



SEIZURE PREDICTION

J. Chris Sackellares, MD

Chief Scientific Officer, Optima Neuroscience, Inc.; Staff Neurologist, Gainesville VA Medical Center; Medical Director, Sunstate Comprehensive Epilepsy Program, Gainesville, Florida

There is mounting evidence that seizures are preceded by characteristic changes in the EEG that are detectable minutes before seizure onset. Using novel signal analysis techniques, researchers are beginning to characterize the transition from the interictal to the ictal state in quantitative terms. This research has led to the development of automated seizure prediction algorithms. Active debate persists regarding the interpretation of research results, methods of signal analysis, as well as experimental and statistical methods for testing seizure prediction algorithms. Developments in this field have led to new theories on the mechanism of seizure development and resolution. The ability to predict seizures could lead the way to novel diagnostic and therapeutic methods for the treatment of patients with epilepsy.

The physiological characteristics of a seizure differ dramatically from that of the interictal state. During the interictal state, the EEG typically is lower in amplitude, less rhythmic, and more irregular in morphology. At the onset of a seizure, there is a sudden change in the amplitude, frequency, and morphology of the EEG signal, an increase in rhythmicity, and a synchronization of activity that takes place across widespread areas of the cerebral cortex. The clinical and EEG changes at the onset of a seizure are so dramatic that they give the impression of occurring without any warning or preceding buildup. Although patients sometimes report prodromal symptoms hours to minutes before seizures, the concept of a prodromal change in the EEG was rarely considered, until recently.

The shift from the interictal condition, during which the patient is relatively asymptomatic, to the seizure, during which

clinical symptoms may range from subtle sensory, cognitive, or emotional changes to complete loss of consciousness and motor control, is considered a state transition. A question of scientific and clinical interest is whether the transition between these physiological conditions is gradual or abrupt. The answer to this question will provide insight into the underlying mechanisms of seizure generation. From a clinical perspective, gradual transition offers the possibility of predicting an impending seizure, while an abrupt transition provides no hope of anticipating the seizure in time to intervene therapeutically.

Evidence of a gradual transition was reported as early as the 1970s when investigators, using linear signal processing methods (1–3), reported changes in EEG characteristics beginning minutes prior to the onset of seizures. Some investigators found changes in interictal spike distribution or incidence approaching seizure onset (4,5), while others found no consistent changes in spike patterns (6–8). These observations were made through analysis of relatively brief EEG samples in a limited number of patients. Even at that time, the researchers realized that the presence of preictal changes in the EEG raised the possibility that seizures could be predicted.

In the late 1980s, faster computers with larger storage capacity made it possible to systematically analyze longer segments of EEG preceding and following seizures from a larger number of patients and to use more sophisticated approaches to signal processing. Motivated by theories that seizures may result from spontaneous state transitions in a chaotic nonlinear system (9–18), some investigators began to apply mathematical techniques developed for the study of complex nonlinear systems to analyze EEGs for characteristics unique to the transitions into and out of seizures (15,16,18–34). As a result, researchers began to report measurable changes in EEG dynamics (temporal and spatiotemporal) that preceded seizures by periods ranging from seconds to hours. These changes were quantified in terms of signal order (vs chaoticity), signal complexity, time dependency, and similarity/synchronization indices—all estimated by constructing multidimensional phase space. Each measure was designed to provide a quantitative method for capturing a different aspect of signal property and, thus, the property of the underlying signal generator. The formal meaning of these measures was well understood when applied to computer-generated output from autonomous models of deterministic autonomous complex nonlinear systems. However, the interpretation of the same measures when applied to noisy, nonautonomous, nonstationary systems, like the human brain, continues to be debated. Nonetheless, the findings provided evidence from several different perspectives that changes occurred in the spatiotemporal

Address correspondence to J. Chris Sackellares, MD, Chief Scientific Officer, Optima Neuroscience, Inc., 101 SE 2nd Place, Suite 201-A, Gainesville, FL 32601. E-mail: jc_sackellares@msn.com

Epilepsy Currents, Vol. 8, No. 3 (May/June) 2008 pp. 55–59
Blackwell Publishing, Inc.
© American Epilepsy Society

properties of the EEG for minutes to hours before the onset of a seizure. These studies have been extensively reviewed (35–37).

It is difficult, if not impossible, to prove whether EEG signals are linear or nonlinear. Yet, an advantage of mathematical techniques developed for analyzing nonlinear systems is that they do not require the assumption that the signal is linear. This feature is an important advantage if there are significant nonlinearities in the signal. However, two disadvantages of nonlinear techniques for EEG analysis are that the methods are novel to EEG research, thus opinions differ as to how the results are to be interpreted (38–43), and they are computationally demanding. The computational intensity of the methods was a major disadvantage before current central processing unit speeds were achieved. The limitations of nonlinear methods have led some researchers to renew efforts to investigate seizure generation with linear signal processing techniques (44–48). Linear methods, such as energy, the spectrogram, and coherence, require the assumption of a linear signal. In many instances, such as the epileptic brain, when the nature of the generator is not well understood, one cannot assume that the signal is linear. Yet, linear measures have been applied successfully to the analysis of a wide range of signals. Some investigators have found evidence for EEG signal changes preceding seizure onset, and some have questioned the necessity of using the more complicated nonlinear methods.

Others have questioned nonlinear techniques on other grounds. Following the published successes in finding what became known as a preictal state, some scientists began to report negative results using the same nonlinear techniques previously described (41,42,49–52). These investigators raised questions about methods that employed the similarity index, the correlation dimension, the correlation integral, and the Lyapunov exponent. In most instances, the researchers did not precisely duplicate the methods they challenged. However, their reports have served to temper initial enthusiasm and confidence in finding clinically useful seizure prediction algorithms. In addition, they stimulated proposals for new experimental and statistical methods for testing the hypothesis of the existence of a preictal state (50,53,54). Recently, a statistically based evaluation of the ability of a number of linear/nonlinear and univariate/bivariate measures to distinguish significantly the preictal from the interictal state has provided further evidence of significant differences in EEG characteristics between the two periods (55). While several measures showed significance differences, bivariate measures were generally more effective.

With growing evidence that seizures are preceded by measurable changes in EEG, some researchers began to develop and test automated seizure prediction algorithms (56–65). These algorithms are computer programs that read the raw EEG signal, calculate measures of specific signal characteristics, compare these measures to threshold values, and generate seizure warn-

ings when pre-established criteria are met. The parameters of the algorithms can be set to alter the sensitivity/specificity ratio. In most cases, specificity is expressed as the false positive rate (i.e., number of false warnings per unit of time). In general, the higher the sensitivity obtained (i.e., the percentage of seizures predicted), the greater is the false positive rate of any prediction algorithm. Initial tests of these prediction algorithms involved EEG recordings from a small number of patients. In some instances, interictal data segments were preselected by the investigators (60). However, the algorithms were not subjected to rigorous statistical validation. Since there are no established seizure prediction algorithms that can serve as a standard, most investigators feel that a statistically based standard should be employed. In later reports, algorithm performance was compared to naïve statistically based prediction schemes that did not utilize information from the EEG (64,65). However, there remains debate as to what constitutes an appropriate experimental design, what statistical comparisons are optimal, and the standards for a good algorithm performance. Notwithstanding ongoing debate (and in some cases, skepticism), the results of these investigations were encouraging. Evaluations of the algorithms were based on recordings from a small number of patients. Most studies employed recordings performed with intracranial EEG electrodes. However, preliminary reports have indicated that it is possible to predict seizures from EEG recordings utilizing scalp electrodes (30,66,67). The ability to predict using intracranial electrode recordings will be important in the development of closed loop seizure control devices. However, prediction from scalp EEG recordings will make it possible to use the devices in a variety of monitoring applications. An obvious application would be monitoring laboratories for epilepsy patients undergoing diagnostic or presurgical evaluations. Other potential applications include intensive care units and emergency departments.

A major barrier to this research is the limited availability of data to test the algorithms. Adequate statistical testing of performance requires high quality, continuous EEG datasets of ample duration and from a sufficient number of patients, with a wide enough variety of seizure types. Very few medical centers have adequate capacity to store and organize large numbers of such datasets. Data sharing among investigators will require a massive effort to generate and organize de-identified research datasets. To date, this objective has not been met. Establishment of a databank of training and test datasets is a challenge for the immediate future.

One of the promises of seizure prediction is that of developing better closed-loop seizure control devices. It is anticipated that closed-loop devices, coupled with seizure prediction, will be more efficient and effective than open-loop devices or devices triggered by seizure detection. Preliminary reports in a rodent model of temporal lobe epilepsy suggest that closed-loop, state-dependent control devices utilizing automated seizure

prediction algorithms are feasible (68–72). Early investigations found that the rodent model exhibited dynamic changes in the EEG during transitions to the ictal state that were similar to those reported in human temporal lobe epilepsy. In addition, they found that electrical stimulation to the hippocampus triggered by a preictal state detection consistently reversed the dynamics of the EEG signal, resetting it back to the values of the interictal state. In addition, the stimulation appeared to delay seizure onset.

Investigations into seizure prediction have raised important questions about seizure control. Although there is debate as to whether seizures and transitions between physiological states can be better explained by the theory of linear or nonlinear dynamics, understanding the dynamics of the epileptic brain remains an important objective. While linear systems respond predictably to external forcing (e.g., electrical stimulation) or change in a control parameter (e.g., release of a GABAergic drug), this is not the case with nonlinear systems, particularly if they are chaotic. Even low-dimensional chaotic systems are highly sensitive to initial conditions, and their behavior cannot be predicted over long periods of time. For this reason, novel approaches to controlling both low- and high-dimensional chaotic systems have been developed (14,17,73,74). Proof of chaos in epilepsy appears to be beyond the capability of current research techniques. Yet, theoretical tenets that explain epilepsy as a dynamical disorder have been compelling to many (9–11,13–34). However, some of the early proponents of these theories have become less convinced of their accuracy, as alternate explanations for empirical experimental results have been put forward. It is likely that progress in understanding the dynamics of epilepsy and advancing the goals of seizure prediction and control will require experimental investigations in animal models of epilepsy.

Research related to seizure prediction has raised new questions about the basic mechanisms underlying seizure generation. The finding that the transition from the interictal to the ictal state evolves over minutes to hours must be incorporated into existing theories of ictogenesis. Investigations into cellular, synaptic, and extracellular processes that influence neuronal excitability may be able to explain seizures. However, epilepsy is a disorder characterized by intermittent recurrence of seizures. Current mainstream approaches to epilepsy research have not yet explained the repeated transition into and out of seizures. Much of the evidence from seizure prediction research suggests the presence of deterministic mechanisms in the EEG generators of the epileptic brain. Yet, the “governing dynamics,” to borrow a phrase from *A Beautiful Mind*, are not understood. Perhaps, integrating known cellular, synaptic, and extracellular changes (a science based largely on neurochemistry, neuroanatomy, and neuropharmacology) with computationally based dynamical systems theory will provide an understanding of the phenomenon of epilepsy.

References

1. Viglione S, Walsh G. Proceedings. Epileptic seizure prediction. *Electroencephalogr Clin Neurophysiol* 1975;39:435.
2. Rogowski Z, Gath I, Bental E. On the prediction of epileptic seizures. *Biol Cybern* 1981;42:9–15.
3. Siegel A, Grady CL, Mirsky AF. Prediction of spike-wave bursts in absence epilepsy by EEG power-spectrum signals. *Epilepsia* 1982;23:47–60.
4. Lange HH, Lieb JP, Engel J Jr, Crandall PH. Temporo-spatial patterns of pre-ictal spike activity in human temporal lobe epilepsy. *Electroencephalogr Clin Neurophysiol* 1983;56:543–555.
5. Wieser HG. Preictal EEG findings. *Epilepsia* 1989;30:669.
6. Gotman J, Marciani MG. Electroencephalographic spiking activity, drug levels and seizure occurrence in epileptic patients. *Ann Neurol* 1985;17:597–603.
7. Gotman J, Koffler DJ. Interictal spiking increases after seizures but does not after decrease in medication. *Electroencephalogr Clin Neurophysiol* 1989;72:7–15.
8. Katz A, Marks DA, McCarthy G, Spencer SS. Does interictal spiking rate change prior to seizures? *Electroencephalogr Clin Neurophysiol* 1991;79:153–156.
9. Milton JG, Longtin A, Beuter A, Mackey MC, Glass L. Complex dynamics and bifurcations in neurology. *J Theoret Biol* 1989;138:129–147.
10. Milton JG. Medically intractable epilepsy. In: Milton J, Jung P, eds, *Epilepsy as a Dynamic Disease*. Berlin: Springer-Verlag, 2003:1–14.
11. Mackey MC, an der Heiden U. Dynamical diseases and bifurcations: understanding functional disorders in physiological systems. *Funkt Biol Med* 1982;1:156–164.
12. Nicolis G, Prigogine I. *Self-Organization in Nonequilibrium Systems: From Dissipative Structures to Order through Fluctuations*. New York: John Wiley & Sons, 1977.
13. Rapp PE, Zimmerman ID, Albano AM, deGuzman GC, Greenbaum NN, Bashore TR. Experimental studies of chaotic neural behavior: cellular activity and electroencephalographic signals. In Othmer HG, ed., *Nonlinear Oscillations in Biology and Chemistry*. Berlin: Springer-Verlag, 1986:175–805.
14. Rapp PE, Latta RA, Mees AI. Parameter dependent transitions and the optimal control of dynamical diseases. *Bull Math Biol* 1988;50:227–253.
15. Iasemidis LD, Sackellares JC, Zaveri HP, Williams WJ. Phase space topography of the electrocorticogram and the Lyapunov exponent in partial seizures. *Brain Topogr* 1990;2:187–201.
16. Iasemidis LD. On the Dynamics of the Human Brain in Temporal Lobe Epilepsy. Ph.D. Dissertation. University of Michigan, Ann Arbor, MI, 1991.
17. Schiff SJ, Jerger K, Duong DH, Chay T, Spano ML, Ditto WL. Controlling chaos in the brain. *Nature* 1994;370:615–620.
18. Iasemidis LD, Sackellares JC. Chaos theory and epilepsy. *Neuroscientist* 1996;2:118–126.
19. Iasemidis LD, Sackellares JC. The temporal evolution of the largest Lyapunov exponent on the human epileptic cortex. In: Duke DW, Pritchard WS, eds., *Measuring Chaos in the Human Brain*. Singapore: World Scientific, 1991:49–82.
20. Iasemidis LD, Principe JC, Czaplowski, Gilmore RL, Roper SN, Sackellares JC. Spatiotemporal transition to epileptic seizures: a nonlinear dynamical analysis of scalp and intracranial EEG recordings. In: Lopes F, da Silva J, Principe C, Almeida LB, eds.

- Spatiotemporal Models in Biological and Artificial Systems*. Amsterdam, The Netherlands: IOS Press, 1997:81–88.
21. Casdagli MC, Iasemidis LD, Sackellares JC, Roper SN, Gilmore RL, Savit RS. Characterizing nonlinearity in invasive EEG recordings from temporal lobe epilepsy. *Physica D* 1996;99:381–399.
 22. Casdagli MC, Iasemidis LD, Savit RS, Gilmore RL, Roper SN, Sackellares JC. Non-linearity in invasive EEG recordings from patients with temporal lobe epilepsy. *Electroencephalogr Clin Neurophysiol* 1997;102:98–105.
 23. Iasemidis LD, Pardalos P, Sackellares JC, Shiau DS. Quadratic binary programming and dynamical system approach to determine the predictability of epileptic seizures. *J Comb Optim* 1001;5:9–26.
 24. Iasemidis LD, Shiau DS, Chaovaitwongse W, Pardalos PM, Carney PR, Sackellares JC. Adaptive seizure prediction system. *Epilepsia* 2002;43, 264–265.
 25. Elger CE, Lehnertz K. Seizure prediction by non-linear time series analysis of brain electrical activity. *Eur J Neurosci* 1998;10:786–789.
 26. Lehnertz K, Elger CE. Spatio-temporal dynamics of the primary epileptogenic area in temporal lobe epilepsy characterized by neuronal complexity loss. *Electroenceph Clin Neurophysiol* 1995;95:108–117.
 27. Lehnertz K, Elger CE. Can epileptic seizures be predicted? Evidence from nonlinear time series analysis of brain electrical activity. *Phys Rev Lett* 1998;80:5019–5023.
 28. Martinerie J, Adam C, le Van Quyen M, Baulac M, Clemenceau S, Renault B, Varela FJ. Epileptic seizures can be anticipated by nonlinear analysis. *Nat Med* 1998;4:1173–1176.
 29. Le Van Quyen M, Martinerie J, Baulac M, Varela F. Anticipating epileptic seizure in real time by a nonlinear analysis of similarity between EEG recordings. *Neuroreport* 1999;10:2149–2155.
 30. Le Van Quyen M, Martinerie J, Navarro V, Boon P, D'Have M, Adam C, Renault B, Varela F, Baulac M. Anticipation of epileptic seizures from standard EEG recordings. *Lancet* 2001;357:183–188.
 31. Navarro V, Martinerie J, Le Van Quyen M, Clemenceau S, Adam C, Baulac M, Varela F. Seizure anticipation in human neocortical partial epilepsy. *Brain* 2002;125:640–655.
 32. Van Drongelen W, Nayak S, Frim DM, Kohrman MH, Towle VL, Lee HC, McGee AB, Chico MS, Hecox KE. Seizure anticipation in pediatric epilepsy: use of Kolmogorov entropy. *Pediatr Neurol* 2003;29:207–213.
 33. Moser HR, Weber B, Wieser HG, Meier PF. Electroencephalograms in epilepsy: analysis and seizure prediction within the framework of Lyapunov theory. *Physica D* 1999;130:291–305.
 34. Drury I, Smith B, Li D, Savit R. Seizure prediction using scalp electroencephalogram. *Exp Neurol* 2003;184 (suppl 1):S9–S18.
 35. Litt B, Echauz J. Prediction of epileptic seizures. *Lancet Neurol* 2002;1:22–30.
 36. Iasemidis LD. Epileptic seizure prediction and control. *IEEE Trans Biomed Eng* 2003;50:549–558.
 37. Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. *Brain* 2006;130:314–333.
 38. Pijn JP, Van Neerven J, Noest A, Lopes da Silva FH. Chaos or noise in EEG signals; dependence on state and brain site. *Electroencephalogr Clin Neurophysiol* 1991;79:371–381.
 39. Manuca R, Savit R. Stationary and nonstationary time series analysis. *Physica D* 1996;99:134–161.
 40. Timmer J. The power of surrogate data testing with respect to nonstationarity. *Phys Rev E* 1998;58:5153–5156.
 41. Lai YC, Harrison MAF, Frei MG, Osorio I. Inability of Lyapunov exponents to predict epileptic seizures. *Phys Rev Lett* 2003;91:068102.
 42. Lai YC, Harrison MAF, Frei MG, Osorio I. Controlled test for predictive power of Lyapunov exponents: their inability to predict epileptic seizures. *Chaos* 2004;14:630–642.
 43. Sackellares JC, Iasemidis LD, Shiau DS, Gilmore RL, Roper SN. Epilepsy—when chaos fails. In: Lehnertz K, Arnhold J, Grassberger P, Elger CE, eds., *Chaos in the Brain?* Singapore: World Scientific 2000:112–133.
 44. Mormann F, Lehnertz K, David P, Elger CE. Mean phase coherence as measure for phase synchronization and its application to the EEG of epilepsy patients. *Physica D* 2000;144:358–369.
 45. Litt B, Esteller R, Echauz J, D'Alessandro M, Shor R, Henry T, Pennell P, Epstein C, Bakay R, Dichter M, Vachtsevanos G. Epileptic seizures may begin hours in advance of clinical onset: a report of five patients. *Neuron* 2001;30:51–64.
 46. Cranston SD, Ombao HC, von Sachs R, Guo W, Litt B. Time-frequency spectral estimation of multichannel EEG using the Auto-SLEX method. *IEEE Trans Biomed Eng* 2002;49:988–996.
 47. Mormann F, Kreuz T, Andrzejak RG, David P, Lehnertz K, Elger CE. Epileptic seizures are preceded by a decrease in synchronization. *Epilepsy Res* 2003;53:173–185.
 48. Corsini J, Shoker L, Sanei S, Alarcon G. Epileptic seizure predictability from scalp EEG incorporating constrained blind source separation. *IEEE Trans Biomed Eng* 2006;53:790–799.
 49. DeClercq W, Lemmerling P, Van Huffel S, Van Paesschen W. Anticipation of epileptic seizures from standard EEG recordings. *Lancet* 2003;361:971.
 50. Winterhalder M, Maiwald T, Voss HU, Aschenbrenner-Scheibe R, Timmer J, Schulze-Bonnhage A. The seizure prediction characteristic: a general framework to assess and compare seizure prediction methods. *Epilepsy Behav* 2003;4:318–325.
 51. Aschenbrenner-Scheibe R, Maiwald T, Winterhalder M, Voss HU, Timmer J, Schulze-Bonnhage A. How well can epileptic seizures be predicted? An evaluation of a nonlinear method. *Brain* 2003;126:2616–2626.
 52. Harrison MA, Osorio I, Frei MG, Asuri S, Lai YC. Correlation dimension and integral do not predict epileptic seizures. *Chaos* 2005;15:33106.
 53. Andrzejak RG, Mormann F, Kreuz T, Rieke C, Kraskov A, Elger CE, Lehnertz K. Testing the null hypothesis of the nonexistence of a preseizure state. *Phys Rev E* 2003;67:010901.
 54. Yang MCK, Shiau D-S, Sackellares JC. Testing whether a prediction scheme is better than guess. In: Pardalos PM, Sackellares JC, Carney PR, Iasemidis LD, eds. *Quantitative Neuroscience: Models Algorithms, Diagnostics and Therapeutic Applications*. Norwell, MA: Kluwer Academic Publishers, 2004, pp. 251–258.
 55. Mormann F, Kreuz T, Rieke C, Andrzejak RG, Kraskov A, David P. On the predictability of epileptic seizures. *Clin Neurophysiol* 2005;116:569–587.
 56. Iasemidis LD, Pardalos P, Sackellares JC, Shiau DS. Quadratic binary programming and dynamical system approach to the predictability of epileptic seizures. *J Comb Optim* 2001;5:9–26.
 57. Pardalos PM, Sackellares JC, Yatsenko VA, Butenko SI. Nonlinear dynamical systems and adaptive filters in biomedicine. *Ann Oper Res* 2003;119:119–142.

58. Iasemidis LD, Pardalos PM, Chaovaitwongse W, Shiau D-S, Narayanan K, Kumar S, Carney PR, Sackellares JC. Prediction of human epileptic seizures based on optimization and phase changes in brain electrical activity. *Optim Methods Softw* 2003;18:81–84.
59. Iasemidis LD, Shiau D-S, Chaovaitwongse W, Sackellares JC, Pardalos PM, Principe JC, Carney PR, Prasad A, Veeramani B, Tsakalis K. Adaptive epileptic seizure prediction system. *IEEE Trans Biomed Eng* 2003;50:616–627.
60. Mormann F, Andrzejak RG, Kreuz T, Rieke C, David P, Elger CE, Lehnertz K. Automated detection of a pre-seizure state based on a decrease in synchronization in intracranial EEG recordings from epilepsy patients. *Phys Rev E* 2003;67:021912.
61. Pardalos PM, Chaovaitwongse W, Iasemidis LD, Sackellares JC, Shiau D-S, Carney PR, Prokopyev OA, Yatsenko VA. Seizure warning algorithm based on optimization and nonlinear dynamics. *Math Program Ser B* 2004;101:365–385.
62. Chaovaitwongse W, Pardalos PM, Iasemidis LD, Shiau D-S, Sackellares JC. Dynamical approaches and multi-quadratic integer programming for seizure prediction. *Optim Methods Softw* 2005;20:383–394.
63. Iasemidis LD, Shiau D-S, Pardalos PM, Chaovaitwongse W, Narayanan K, Awadhesh P, Tsakalis K, Carney PR, Sackellares JC. Long-term prospective on-line real-time seizure prediction. *Clin Neurophysiol* 2005;116:532–544.
64. Chaovaitwongse W, Pardalos PM, Iasemidis LD, Carney PR, Shiau D-S, Sackellares JC. A performance of a seizure warning algorithm based on the dynamics of intracranial EEG. *Epilepsy Res* 2005;64:93–113.
65. Sackellares JC, Shiau DS, Principe JC, Yang MCK, Dance LK, Suharitdamrong W, Chaovaitwongse W, Pardalos PM, Iasemidis LD. Predictability analysis for an automated seizure prediction algorithm. *J Clin Neurophysiol* 2006;29:509–520.
66. Sackellares JC, Iasemidis LD, Shiau D-S, Suharitdamrong W, Dance LK, Chaovaitwongse W, Pardalos PM, Carney PR. An automated seizure warning algorithm for scalp EEG. AES Conference. *Epilepsia* 2003;44(suppl 9):228.
67. Shiau D-S, Iasemidis LD, Suharitdamrong W, Dance LK, Chaovaitwongse W, Pardalos PM, Carney PR, Sackellares JC. Detection of the preictal period by dynamical analysis of scalp EEG. AES Conference. *Epilepsia* 2003;44(suppl 9):233–234.
68. Nair SP. Brain Dynamics and Control with Applications in Epilepsy. Ph.D. Dissertation. University of Florida, Gainesville, FL, 2006.
69. Nair SP, Shiau DS, Norman WM, Shenk D, Suharitdamrong W, Iasemidis LD, Pardalos PM, Sackellares JC, Carney PR. Dynamical changes in the rat chronic limbic epilepsy model. *Epilepsia* 2004;45:211–212.
70. Nair SP, Sackellares JC, Shiau DS, Norman WM, Pardalos PM, Principe JC, Carney PR. Effects of acute hippocampal stimulation on EEG dynamics. Proceedings of the 28th IEEE EMBS Conference, New York, NY, 2006:4382–4386.
71. Nair SP, Shiau DS, Iasemidis LD, Norman WM, Pardalos PM, Sackellares JC, Carney PR. Seizure predictability in an experimental model of epilepsy. In: Pardalos PM, Boginski VL, Vazacopoulos A, eds. *Data Mining in Biomedicine*. New York: Springer Optimization and Its Applications 7, Springer, 2007: 535–558.
72. Shiau DS, Nair SP, Iasemidis LD, Carney PR, Norman WM, Principe JC, Pardalos PM, Suharitdamrong W, Cho J, Sackellares JC. Seizure warning and dynamic response to electrical stimulation in a rodent model of chronic limbic epilepsy. IFMBE Proceedings of 3rd European Medical and Biological Conference, Prague, Czech Republic, 2005:11.
73. Ott E, Grebogi C, Yorke JA. Controlling chaos. *Phys Rev Lett* 1990;64:1196–1199.
74. Ding M, Yang W, In V, Ditto L, Spano ML, Gluckman B. Controlling chaos in high dimensions: theory and experiment. *Phys Rev E* 1996;53:4334–4344.