Lai *et al.* Reply: The main motivation behind our original work [1] was to satisfy the very basic requirement for control tests in scientific research. In order to justify the usage of Lyapunov exponents as seizure prediction measures, there is an underlying assumption that the exponents are able to reveal changes in the structure of the brain's dynamical system. This required controls, which we imagined as changes due to drift in a system parameter through a dynamical crisis, at which a chaotic attractor suddenly increases its size. Our model can thus generate time series that mimic this common feature of electroencephalogram or electrocorticogram (ECoG) signals during a seizure. The idea is fairly straightforward: if Lyapunov exponents, obtained from time series of well-controlled dynamical systems, are not useful for tracking visibly apparent changes in the dynamical evolution, then it reduces the likelihood that the exponents would be useful for seizure prediction since the brain dynamical system is much more complicated and noisy. Our results with a map system and with a flow exhibiting a local Hopf bifurcation [2] and computations with ECoG data all indicate strongly that the Lyapunov exponents are not the tool of choice for seizure prediction.

The authors stated repeatedly in their Comment [3] that our algorithm for computing the Lyapunov exponents was flawed. The algorithm we used is the standard one due to Eckmann *et al.* [4], which computes all Lyapunov exponents, and its validity was verified on time series from model nonlinear systems with known exponents (including maps and flows). Their criticism in [5] of the method by Eckmann *et al.* for estimating the maximum Lyapunov exponent $\lambda_{\max}$ is due to ''considerable variations in the estimates with the embedding dimension,'' yet their own reported $\lambda_{\max}$ estimates also exhibited significant variations with the embedding dimension. We note that the authors used only maps (not flows) for validation of their algorithm prior to application to ECoG [5]. The inconsistency continues in their Comment with their criticism of our choice of control model on the grounds that it is a map and not comparable with the brain, a continuous-time system. While we never meant to imply modeling brain using a map, our use of a map *for a control test* is justifiable [1,2] and the observations derived from its study are useful in the proper (limited) context.

Figure 1 in the Comment only illustrates the fact that seizure *detection* is possible using $\lambda_{\max}$ estimates. We note, however, that *detection is not the same as prediction*. The possibility of detection using $\lambda_{\max}$ estimation is not at all surprising, given that many different types of statistical measures can detect seizures [6] and several do so with far better accuracy, efficiency, and *reproducibility*. Our Letter, the Comment, and prior work of the Comment's authors and others all indicate that seizure detection with $\lambda_{\max}$ is highly dependent upon numerous computational parameter choices and now possibly even on choice of estimation algorithm.

The authors also claimed that the predictive ability for seizures lies in a transient statistical correlation of $\lambda_{\max}$ from individual ECoG recording sites (''entrainment''). Once multichannel entrainment measures are added into the mix, the resulting explosion in computational degrees of freedom associated with selecting specific groups of contacts (which is further compounded by the authors' proposed method [7], which allows for selecting a new group after each seizure) coupled with the critical dependence of $\lambda_{\max}$'s ability to simply track system dynamics sufficient for *detecting* state changes, emphasizes the need for control tests and independent validation. This is necessary to avoid the potential for fitting results to the data and to enable independently reproducible results.

Regarding the authors' statement on dynamical noise in the brain, we remark that, while noise can be beneficial through the mechanism of stochastic resonance, it is detrimental to the computation of Lyapunov exponents from time series and consequently to the predictive power of the exponents, as we demonstrated [1]. The Comment authors apparently misunderstood the meaning of stochastic resonance to claim that noise can enhance the predictability for seizures.

Finally, we remark that there are subtle but profound differences between hypothesis-based and result-driven approaches. We acknowledge the practical value of the latter, especially in the field of medicine where this approach may find application. We thank the authors for bringing to the forefront the differences.

Ying-Cheng Lai,[1] Mary Ann F. Harrison,[2] Mark G. Frei,[2] and Ivan Osorio[2,3]
[1]Departments of Mathematics and Electrical Engineering
Arizona State University
Tempe, Arizona 85287, USA
[2]Flint Hills Scientific L.L.C.
5020 Bob Billings Parkway, Ste. A
Lawrence, Kansas 66049, USA
[3]Department of Neurology
University of Kansas Medical Center
3901 Rainbow Boulevard
Kansas City, Kansas 66160, USA

Received 10 September 2004; published 3 January 2005
DOI: 10.1103/PhysRevLett.94.019802
PACS numbers: 87.19.La, 05.40.Ca, 05.45.Tp

[1] Y.-C. Lai *et al.*, Phys. Rev. Lett. **91**, 068102 (2003).
[2] Y.-C. Lai *et al.*, Chaos **14**, 630 (2004).
[3] L. D. Iasemidis *et al.*, preceding Comment, Phys. Rev. Lett. **94**, 019801 (2005).
[4] J.-P. Eckmann *et al.*, Phys. Rev. A **34**, 4971 (1986).
[5] L. D. Iasemidis *et al.*, Brain Topography **2**, 187 (1990).
[6] I. Osorio *et al.*, J. Clin. Neurophysiol. **18**, 269 (2001).
[7] L. D. Iasemidis *et al.*, IEEE Trans. Biomed. Eng. **50**, 616 (2003).

