Epilepsy research using nonlinear signal processing

Angus Wallace BSc, BEng (Biomedical Honours)

July 9, 2008

Abstract

This thesis applies several standard nonlinear quantifiers to EEG analysis to examine both human primary generalised epilepsy (PGE) and rat models of human epilepsy.

We analysed rat EEG, and then used the analysed data, in parallel with an impedance recording, to better understand the events during experiments. Next, the nonlinear analysis of EEG was used to attempt to model the behaviour of the impedance data. This modelling did not yield a useful predictive tool, so we recommend the continued recording of impedance data as a means of augmenting EEG recordings.

The analyses were also applied to human data, and showed differences between the PGE and control groups in apparently normal EEG. We then attempted to use these differences to detect the presence of PGE in an unclassified subject – a diagnostic tool. This was done using a feed-forward neural network. We found that the inter-group differences were exploitable and facilitated the diagnosis of PGE in previously unknown subjects. The extent to which this is useful as a diagnostic tool should be assessed by further trials.

Finally, the analyses were used to examine data from a paralysed human subject, in an attempt to identify the mental task being performed by that subject. This was not successful, suggesting that the same analyses that were useful in discriminating between PGE and control were not useful in detecting the mental state of the subject. It was also apparent that the presence of EMG (in an unparalysed state) assisted task-classification.

TABLE OF CONTENTS

List of Figures

Acknowledgements

I owe many people thanks.

Firstly, thank you Selina, for your support and encouragement throughout my degree. Thanks, mum and dad, for always indulging my curiosity and interest in science. Thank you Carla and Brian for your help and support. Your proof-reading was very valuable, Brian – cheers. To my friends for their help and support – not only in the context of this thesis, but in all things. In particular, thank you Jesse, Hannah, Owen, Martin and Gez.

I think there are few people who have been as lucky as I to have such fantastic supervisors, thank you Kenneth and John. Your advice and support has been fantastic, and it has been a pleasure to work and socialise with you. Similarly, the assistance and friendship provided by my colleagues in the human lab and the rat lab has been wonderful. Marita, Emma, Trent, Sean and Steve, your advice, help and humour has been great. Thanks also to my Swedish collegues, especially Torsten and Michal for facilitating this research. Finally, thank you to all the volunteers who participated in our experiments – your time and effort are very much appreciated.

This work has been supported by a Flinders University Research Scholarship, a Wellcome grant, STINT and NHMRC grants.

Declaration

The work contained herein is my own, unless otherwise stated. This thesis is submitted in total fulfilment of the degree of Doctor of Philosophy at The Flinders University of South Australia.

Ethics approval was sought and obtained for all the data-acquisition experiments described herein.

Chapter 1

Introduction

1.1 What will be in this thesis

This thesis applies mathematical algorithms to the analysis of EEG data. The work is novel partly because of the data being analysed, and partly the approach. There are few groups applying a two-pronged human and animal-model EEG analysis approach that is comparative. Few also record data at the (high) sampling rate employed by us. Furthermore, although the analyses themselves are not novel, the signal-processing approaches are, as far as I have found, not attempted elsewhere. In particular the combination of nonlinear quantification of EEG and neural network training and modelling is a little-investigated area.

Because this thesis is concerned with the application of well-known nonlinear algorithms, it is useful to discuss what is available (the signal processor's *toolkit*), what was chosen, and why. It begins with an examination of signal processing. Linear analyses are described first, followed by nonlinear, as well as an explanation of the meaning of the terms *linear* and *nonlinear*. Both chapters 2 and 3 relate the analyses to EEG and epilepsy research, so that the practical aspects are apparent and the limitations clear.

Chapter 4 discusses classification, and examines several methods as well as their relative merits and disadvantages.

Chapter 5 introduces some physiological detail about the brain, including an examination of the important structures. It discusses the origin and limitations of EEG, and some means of analysing EEG data. It then discusses the current state of epilepsy research and has a brief examination of general signal-processing-based neuroscientific research.

The analyses contained in this thesis were performed on data collected in acquisition experiments in two epilepsy research laboratories in the Flinders Medical Centre, South Australia. I was not involved in the conception and goal-design stages of these acquisition experiments. However, I was involved with the execution of some of the rat experiments, and in the group discussing future developments and directions for the experiments. I was also involved in some of the fine-detail planning in the human experiments. The work in this thesis was performed on data derived from these experiments after the fact, and represents an extension of the original methodology around which the acquisition experiments were designed.

I have made a conceptual separation between the data acquisition experiments (where the data were acquired, but for a different purpose than that discussed in this document) and my signal-processing experiments (where I analysed the data and attempted to draw conclusions). For this reason, I have included a separate chapter on data acquisition. This helped prevent repetition (because I made multiple uses of the data from the data-acquisition experiments), but also helps to maintain the aforementioned conceptual separation between the data-acquisition and the data-analysis experiments. The three data acquisition experiments are discussed in the three sections of Chapter 6. Similarly, I used similar tools for the analysis of data in all of my experiments, and these tools are discussed in Chapter 7, which provides detail of those algorithms and processes.

Chapters 8 through 12 detail my analysis experiments. These are all de-

signed to explore the possibilities of using nonlinear analyses, modelling and classification to analyse EEG data.

1.2 Epilepsy and EEG analysis

Epilepsy is a poorly understood neurological condition that affects approximately 8 people in one thousand. Symptoms of the disease vary, but for many, epilepsy is a serious impingement on their quality of life. Poor understanding means that drugs prescribed to alleviate symptoms tend to be rather crude and ineffective – in fact, of the sufferers treated, 20% are not significantly assisted by drug therapy [48]. There are many different types of epilepsy, and all are characterised by seizures: periods of abnormal brain activity resulting in altered consciousness or loss of consciousness.

Electroencephalogram (EEG) is probably the most commonly applied neurological tool. EEG is a recording of electrical signals that the brain produces during its operation, and is thought to reflect the internal operation of the brain. The transition from normal EEG to a seizure, in a subject with primary generalised epilepsy, is shown in figure 1.1.

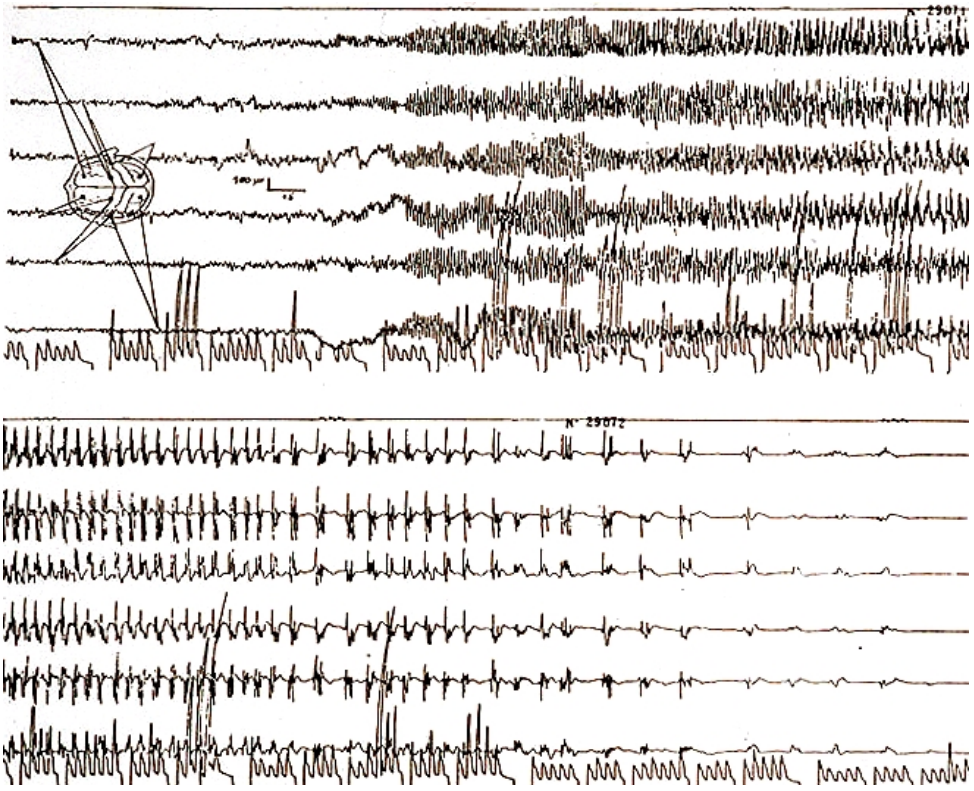

Figure 1.1: Human multichannel EEG showing seizure
This is an EEG trace, recorded by Gastaut and Broughton in 1976. It shows 6 channels of EEG in two rows. In the first row, there is a progression from relatively normal EEG through to a seizure, which calms in the second row.

The type of epilepsy shown in figure 1.1 is generalised, meaning that it emerges, simultaneously, across the entire brain[1]. The causes of generalised seizures are not understood, nor are the processes by which they begin and end. We do know of a genetic predisposition to such seizures (specific genes are associated with ion channel abnormalities), but this does not completely describe why some people are susceptible to such seizures while others are not, nor why some people respond well to medication while others do not.

The examination of EEG by a qualified and experienced technician or clinician is a very useful practice, and one that is likely to continue for some time. Such examination is able to uncover previously unknown pathologies, or allow a specific diagnosis to be made. However, this process is subjective, and

[1]There is another type of seizure, called a focal seizure, which looks similar, but affects only one area within the brain. A focal seizure may generalise (become a whole-brain event) at which point it looks similar to the generalised seizure shown in figure 1.1.

is not systematic nor necessarily repeatable [61]. Applying signal processing techniques (linear and nonlinear) allow the visualisation and quantification of different aspects of the EEG data. These are generally repeatable, automated and systematic, which are all advantages over the visual inspection of EEG.

For the purpose of better understanding epilepsy, it would be helpful to better understand the relationship between the disease, the symptoms, and the EEG. This is something that is needed because our understanding of the methods of brain function is rudimentary – the mechanisms of memory storage and retrieval, information processing, integration, decision making, high-level pattern recognition, and many others, are as yet poorly understood. What we do have is an understanding of many low-level mechanisms of the brain (the operation of neurons and simple neural circuits) and knowledge of the high-level function and operation of the *mind* (as studied in psychology, sociology, and other areas). What is lacking is a unifying theory by which we can move between these two worlds, the micro and the macro, and understand the systems' levels as greater and greater levels of complexity are reached.

One method of gaining insight into a complex system such as the brain is to examine it when its behaviour is dysfunctional, by highlighting aspects of behaviour that are otherwise occluded – it can act as an "extra data point." Because of this, a comparison between subjects with and without epilepsy can potentially provide useful data about brain function.

The process of analysing the brain in this way is made difficult, because our tools for examining functions of the living brain are crude. The principal tool is EEG, and this has limited spatial resolution and specificity (sections 2.2.8 and 5.2.1). Also, our ability to understand and analyse complex systems in general is limited. Emergent characteristics of complex systems are poorly understood, so the application of reductionist analysis techniques to such systems tends to result in a partial and fragmented comprehension. This is partly because our tools for the analysis of nonlinear systems are somewhat rudimentary,

and the collaboration between experts in nonlinear theory and neuroscience is somewhat immature (although great strides have been made in the last decade). Despite these shortcomings, there has been much success in the analysis of EEG using both linear and nonlinear tools. This is largely because it seems as though EEG is reflective of brain state and activity, despite its coarse-grained nature.

There is a long and successful tradition, probably 50 years, of linear analysis of EEG. Increasingly, we are becoming aware of some of the limitations of linear analysis – these are chiefly associated with linear analyses' inherent assumptions and resultant constraints. Nonlinear analysis makes fewer assumptions about the data and the system, and it also provides new tools and perspectives from which to approach signal processing.

1.3 How to analyse signals

Broadly speaking, there are two main groups of analyses. The first are the "linear" analyses. These are analyses which assume that the system under scrutiny obeys the rules of linear systems – a rule called *superposition*, which means that such a system can be expressed as the sum of its parts (more detail in chapter 2).

This is a useful principle, and allows the reductionism that is so important to many areas of scientific research. However, it is now recognised that most physical systems do not perfectly exhibit this characteristic, so that the employment of linear analyses means approximating systems as linear. Often, assumptions such as these do not greatly impact on the effectiveness – for example spectrographic analysis is commonly employed as a means to analyse systems known to exhibit nonlinear behaviour.

A nonlinear system is one which doesn't exhibit superposition and hence cannot be described by linear equations. The result of this is that nonlinear systems are in general not solvable mathematically, except in particular cases

for particular states of the system. This was particularly the case prior to the modelling afforded by computers. Nonlinear analysis does not make the aforementioned assumptions of superposition, and the result is that the conclusions drawn from such analyses can be more generalisable.