

for tests of relevant null hypotheses^{6,7} and their immediate relation to the detection method in the diagnosis of medical disorders. Ultimately, the operational use of proposed complicated statistics can be justified only by showing that they out-perform well-understood traditional statistics (such as variance) or provide complementary information. The fact that the signal itself may be demonstrably nonlinear is simply not the relevant question when event detection is the aim.

To establish the efficacy of any new detection approach to medical diagnosis, we argue first for surrogate data tests against a null hypothesis relevant to some simple traditional statistic, and second for quantification of the false alarm rate. In the present case, the first point could be addressed using surrogates that preserve the temporal variation in the variance; the second point would require an experimental design including long records of seizure-free data.

Competing interests statement

The authors declare that they have no competing financial interests.

PATRICK E. MCSHARRY^{1,2},
LEONARD A. SMITH^{1,3} &
LIONEL TARASSENKO²

¹Mathematical Institute and ²Department of Engineering, University of Oxford, Oxford, UK

³Centre for the Analysis of Time Series, London School of Economics, London, UK
E-mail: mcsharry@maths.ox.ac.uk

Martinerie et al. reply—Until 1998, neuroscientists thought that epileptic seizures began abruptly, just a few seconds before clinical onset. It was during that year that two independent studies^{4,8} showed that the non-linear time series analysis of EEG data could reveal dynamical changes several minutes before seizure onset. The usefulness of non-linear measures for the detection of pre-ictal changes has since been confirmed⁹. This new approach has opened a new field of seizure anticipation and defined a framework for better understanding of seizure generation mechanisms.

McSharry et al. have re-analyzed our 1998 database and have shown that the non-linear index is sensitive to amplitude variance fluctuation. We have been aware of this limitation for some

time now. We developed, in 1999, a new method¹⁰ that did not involve the reconstruction of the dynamics from the amplitude of the signal, presenting a number of practical advantages over our previous method. The new method measures similarity to quantify the extent to which the EEG dynamics, reconstructed from the phase information, differ between periods taken at distant moments in time. The phase is defined as the time between two successive zero-crossing intervals. This relative measure reveals the spatial distribution of pre-ictal dynamic changes (both linear and non-linear) that involve the epileptogenic area but do not seem to be confined to the restricted ictal onset region. Furthermore, it is very robust against noise and artifacts, and fast enough to be carried out in real time.

The surrogate data that we had selected for the 1998 study to test the presence of deterministic structure in the time series⁴ had been built for each block of data (20 s; this may not have been clear in the paper) and were designed to reject a null hypothesis of a non-linear transformation of linearly filtered noise. Thus, the variances of the raw data and surrogate data were the same. We found a statistical difference between the values of $C(r_0)$ calculated from the raw data and those calculated from the surrogate data, which led us to reject this null hypothesis. We know that one should be extremely careful with the use of surrogate procedures (which can be very sensitive to the presence of spikes in the data and detect spurious non-linearity¹¹, for example). It is advisable to obtain consistent results with more than one type of surrogate, to get an indication of non-linear deterministic structure. New strategies and algorithms are now available¹².

In conclusion, our recent results^{13,14} using the similarity method support the idea that pre-ictal dynamic changes (either linear, non-linear or both) have a higher probability of occurring before epileptic seizures. As previously reported¹⁵, McSharry et al. suggest that some linear methods can detect pre-ictal changes in a manner similar to non-linear methods. Both analyses probably constitute different ways of viewing the same thing and some combination of them will be a good method for reliable seizure anti-

pation. Real progress may require collaboration between research groups, which has already begun in an international program (special interest group session on engineering and epilepsy, 56th Annual Meeting of the American Epilepsy Society, Seattle, Washington, December 6–10, 2002; and the First International Conference on Seizure Anticipation, Bonn, Germany, April 24–27, 2002).

Competing interests statement

The authors declare that they have no competing financial interests.

J. MARTINERIE¹, M. LE VAN QUYEN¹,
M. BAULAC^{2,3} & B. RENAULT¹

¹CNRS/Laboratoire de Neurosciences Cognitives et Imagerie Cérébrale,

²Unité d'Epileptologie and ³INSERM/Unité Cortex et Épilepsie,

Hôpital de la Salpêtrière, Paris, France

E-mail: Jacques.Martinerie@chups.jussieu.fr

- Schreiber, T. Is nonlinearity evident in time series of brain electrical activity? in *Chaos in Brain?* (eds. Lehnertz, K., Elger, C.E., Arnhold, J. & Grassberger, P.) 13–22 (World Scientific, Singapore, 2000).
- Theiler, J. On the evidence for low-dimensional chaos in an epileptic electroencephalogram. *Phys. Lett. A* **196**, 335–341 (1995).
- Grassberger, P. & Procaccia, I. Characterization of strange attractors. *Phys. Rev. Lett.* **50**, 346–349 (1983).
- Martinerie, J. et al. Epileptic seizures can be anticipated by non-linear analysis. *Nat. Med.* **4**, 1173–1176 (1998).
- Theiler, J., Eubank, S., Longtin, A., Galdrikian, B. & Farmer, J.D. Testing for nonlinearity in time series: the method of surrogate data. *Physica D* **58**, 77–94 (1992).
- Smith, L.A. Identification and prediction of low-dimensional dynamics. *Physica D* **58**, 50–76 (1992).
- Allen, M.R. & Smith, L.A. Monte Carlo SSA: detecting irregular oscillations in the presence of coloured noise. *J. Clim.* **9**, 3373–3404 (1996).
- Lehnertz, K. & Elger, C.E. Can epileptic seizures be predicted? Evidence from nonlinear time series analysis of brain electrical activity. *Phys. Rev. Lett.* **80**, 5019–5022 (1998).
- Sackellares, J. et al. *Chaos in the Brain?* (eds. Lehnertz, K. et al.) 112–133 (World Scientific, Singapore, 2000).
- Le Van Quyen, M. et al. Anticipating epileptic seizure in real time by a nonlinear analysis of similarity between EEG recordings. *NeuroReport* **10**, 2149–2155 (1999).
- Schreiber, T. & Schmitz, A. Surrogate time series. *Physica D* **142**, 346–382 (2000).
- Rapp, P.E. et al. Surrogate data pathologies and the false-positive rejection of the null hypothesis. *Int. J. Bifurcation Chaos* **11**, 983–997 (2001).
- Le Van Quyen, M. et al. Anticipation of epileptic seizures from standard EEG recordings. *Lancet* **357**, 183–188 (2001).
- Navarro, V. et al. Seizure anticipation in human neocortical partial epilepsy. *Brain* **125**, 640–655 (2002).
- Litt, B. et al. Epileptic seizures may begin hours in advance of clinical onset: a report of five patients. *Neuron* **30**, 51–64 (2001).