Comparison of predictability of epileptic seizures by a linear and a nonlinear method

Patrick E. McSharry[1,2], Leonard A. Smith[2,3] and Lionel Tarassenko[1]

Abstract— **The performance of traditional linear (variance based) methods for the identification and prediction of epileptic seizures are contrasted with "modern" methods from nonlinear time series analysis. We note several flaws of design in demonstrations claiming to establish the efficacy of nonlinear techniques; in particular, we examine published evidence for precursor identification. We perform null hypothesis tests using relevant surrogate data to demonstrate that decreases in the correlation density prior to and during seizure may simply reflect increases in the variance.**

Keywords— **Epilepsy, nonlinear, time series, prediction, surrogates, null-hypothesis.**

I. Introduction

EPILEPSY is the most common serious neurological disorder, affecting 1% of the population at some time in their life. Reliable and robust indicators of a seizure ahead of its onset would have considerable impact on the quality of life of a very large number of sufferers. They would also alleviate the work of EEG technicians who continue to score multi-channel records manually as automated seizure detection methods remain too inaccurate.

While it is likely that the processes underlying the EEG signal are nonlinear [1], [2], there is little concrete evidence that such signals are low-dimensional or display deterministic chaos. Nevertheless, a number of nonlinear statistics have been used, with varying degrees of success, to detect and predict epileptic seizures, these include: correlation density [3], [4], cross-correlation integral [5], [6], [7], Lyapunov exponents [8], [9], [10], synchronisation [11], [12], similarity measures [13], recurrence quantification [14] and nonlinear predictability [15], [16], [17], [18], [19]. One proposed mechanism for an epileptic seizure is that neurons in a particular region of the brain become synchronised [20], leading to a reduction in complexity. Some evidence of this synchronisation has been found by investigating EEG signals from neighbouring channels using intracranial [21], [11] and scalp [22] electrodes. It is the quantification of this relationship and how it is reflected in linear and nonlinear statistics applied to EEG signals that motivates this article.

Regardless of fundamental dynamics, the operational question is whether or not the fundamental nonlinearities are sufficiently robust that they may be exploited in the EEG signals: can modern nonlinear methods systematically outperform traditional "linear" methods based on analysis of variance? Martinerie *et al.* [4] claim that "deterministic non-linear processes are involved in pre-ictal neural reorganization in transition to seizure". In this article, we show that there is no clear evidence of improved performance for nonlinear methods applied to the database of intracranial EEG recordings previously investigated by Martinerie *et al.* [4]. In particular, we contrast a simple linear statistic (variance), with a nonlinear statistic (the correlation density [23]) used in [4].

The outline of the paper is as follows: section II outlines the procedure used for collecting the EEG recordings and summarises various statistical methods that may be used to analyse the EEG. Section III presents the results of computing moving estimates of both variance and the correlation dimension for the EEG recordings. The conclusion is given in section IV.

II. Methods

A. Intracranial EEG recordings

The recordings [4] are of 19 seizures collected from a group of 11 patients, each having medial temporal lobe epilepsy associated with hippocampal sclerosis. Electrodes, consisting of insulated wires with eight contacts separated by 8mm, were stereotaxically introduced along a posterior trajectory using MRI for guidance. Four contacts were located in the epileptogenic zone, the amygdalo-hippocampal complex; the more anterior contact was in the amygdala; and the remaining three were in the hippocampus. The data was then passed through a 32-channel amplifier system with band-pass filter settings of 0.5-99 Hz using an external reference over linked ears. Each of the recordings is 40 minutes in duration with 20 minutes of inter-ictal activity prior to the seizure. The data were digitised at 200 Hz, with 12-bit resolution, and de-trended: the dc-drift was removed by linear regression in each time analysis window. The spatial origin where the onset of the seizure is believed to occur, known as the epileptogenic zone, was confirmed using video monitoring. For each recording, four electrodes close to the epileptic focus were chosen. The time taken as reference for seizure onset was obtained by visual detection of ictal activity on the basis of low-voltage fast rhythmic activity ($>$ 10 Hz). Almost all patients were awake during the seizure, except for patients 4 and 7.

B. Linear statistics

One of the simplest linear statistics that may be used for investigating the dynamics underlying the EEG is the variance of the signal calculated in consecutive non-overlapping windows [24]. Let s_i denote the EEG signal at time i. The

[1]Department of Engineering Science, University of Oxford, Oxford OX1 3PJ.
[2]Mathematical Institute, University of Oxford, Oxford OX1 3LB.
[3]Centre for the Analysis of Time Series, London School of Economics, London WC2A 2AE.
E-mail: mcsharry@robots.ox.ac.uk

variance of this EEG signal is given by

$$\sigma^2 = \langle s_i^2 \rangle - \langle s_i \rangle^2, \quad (1)$$

where $\langle \cdot \rangle$ is the average taken over the time interval being considered. Esteller *et al.* [25] suggest measuring the energy (simply $\langle s_i^2 \rangle$) of the signal in consecutive windows of the EEG signal.

Another useful linear approach for investigating the EEG signal is its power spectrum [26], [27], [28], [29]. There are a number of different statistics which aim to summarise the information contained in the power spectrum. These include calculating the total integral of the power spectrum over all non-zero frequencies (note that this equals the variance of the signal), and the median frequency which estimates the "typical" frequency present in the signal [30]. Quasi-periodic fluctuations or 'rhythmic' behaviour characterised by a peak in the power spectrum at a specific frequency may be used to identify epileptic seizures in some cases [31].

C. Nonlinear statistics

C.1 State space reconstruction

The nonlinear analysis of data usually requires a state space reconstruction in order to investigate the underlying dynamics [32]. A delay vector reconstruction [33], [34], [35] of the signal s_i is defined by

$$\mathbf{x}_i = \left[s_{i-(m-1)\tau}, \ldots, s_{i-\tau}, s_i \right]$$

where m is the reconstruction dimension and τ is the time delay. This reconstruction may be obtained from spatial electrodes, time delays at one particular electrode, or a spatio-temporal mixture of these. If synchronisation between spatially localised electrodes is the hallmark of an epileptic seizure, then it is important to use a spatio-temporal reconstruction. Indeed any spatial correlations (whether linear or nonlinear) will show up in such a reconstruction space.

In the results presented here, $m = 4$ and τ was chosen using the geometrical approach introduced in [36], in order to facilitate comparisons with [4]. Four delays on each of the four channels yielded a 16-dimensional state space. Following Martinerie *et al.* [4] Principal Component Analysis [37] was applied to the state vectors within the learning set to obtain the set of principal axes with their associated singular values. States within the 16-dimensional state were projected onto the 8 principal axes with the largest singular values and the correlation density calculated in this 8-dimensional space.

C.2 Correlation density

One statistic which is capable of detecting both linear and nonlinear correlations is the correlation density $C(r)$ [23]; this may be computed by counting the fraction of pairs of points which are separated by a distance less than r. In mathematical terms, this may be written as

$$C(r) = \frac{1}{N(N-1)} \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \Theta(r - ||\mathbf{x}_i - \mathbf{x}_j||),$$

where Θ is the Heaviside unit function and $|| \cdot ||$ is the maximum norm distance.

Lerner [3] tracked the onset and progress of an epileptic seizure using the correlation density rather than the correlation dimension [23] claiming that the former gives results which are robust with respect to parameters such as the embedding dimension, the time delay and the particular value of r_0 used to evaluate $C(r_0)$.

D. Surrogate data

To determine whether or not there is information in changes in $C(r_0)$ beyond that available from observing that some linear statistic has changed, we constructed surrogate data sets with, for example, the same variance and tested whether observing changes in $C(r_0)$ in the real EEG signal yields precursors not seen in the surrogate. Any 'nonlinear' precursors in the real data are destroyed (by construction) in the surrogate data. Thus the idea is to construct data which 'looks like' the real data from a linear perspective and see if the nonlinear statistic of choice can distinguish the real recording from the surrogates.

To test how much of the variation in $C(r_0)$ results from changes in the variance associated with separate electrodes, we constructed surrogate time series [38], [39], [40], [41], [42] to mimic the linear temporal correlations. We employed the technique introduced in [39], [42] using freely available software documented in [43] to produce surrogates. Each surrogate maintains the probability distribution function and approximates the power spectrum of the real data, thereby preserving linear temporal correlations. These surrogates do not maintain any nonlinear correlations.

Relevant surrogates reflect the obvious properties of the data, in particular that the variance in different windows (or blocks) of the data changes with time. Hence we refer to these surrogates as *block* surrogates. All surrogates employed in this paper are block surrogates, that is they were constructed window by window so as to replicate the obvious time dependency of the linear correlations found within each window in the original recordings. Blocks of 30 seconds duration were used. We constructed block surrogates independently for each electrode as described above and refer to these as Block Univariate (BU) surrogates.

Another obvious property of the data is the cross correlation between electrodes; surrogates which retain both the linear temporal and linear spatial cross correlations are referred to as *multivariate surrogates* [40]. In this particular case the multivariate aspect is restricted to the linear cross-correlations (either global or within each block). Obviously, we may have either Global Multivariate (GM) surrogates (as used in [4]) or Block Multivariate (BM) surrogates.

III. Results

A. Variance

Spatio-temporal changes in each of the 19 intracranial recordings from 11 patients are illustrated using a moving window estimate of the variance (Fig. 1). The first num-

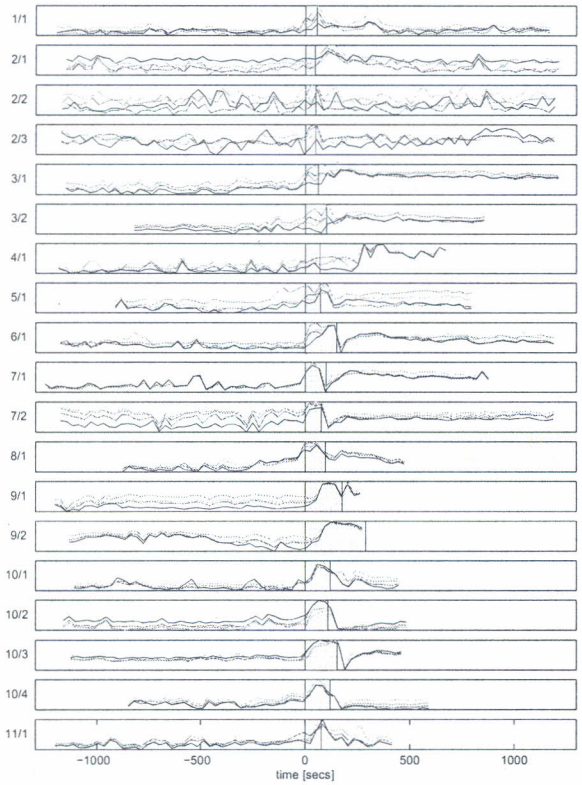

Fig. 1. Moving variance for each of four intracranial electrodes from the 19 recordings investigated in Martinerie *et al.* [4]. Each label specifies the patient (1 to 11) and recording number for that patient. Seizure periods are illustrated by the shaded regions. The vertical axes have a logarithmic scale ranging between the minimum and maximum variances.

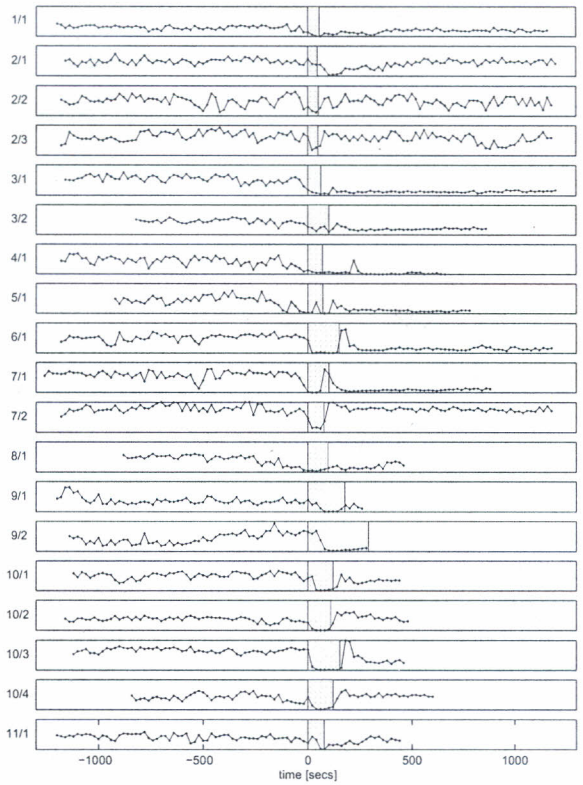

Fig. 2. Analysis of intracranial EEG recordings using $C(r_0)$ calculated in non-overlapping 30 second windows. Seizure periods are illustrated by the shaded regions. The vertical axes have a linear scale ranging from 0 to 1.

ber of the label is the patient index and the second is the recording index. In each panel, the lines denote the variance computed over non-overlapping 30-second windows for each of the four intracranial electrodes used for recording the EEG at the epileptic zone [4]. The shaded region in each panel denotes the time period which clinicians have marked as containing the epileptic seizure for that particular recording.

The moving variance (Fig. 1) captures information about the temporal and spatial activity. Note the marked increase in variance during all the seizures apart from recordings 2/1 and 4/1 where the variance increases after the seizure finishes. This late identification may be due to an error in the method used for calculating reference times for the seizure onset [4]. There is generally good agreement between the levels of variance at the four electrodes, except for recordings 2/2 and 2/3. Note also that during the seizure in recording 3/2, one electrode registers decreasing variance whereas the others show increasing levels of variance. Variance provides a benchmark with which other statistics must be compared, in as much as the use of complicated nonlinear statistics can only be justified when they are seen to outperform traditional alternatives.

B. Correlation density

Martinerie *et al.* [4] calculated $C(r_0)$ for the recordings in the same database as that which we investigated here and reported that it yielded precursors to epileptic seizures in 10 out of the 11 patients (all apart from patient 9). We calculated $C(r_0)$ in non-overlapping 30-second windows for the intracranial EEG data (Fig. 2), using a value of r_0 (following [4]) such that $C(r_0) \approx 0.5$ during the first 30-second window.

Recall that the correlation density $C(r)$ is the fraction of pairs of points in the reconstructed state space which lie within a given length scale r and therefore provides a geometrical measure of the clustering properties of the points. Once r_0 is fixed, there is an obvious relationship between changes in the variance and changes in $C(r_0)$: if the variance increases then $C(r_0)$ will decrease (Fig. 1 and 2). Note that while variance is computed from distances between the signal and the average at one electrode, $C(r_0)$ is calculated from distances within the spatio-temporal reconstruction state space, thereby incorporating both spatial and temporal correlations.

On the other hand changes in the temporal correlations at a single electrode will change the distribution of points in the reconstructed state space even if the variance is constant. Such a change in the distribution of points almost certainly changes $C(r_0)$, similarly for changes in the spatial

correlation between electrodes. Finally nonlinear spatio-temporal correlations which do not affect linear statistics can also change $C(r_0)$. All this implies that changes in $C(r_0)$ would not necessarily be picked up by the variance. The use of nonlinear methods for diagnosing medical disorders can only be justified by showing that they outperform well-understood traditional linear statistics. In the following, we stress the need for relevant null hypotheses and demonstrate that these should relate to the detection method being tested.

C. Null hypothesis testing

Martinerie *et al.* [4] "constructed multivariate surrogate data from each raw data set in such a way that the linear correlation within each component time series and the cross-correlation between them is preserved". It is obvious (Fig. 1) that such GM surrogates do **not** reflect the temporal changes in variance. If the entire duration of a recording is used to construct the surrogates (as was done in [4]), then temporally localised events displaying large variance tend to be dispersed throughout the surrogate. The real recording is easily distinguished by eye from among a group of such GM surrogates. Thus it is not surprising that the values of $C(r_0)$ calculated for the real recording (Fig. 2 of [4]) are wildly different to those calculated for the surrogates. The results reported in [4] are 'statistically significant', but the null hypothesis is medically irrelevant. Changes in variance (heteroscedasticity) can be as easily detected by monitoring the variance as by the more complicated estimation of $C(r_0)$. The use of the GM surrogates implies that the variance changes before the seizure, not that $C(r_0)$ outperforms a linear statistic.

The use of block surrogates is crucial to applications like this. There is a strong argument that surrogate data 'should' address a well defined null hypothesis. More important, however, is that it address a relevant null [41]. GM surrogates are particularly inappropriate in this study since we wish to assess the usefulness of nonlinear methods against time dependent (block-wise) linear statistics.

For recording 8/1 we calculated the variance averaged across the four electrodes (Fig. 3a). In addition $C(r_0)$ was calculated for this recording and ten BU surrogates (Fig. 3b). These surrogates also display decreasing values of $C(r_0)$ when approaching the seizure, suggesting that this phenomenon is simply due to an increase in variance. Nonetheless there are differences between the BU surrogates and the original recordings suggesting that spatial correlations and perhaps nonlinear correlations are also relevant for determining $C(r_0)$. We also constructed ten BM surrogates which also preserve the linear spatial correlations. Inclusion of the linear spatial correlations provides a better agreement between $C(r_0)$ calculated for the real recording and the BM surrogates (Fig. 3c). There are still some discrepancies between $C(r_0)$ derived from the real recording and the BM surrogates which are due to nonlinear effects. While $C(r_0)$ stays within five standard deviations of the mean of the $C(r_0)$ values calculated using the BM surrogates, it remains above this threshold (corresponding approximately to the 95% significance level) both during and for 350 seconds after the seizure. This suggests that while there is no evidence of nonlinearity before the seizure, there may be nonlinear activity both during and after the seizure onset. Note, however, that there is no reason to invoke nonlinear activity in order to explain the decrease in $C(r_0)$ prior to the seizure.

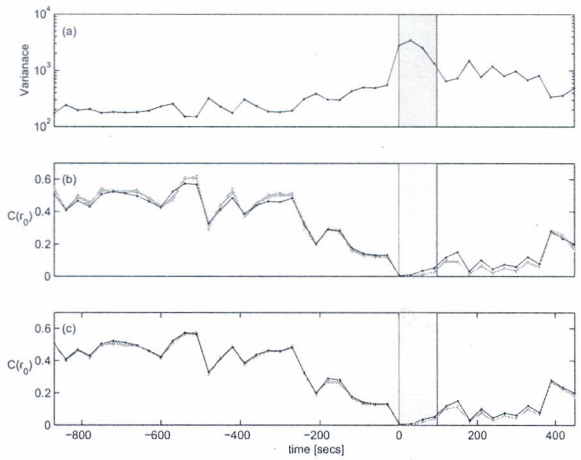

Fig. 3. Analysis of recording 8/1: (a) variance averaged across four electrodes, (b) $C(r_0)$ for original recording (black) and BU surrogates (grey) and (c) $C(r_0)$ for original recording (black) and BM surrogates (grey). Seizure periods are illustrated by the shaded regions.

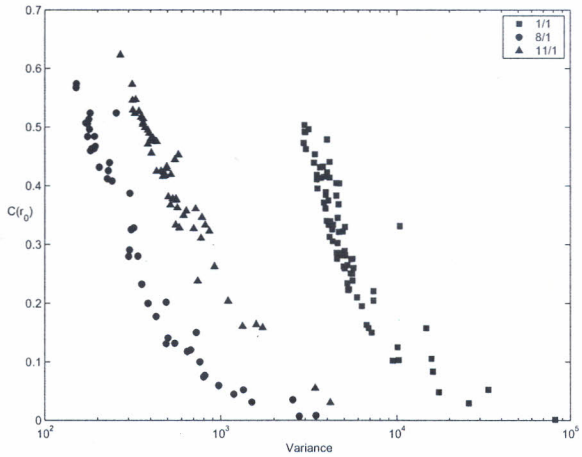

Fig. 4. Comparison of $C(r_0)$ with variance for recordings 1/1 (squares), 8/1 (circles) and 11/1 (triangles), showing the clear relationship between $C(r_0)$ and variance. Note the logarithmic scale on the horizontal axis.

A comparison between $C(r_0)$ and variance for a number of recordings (Fig. 4) shows that $C(r_0)$ is highly dependent on the variance. This demonstrates that in these cases there is little information in $C(R_0)$ that is not available in the variance. There is little justification for using $C(r_0)$ instead of variance as a statistic for predicting the epileptic seizures in this database.

IV. Conclusion

Whatever statistic is measured, detecting a "precursor" requires one to define some algorithm for identifying some recognisable change in that statistic. It is not our intent to discuss the details of such algorithms, beyond noting that, given the similarity of BM surrogates to the real data, it is likely that any precursor seen in a complicated nonlinear statistic would also be seen in variance. Rather, we stress the need for any such algorithms to be tested for false positives: long durations of seizure-free data *must* be analysed to see how many false positives an algorithm produces. We have been unable to obtain such long duration records on any of the patients for which previous techniques have been published.

The most striking result from this investigation is that variance seems to perform just as well as the nonlinear technique considered here. We employed BU and BM surrogates to determine the role of different linear correlations in determining the value of $C(r_0)$. These surrogates were constructed window by window to preserve the variance in each window used for calculating $C(r_0)$. Both temporal and spatial linear correlations were required to yield similar values of $C(r_0)$. Martinerie *et al.* [4] used GM surrogates, effectively assuming the variance of the signal was *constant* in time. These surrogates are inappropriate if the signals are obviously heteroscedastic (as the EEG signals are) and the (high) significance levels they report are irrelevant to the question of whether or not a nonlinear statistic is *required*. Their significance tests are completely consistent with *changes* in variance being a precursor (their surrogates are flawed). For all the recordings considered, our results show that the changes in variance account for their [4] observed changes in $C(r_0)$ and provide no evidence for additional information in $C(r_0)$ beyond that provided simply by measuring the variance.

To establish the clinical use for any seizure detection or prediction scheme it is necessary to test on out-of-sample data sets. This test should include evaluating a given statistic on numerous EEG recordings which are known not to contain an epileptic seizure. Comparisons between different statistics could be facilitated by calculating the number of false positives. Whilst there are a number of groups applying various statistical methods to databases of EEG recordings, there has been remarkably little effort made to contrast these methods [4], [44], [13], [10] and to evaluate their performance on different databases. To establish whether any of these methods can be used in a clinical setting will require either the collection of a very large database of recordings of sufficient duration (many hours) and/or increased co-operation between a number of independent research groups.

Acknowledgements

We would like to thank Martinerie *et al.* [4] for supplying their database of intracranial EEG recordings. This research was supported by EPSRC grant GR/N02641 and ONR grant N00014-99-1-0056.

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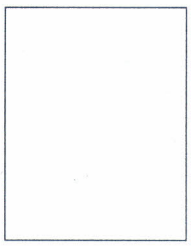
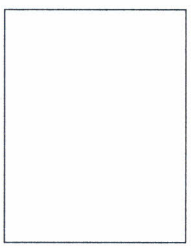
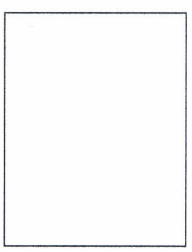


Patrick E. McSharry was born in Leitrim, Ireland in 1972. He received the BA in Theoretical Physics in 1993 and the MSc in Electronic & Electrical Engineering in 1995 from Trinity College Dublin. He was awarded the Scatcherd Scholarship in Science and a Marie Curie Research Fellowship in 1995 and received the DPhil in Mathematics from the University of Oxford in 1999. He is currently with the Department of Engineering Science and the Oxford Centre for Industrial and Applied Mathematics in the University of Oxford. His research interests include time series analysis, quantitative data analysis, mathematical modelling, forecasting and biomedical signal processing.



Leonard A. Smith received a BS in Physics, Mathematics and Computer science from the University of Florida and a PhD in Physics from Columbia University. He is a Reader in Statistics at the London School of Economics (LSE) and a Senior Research Fellow at Pembroke College, Oxford. He is also Director of the Centre for Analysis of Time Series at LSE and was 2002 Selby Fellow of the Australian Academy of Science. His research interests include ultimate limits to predictability; the generation and evaluation of estimates of forecast uncertainty in physical and mathematical systems; nonlinear modelling techniques; and nature of the relationship, if any, between physical systems and our models of them; the definition of noise; and nonlinear time series analysis.



Lionel Tarassenko MA, DPhil, FREng, FIEE was born in Paris in 1957. He gained the degrees of BA in Engineering Science in 1978, and DPhil in Medical Engineering in 1985, both from Oxford University. After graduating, Lionel Tarassenko worked for Racal Research Ltd on the development of digital signal processing techniques, principally for speech coding. He returned to Oxford University at the end of 1981 to study for a DPhil in medical electronics. He then held a number of positions in academia and industry, before taking up a University Lecturership in Oxford in 1988. Since then, he has devoted most of his research effort to the development of neural network techniques and their application to signal processing and diagnostic systems. He has been the holder of the Chair in Electrical Engineering at Oxford University since October 1997. He was elected to a Fellowship of the Institution of Electrical Engineers (IEE) in 1996, when he was also awarded the IEE Mather Premium for his work on neural networks, and to a Fellowship of the Royal Academy of Engineering in 2000.