present appear indistinguishable using standard clinical techniques.

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Introduction

The electroencephalogram (EEG) is a cost-effective, non-invasive technique for capturing information about macroscopic brain dynamics. Since its inception in the mid 1920s (Berger, 1929) it has become a common tool for studying brain activity, particularly in the clinical setting. Advantages of the EEG include its non-invasive nature and cost, as well as a well documented relationship between state of arousal and dynamic waveforms of activity (e.g. sleep and delta rhythms; drowsiness and theta rhythms — see Niedermeyer and Lopes da Silva (2005) for a comprehensive review).

However, one of the challenges of interpreting EEG is understanding the underlying generators of the dynamic waveforms recorded using EEG and the mechanisms responsible for transitions between apparently normal and pathological brain states. A further challenge in the case of neurological disorders, is the likely patient-specific breakdown in these generators or mechanisms and determining the most appropriate way to characterise this. For these reasons, nonlinear differential equations are a natural candidate for exploring the generators of EEG (and Magnetoencephalography (MEG)). Their use in studying EEG dynamics has a history that may be traced back to the 1970s and the work of Lopes da Silva (Lopes da Silva et al., 1974) and Freeman (Freeman, 1975). These pioneering works led to a number of groups in the 1990s proposing models of resting state EEG phenomena such as the α-rhythm (Jansen and Rit, 1995; Liley et al., 2002; Robinson et al., 1997) which in turn prompted considerable activity developing models of the macroscopic brain dynamics recorded using EEG (see Coombes, 2010; Deco et al., 2008 for recent comprehensive reviews). Within the field of nonlinear differential equations, *bifurcation theory* is a tool for systematically studying the relationship between the output of the model and variation of underlying systems parameters, and this has been used to the study the dynamics of a number of macroscopic brain models (see for example Breakspear et al., 2006; Grimbert and Faugeras, 2006).

Our current work is motivated by the study of epilepsy, one of the most common serious primary brain diseases (with a worldwide prevalence approaching 1% (Banerjee et al., 2009)). Epilepsy carries with it significant costs, both financially (estimated at 15.5 billion euros in the EU in 2004, with a total cost per case between 2000 and 12,000 euros (Pugliatti et al., 2007)) and in terms of mortality (some 1000 deaths directly due to epilepsy per annum (Nashef and Shorvon, 1997) in the UK alone). Additionally, the seemingly random occurrence

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of seizures means that it is a debilitating condition resulting in a significant reduction in quality of life for people with epilepsy.

In the case of idiopathic generalised epilepsies (IGE), a patient history combined with the presence of a 3 Hz spike and wave (SW) discharge (a waveform with a prominent spike and slower wave component) in a routine EEG is often sufficient for diagnosis and has typically merited little further study. The idea that seizures may simply occur due to processes equivalent to a random switch were popularised from animal models of epilepsy (Suffczynski et al., 2004). However, subsequent studies of seizure frequency and duration in human patients suggested that the concept of a purely random switch is incorrect (Suffczynski et al., 2005). Indeed, closer inspection of clinical recordings from subjects with absence seizures shows that as the seizure develops, the recorded waveform evolves dynamically and often dramatically. For example, the amplitude of the spike may increase or decrease, additional spikes may appear – giving rise to so-called "poly-spike and wave" (PSW) complexes – and the wave and spike may interchange during the course of the seizure. Perhaps most significantly, the evolution of macroscopic brain dynamics is often similar when comparing recordings of different seizures from the same channel of the same subject, suggesting that the same underlying physiological mechanisms occurring come into play each time (see Fig. 1).

These observations have motivated a number of modelling studies to explore the mechanisms underpinning the transition between inter-ictal and ictal dynamics both in IGE (Breakspear et al., 2006; Marten et al., 2009a; Robinson et al., 2002; Rodrigues et al., 2006; Rodrigues et al., 2009; Suffczynski et al., 2004) and in other epilepsies (Liley and Bojak, 2005; Wendling et al., 2005). Most recently in Marten et al. (2009b) we described two mechanisms for the transitions between apparently normal and seizure states, as well as the transitions observed during seizures (e.g. the addition of extra spikes as the absence seizure evolves). Using a combination of mathematical analysis and numerical continuation methods (Dhooge et al., 2003; Rodrigues et al., 2010), bifurcations (both real and false) were shown to explain the appearance of oscillatory activity in EEG and the appearance of spikes. These studies also highlighted how changes in different parameters (for example excitation and inhibition) give rise to transitions in macroscopic brain dynamics that are equivalent to those observed clinically from EEG. It is this similarity in macroscale dynamics, resulting from fundamentally different underlying mechanisms, which could explain why clinical diagnosis based upon a cursory study of EEG often result in non-specific treatment outcomes (Benjamin et al., 2011).

In the current manuscript, we introduce a framework for estimating the parameters of an underlying model (in this case the brain model we studied in Marten et al., 2009b) such that the output of the model is matched to specific (user-determined) features of the temporal evolution of the EEG. However, the framework we describe is generic and can be usefully applied in any setting where there is a desire to fit a generative model to the dynamic features of macroscale neural recordings. Importantly, it overcomes the issue of the complex bifurcation structures which nonlinear models typically exhibit and often confound more straightforward parameter estimators. The underlying hypothesis of our work is that changes in model parameters reflect changes in underlying (but potentially unidentified) physiological processes and that the evolution of seizures can be related to parameter shifts over time. For this purpose we developed a genetic algorithm that can estimate a set of model parameters in finite time and explore how these parameters vary during the course of a seizure. As described above, the method we propose differs significantly from previous attempts to estimate parameters from EEG in that we attempt to fit the specific *characteristics* of each SW cycle of a seizure, rather than attempting to estimate parameters by fitting to spectral features in the frequency domain averaged over a longer period of time (Robinson et al., 2004; Wendling et al., 2005). To illustrate why it may be more appropriate to consider parameter estimation in the time-domain for a dynamically evolving process, rather than from power spectra in the frequency domain, we refer the reader to Fig. 6 of the article of Stam (Stam, 2005). In this Figure the author demonstrates how a precise match in power spectra can be achieved, even though the temporal dynamics of the approximation are wrong at almost every point in time.

The remainder of the paper is arranged as follows. In the Methods section we describe the background to the mathematical model whose parameters we wish to estimate and describe the assumptions that we make to allow us to relate clinical recordings with the model output. Subsequently we describe the genetic algorithm that we use to obtain parameter estimates. In the Results section we present the results of the algorithm, comparing parameter estimates with random selections of parameters, before considering the results from three subjects, each having two seizures. In the Discussion section we discuss our findings, make suggestions for improving both model and algorithm and comment on the direction of future research.

Methods

A generative model for EEG recordings

The macroscopic brain activity recorded by EEG can be thought of as the summation of the interactions of large populations of cortical neurons, predominately cortical pyramidal cells, which receive both excitatory and inhibitory postsynaptic potentials and as an output

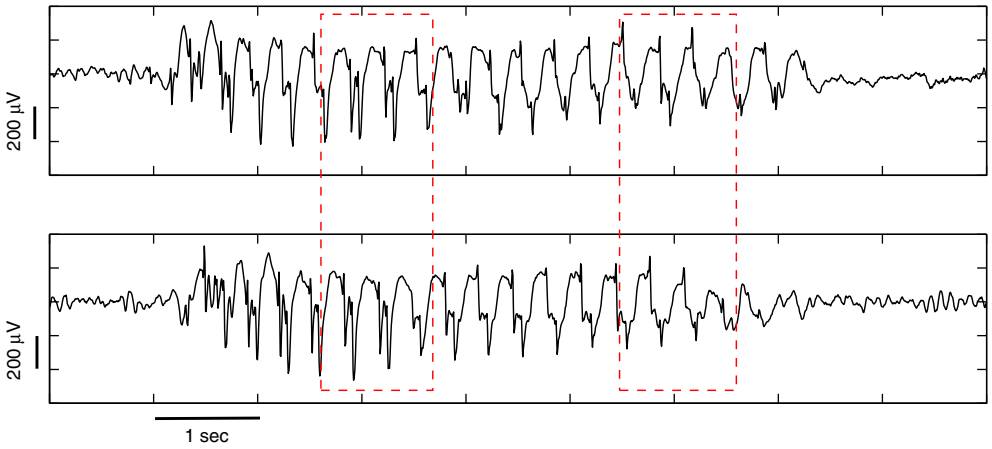

Fig. 1. Exemplar spike–wave discharges. Two separate spike and wave discharges (upper and lower panels), recorded from the same patient. The red dashed boxes illustrate similarly evolving features across each discharge. The recordings are taken from electrode placing O2, using a standard 10–20 system.

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