EPILEPTIC SEIZURE FOREWARNING
BY NONLINEAR TECHNIQUES

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under

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ABSTRACT

Nicolet Biomedical Inc. (NBI) is collaborating with Oak Ridge National Laboratory (ORNL) under a Cooperative Research and Development Agreement (CRADA) to convert ORNL's patented technology for forewarning of epileptic seizures to a clinical prototype. This technical report describes the highlights of the first year's effort. The software requirements for the clinical device were specified from which the hardware specifications were obtained. ORNL's research-class FORTRAN was converted to run under a graphical user interface (GUI) that was custom-built for this application by NBI. The resulting software package was cloned to desktop computers that are being tested in five different clinical sites. Two hundred electroencephalogram (EEG) datasets from those clinical sites were provided to ORNL for detailed analysis and improvement of the forewarning methodology. Effort under this CRADA is continuing into the second year as planned.

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1. INTRODUCTION

Epilepsy from all causes affects about 2.5 million U.S. victims, with 125,000 new cases annually. Epilepsy involves uncontrolled neuron firings, including sustained rhythmic activity (seizures), brief transient discharges (spikes), or combinations (spike-wave discharges). A seizure can cause muscle tremors, unconsciousness, loud vocalization, and uncontrolled bladder/bowel function. Drug therapy frequently causes side effects that are worse than the uncontrolled seizure itself, such as drowsiness, poor memory, lack of coordination, disorientation, and impaired thinking. Moreover, 25–30% of epileptic patients are unresponsive to antiseizure drugs. Patients' lives are severely disrupted by awkward social interactions, unstable employment, and huge medical bills.

Seizure warning is important because severe epilepsy frequently is coincident with sudden death due to accidents, breathing interruption, and cardiac failure. This threat is particularly serious for patients who cannot make their needs known, such as adults with other disabilities and small children. Clinical or hospital monitoring is very expensive. Home monitoring is much less expensive but requires a wall-powered monitor, thus severely restricting patient mobility. Reliable warning will facilitate data review, diagnosis, and prompt medical care.

2. BACKGROUND

Researchers at Oak Ridge National Laboratory (ORNL) have developed and applied nonlinear techniques to a variety of physical processes for diagnosis and control. The ORNL team analyzed scalp electroencephalogram (EEG) data via conventional nonlinear methods, under the sponsorship of the ORNL Laboratory-Directed Research and Development program in 1994–1995. That work found inconsistent detection and forewarning capability in mutual information, correlation dimension, and Kolmogorov entropy of scalp EEG [1]. Three U.S. patents also grew from that effort. Scalp EEG includes electrical artifacts from eyeblinks and other muscular activity, which are removed with a novel zero-phase quadratic filter while preserving the nonlinear amplitude and phase relationships [2]. Nonlinear analysis of this artifact-filtered data then detects [3] and predicts [4] epileptic seizures from one channel of scalp EEG. Application of these same methods to other data showed that better techniques were needed for detecting a change in the system condition, such as forewarning of failure in electrical machines and cardiac fibrillation from electrocardiogram data. Subsequent research in 1995–1997 [5] developed a new nonlinear method for detection of condition change using a discretized phase-space analysis after artifact filtering. This approach was later patented [6]. Details of this method with applications to epilepsy forewarning were presented recently at technical conferences [7–9] and published as a peer-reviewed paper [10]. Patent-pending improvements [11] have been added to the methodology; a companion paper has been accepted for publication [12] as part of the effort under this Cooperative Research and Development Agreement (CRADA). The methodology is implemented as research-class FORTRAN on a desktop computer.

On February 16, 1999, Dr. Jon Joseph [Nicolet Biomedical Inc. (NBI)] contacted Dr. Lee Hively (ORNL) about the possibility of a collaboration to commercialize the seizure forewarning technology. Dr. Joseph met with ORNL staff on April 12, 1999, and asked ORNL to demonstrate the technology on NBI data. Dr. Joseph and Leah Hanson (NBI) met with ORNL staff again on August 30, 1999, to discuss the results of ORNL's analysis of 20 datasets, using the previously published methodology [10]. Based on the successful outcome of this demonstration, NBI decided to pursue collaboration with ORNL under a CRADA [13], which began on October 1, 1999. Appendix A of this report shows the scope of work from the CRADA document broken into specific tasks. This report is a living document, recording the present status of the CRADA activity and ultimately will become the final report of the CRADA work.

This report is intended as an initial starting point, which will change in scope, perspective, and details as the work progresses.

3. PURPOSE

Work under this CRADA seeks to develop a combination of existing computer hardware and ORNL-patented software into a clinical prototype to forewarn of an impending epileptic seizure. This effort is the first step in bridging the gap between ORNL's existing research-class software and commercialization of a prototype medical device. Specific technical goals include validation of the epilepsy forewarning methodology and development of a prototypical clinical device for epilepsy warning. The specific technical objectives are: a scientific basis for the epilepsy forewarning, software to analyze real-time scalp EEG data for preseizure indications, and a user interface between the ORNL software and existing commercial software. This effort will also seek improvements in the device features.

4. CRADA PROGRESS

In fulfillment of CRADA Task 1.1, NBI provided over 200 EEG datasets (more than 65 GB) from five clinical sites to ORNL. NBI provided a Pentium III PC with a 60 GB hard drive at no cost to ORNL in August 2000 to store and analyze this data under CRADA Task 1.2. A technical paper [12] was recently accepted for publication in *Chaos*, describing advancements in the method under CRADA Task 1.3. ORNL also issued an invention disclosure [14] covering the new ideas from the first year's work. Task 1 is continuing into the second project year as described in the CRADA statement of work.

In fulfillment of CRADA Task 2.1, Appendix B shows the functional requirements and features of the prototype seizure-forewarning device. These requirements include the I/O needs (configurable parameters for the warning algorithm, such as sampling rate and EEG channel for analysis) with results displayed via a graphical user interface (GUI) to the user. NBI and ORNL worked jointly to specify the I/O requirements for ORNL's deliverable (the clinical warning algorithm), including specifications for the EEG data, preseizure indications, and nonlinear methodology options.

Appendix C shows the functions of the nonlinear analysis software (NAS) for seizure forewarning. To meet the requirements of Appendices B–C, NBI procured commercial PC hardware and software, as shown in Appendix D. In fulfillment of CRADA Task 2.2, NBI constructed a GUI on this computer allowing user interaction with the seizure forewarning system according to the requirements in Appendix B. The GUI handles the variable parameters for the warning algorithm (such as sampling rate and EEG channel for analysis), error reporting and recovery (such as the presence of constant signal), choice of methodology options, and displays the preseizure indications from the warning algorithm. The GUI includes a database of patient information, as shown in Appendix E, that documents the specific conditions of each EEG dataset, such as time annotations of activities during the monitoring period, seizure occurrence and type, recommended EEG channel for analysis, basic patient information (sex, age), and a summary of the nonlinear analysis results. NBI provided a data interface to convert near-real-time EEG data to a form that is analyzable by the ORNL warning algorithm as well as storing an archival form of the digital data. Appendix F shows the functionality and appearance of the GUI.

In fulfillment of CRADA Task 2.3, ORNL modified the research-class FORTRAN code to perform nonlinear analysis of near-real-time EEG for epilepsy forewarning. This software has two components. The first provides measures of EEG data quality to avoid meaningless results from data of inadequate quality. The ORNL software passes these measures to the NBI GUI as warning alerts. The second component is the nonlinear analysis to forewarn of an epileptic seizure. ORNL revised the data quality check and forewarning algorithm to satisfy the requirements of Appendices A–C. NBI provided a

commercial copy of Microsoft[TM] Visual C++ Development System to ORNL without charge as part of this effort. ORNL worked with NBI to implement the nonlinear analysis software on the prototype clinical computer.

In fulfillment of CRADA Task 2.4, NBI and ORNL tested the prototype using EEG data from Task 1.1 and revised the software appropriately. In fulfillment of CRADA Task 2.5, ORNL worked with NBI staff on training for use of the prototype. Electronic exchange of files avoided the time and cost of travel to ORNL by NBI staff for testing and training as originally planned under CRADA Tasks 2.4–2.5.

In fulfillment of CRADA Task 3.1, NBI cloned the prototype from Task 2.4, including the GUI, data interface, and forewarning algorithm. NBI then installed prototype systems in the epilepsy monitoring units at five clinical sites. The first prototype was installed on April 28, 2000, at the University of Wisconsin, Madison. Later installations included Strong Memorial Hospital at University of Rochester, New York (installed June 15, 2000); Henry Ford Hospital in Detroit, Michigan (installed June 23, 2000); Parkland Hospital in Dallas, Texas (installed June 29, 2000); and Med City Dallas in Dallas, Texas (installed June 30, 2000). NBI has a Web site for the forewarning project at www.forecastsz.com .

Analysis of the first clinical dataset from the University of Wisconsin showed 52 min of seizure forewarning on the seventh day of continuous monitoring without any false positive indications. Appendix G is a one-page description of the analysis of this dataset. NBI and ORNL simultaneously issued press releases based on this success. The ORNL press release included a two-page explanation of the forewarning technology (Appendix H). The team agreed in advance of the public release that Lee Hively (ORNL) would handle questions about the underlying nonlinear technology, and that Char Merican (NBI) would address questions about commercialization and subsequent phases of the work. The table below summarizes the media queries from the United States, United Kingdom, and France. Appendix I shows two samples of the resulting printed publications.

Media Type	Contract	Date
Science Update (radio) by Amer. Assoc. Advan. Sci.	Kandice Carter	7/12/00 [15]
New Scientist (U.K. scientific journal)	Ian Sample	7/14/00 [16]
Web site (www.howstuffworks.com)	Kevin Bonsor	7/14/00
Oak Ridger (newspaper in Oak Ridge, Tennessee)	Paul Parson	7/18/00 [17]
The Sunday Times (U.K. newspaper)	Mark Prigg	7/19/00
The Sun (UK newspaper)	Roger Dobson	7/25/00
French Biomedical Web site (www.doctissimo.fr)	Alain Sousa	7/28/00
Med Star Television (U.S.)	Will Grace	7/28/00
TV Science News (American Institute of Physics)	Emily Lorditch	8/10/00
Medical Device and Diagnostic Industry (Journal)	(Article)	9/18 [18]

Detailed analysis of 200 EEG datasets under CRADA Task 1.3 is ongoing. Preliminary results of these analyses are shown in Appendix J. The sum of false positives (47.7%) and false negatives (0.8%) is better than the present state-of-the-art algorithm for just seizure detection alone, which has 30% false positives and 30% false negatives.

5. CONCLUSIONS

Work under CRADA No. ORNL 99-0559 is proceeding on schedule and within budget. Receipt of EEG data (Task 1.1), data analysis (Task 1.2), and improvement of the forewarning methodology (Task 1.3) are continuing into the second project year as expected. Specification of the prototype requirements (Task 2.1) was completed in October 1999. Development of the computer interface (Task 2.2), prototype construction (Task 2.3), testing (Task 2.4), and training (Task 2.5) were completed on June 30, 2000. Clinical testing of the prototype units (Task 3.1) is continuing into the second project year as expected. Travel to the clinical sites for physician input on the prototypes (Task 3.2) is not yet needed. Recent public releases on development of the technology have been well received by the international press.

6. ACKNOWLEDGEMENTS

7. REFERENCES

1. L. M. Hively, N.E. Clapp, C. S. Daw, W. F. Lawkins, *Nonlinear Analysis of EEG for Epileptic Seizures*, ORNL/TM-12961, Oak Ridge National Laboratory, Oak Ridge, TN, April 1995.

2. N. E. Clapp, L. M. Hively, Method and Apparatus for Extraction of Low-Frequency Artifacts from Brain Waves for Alertness Detection, U.S. Patent #5,626,145, May 6, 1997.

3. L. M. Hively, N. E. Clapp, C. S. Daw, W.F. Lawkins, *Apparatus and Method for Epileptic Seizure Detection using Nonlinear Techniques*, U.S. Patent #5,743,860, April 28, 1998.

4. L. M. Hively, N.E. Clapp, C. S. Daw, W.F. Lawkins, *Epileptic Seizure Prediction by Nonlinear Methods*, U.S. Patent #5,857,978, January 12, 1999.

5. L. M. Hively, *Data-Driven Nonlinear Technique for Condition Monitoring*, Proc. Maintenance and Reliability Conference, Vol. 1, pp. 16.01–16.10, Knoxville, TN, (1997).

6. L. M. Hively and E. G. Ng, *Integrated Method for Chaotic Time Series Analysis*, U.S. Patent #5,815,413, September 29, 1998.

7. P. C. Gailey, L. M. Hively, and V. A. Protopopescu, "Detection of Condition Change in Nonlinear Times Series Using a Connected-Phase-Space PDF," *Proc. Am. Phys. Soc.,* paper LC32.06, March 23, 1999.

8. L. M. Hively, P. C. Gailey, V. A. Protopopescu, "Sensitive Measures of Condition Change in EEG Data," *Workshop on 'Chaos in Brain?'* World Scientific Publ. (pp. 333–336), Bonn, March 1999.

9. P. C. Gailey, L. M. Hively, V. A. Protopopescu, *Robust Detection of Dynamical Change in EEG*, Proceedings of 5th Experimental Chaos Conference, Orlando, Florida, June 28–July 1, 1999.

10. L. M. Hively, P. C. Gailey, and V. A. Protopopescu, "Detecting Dynamical Change in Nonlinear Time Series," *Physics Letters A* **258,** 103–114 (1999).

11. L. M. Hively, V. A. Protopopescu, P. C. Gailey, *Improvements in Condition Assessment of Nonlinear Processes,*" U. S. Patent pending, ERID-0694, March 7, 2000.

12. L. M. Hively, V. A. Protopopescu, P. C. Gailey, "Timely Detection of Dynamical Change in Scalp EEG Signals," accepted for publication in *Chaos* (2000).

13. CRADA #99-0559, "Epileptic Seizure Prediction by Nonlinear Techniques," between Lockheed Martin Energy Research Corporation and Nicolet Biomedical Inc., September 8, 1999.

14. L. M. Hively, "Further Improvements for Detection of Nonlinear Condition Change," UT-Battelle Invention Disclosure, October 12, 2000.

15. "Seizure Alert," http://www.aaas.org/her/sciup/documents/august00.html#000814 (August 14, 2000).

16. Ian Sample, "Early Warning of Epileptic Seizures, *New Scientist,* p.17, July 29, 2000 (see Appendix I).

17. Paul Parson, "ORNL-Nicolet Partnership Promises Help for Epileptics," front page of *Oak Ridger*, Monday, July 24, 2000 (see Appendix I); http://www.oakridger.com/stories/072400/new_0724000040.html.

18. "Device Could Provide Early Warning of Seizure," *Medical Device & Diagnostic Industry*, p. 24, September 2000.

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APPENDIX A: SCOPE OF PHASE-ONE WORK UNDER THE CRADA

The Participant (NBI) will perform work under its own internal support. The Contractor (ORNL) will perform activities that are funded primarily by the Participant and to a lesser degree by the Department of Energy under this CRADA. This work will be performed in one phase spanning 15 months and will focus on development of a clinical prototype to warn of an impending epileptic seizure. If the results of this work are successful, the scope of the project may be expanded depending on the needs of the Participant and subject to the availability of additional funding. The Contractor and Participant will have a part in each of the three tasks of this work: (1) data acquisition and tuning of the warning algorithm, (2) integration and testing of Contractor software for a clinical setting, and (3) prototype test at clinical sites.

Task 1.1—Provide EEG datasets (Participant): The Participant will provide at least 200 datasets in usable format to the Contractor. The Participant will also develop a database for interpretation of the data, such as time annotations of activities during the monitoring period, seizure occurrence and type, recommended EEG channel for preseizure analysis, and basic patient information (sex, age). The database development will also include the analysis results from Task 1.2. This task will span the entire 15-month CRADA period.

Task 1.2—Analyze EEG data (Contractor): The Contractor will convert the EEG data from Task 1.1 into analyzable form, retaining at least one archival copy of the data on writable CD-ROM. The Contractor will analyze the data using Contractor-patented nonlinear methods. The Contractor will provide the results of this analysis to the Participant for inclusion in the database developed under Task 1.1. This task will span the entire 15-month period of the CRADA.

Task 1.3—Improve the warning algorithm (Contractor): The Contractor will revise the seizure warning algorithm based on the results of Task 1.2 and clinical feedback (such as ease of use, false positives, false negatives, and forewarning time). The Contractor will evaluate the cause(s) of inadequate performance. The Contractor then will seek improved warning in terms of an expanded framework for nonlinear analysis, formulation, and implementation of measures that are more discriminating, better methodology parameters, and formulation of statistics to improve forewarning time. The Contractor will revise and test the warning algorithm with these improvements and update the clinical versions of the code as appropriate. This task will span the entire 15-month period of the CRADA.

Task 2.1—Specify I/O requirements for interface (Participant and Contractor): The Contractor will provide the I/O needs (configurable parameters for the warning algorithm, such as sampling rate and EEG channel for analysis) to the Participant for development of a prototype with defined input and output. Based on these I/O needs, the Participant will specify the I/O requirements for the Contractor's deliverable (clinical warning algorithm), in consultation with the Contractor, including specifications for the EEG data, preseizure indications, and methodology options. The initial requirements will be defined within 1 month after the effective date of the CRADA and subsequently revised as necessary.

Task 2.2—Provide computer with interface (Participant): The Participant will develop a user interface between the Participant's software for epilepsy monitoring and the Contractor's warning algorithm. This user interface will, for example, handle the variable parameters for the warning algorithm (such as sampling rate and EEG channel for analysis), error reporting and recovery (such as the presence of constant signal), choice of methodology options, and display the preseizure indications from the warning algorithm. This task also includes software to convert near-real-time EEG data to a form that is analyzable by the Contractor's warning algorithm, as well as storing an archival form of the digital data for subsequent analysis in Task 3.1. The Participant will provide an appropriate computer to the Contractor with an implementation of user interface and data conversion software on which the software for Tasks 2.3–2.4 will be installed and tested. This task will be completed initially within 3 months after

the effective date of the CRADA with revisions during the subsequent 12 months of the CRADA as needed.

Task 2.3—Build initial prototype for clinical setting (Contractor): The Contractor will incorporate the results from the above tasks into a prototype for use in a clinical setting. The Contractor also will revise the warning algorithm to satisfy the user interface requirements of Tasks 2.1–2.2. The Contractor will include a data quality check for the EEG data with appropriate operator alerts. The Contractor will install the clinical prototype software on the computer from Task 2.2. This task will be initially completed within 5 months after the effective date of the CRADA and updated subsequently as appropriate.

Task 2.4—Testing (Contractor and Participant): The Participant and Contractor will develop a validation and verification testing protocol for the prototype. The Contractor then will test the prototype via this validation and verification protocol using data from Task 1.1 with appropriate software updates as necessary. This task will be completed initially within 6 months after the effective date of the CRADA with revisions during the subsequent 9 months of the CRADA as necessary.

Task 2.5—Training (Contractor and Participant): The Contractor will provide appropriate training to the Participant's staff. At the conclusion of the testing (Task 2.4) and training, the Participant will take possession of the computer from Task 2.4, including the Participant-developed user interface and the Contractor-developed warning algorithm. This task will be initially completed within 6 months after the effective date of the CRADA with updates during the subsequent 9 months of the CRADA as needed.

Task 3.1—Test prototype at 3-5 clinical sites (Participant and Contractor): The Participant wants to test the epilepsy-forewarning device at several clinical sites. The Participant will provide clones of the prototype from Task 2 to clinical test sites. The Contractor will work with the Participant to establish data links with the clinical test sites for exchanging of data and updating of the preseizure warning code. This task will begin when the initial prototype hardware is available and will span the remainder of the 15-month period of the CRADA as updates and improvements are made.

Task 3.2—Travel to clinical sites (Participant and Contractor): Contractor and Participant staff will visit clinical sites to obtain clinical input on the prototype and its performance. This task will span the entire 15-month period of the CRADA period.

Additional tasks may be added to this statement of work via a CRADA amendment depending on the needs of the Participant, contingent on the results of this CRADA, and subject to the availability of additional funding.

APPENDIX B: FUNCTIONAL REQUIREMENTS FOR
PROTOTYPE WARNING DEVICE

Figure B1 shows a schematic diagram of the system interactions among the patient, the existing NBI Data Acquisition Computer (DAC), and the prototype Nonlinear Analysis Computer (NAC). Multichannel, analog EEG data is acquired in real-time from the patient via the DAC. The multichannel EEG data is provided from the DAC as input to the NAC in near-real time. The NAC processes this data according to user-defined protocols and outputs the analysis results to the user. The corresponding functional systems requirements are outlined below. ORNL worked with NBI to prepare an initial set of systems requirements by November 11, 1999, according to CRADA Task 2.1.

Input to NAC from DAC: near-real-time multichannel EEG
CD-ROM: archival multichannel EEG
GUI: set by user

Parameters for analysis of EEG
- sampling rate (set initially to a default of 250 Hz)
- number of data channels (typically 23–32, and set initially to a default of 32)
- channel for analysis (from menu, based on chosen number of channels)
- threshold level for change detection (typically $2 < U_c < 5$, and set initially to a default of 3.09)
- number of sequential occurrences above threshold for preseizure change indication (default = 2)– user functions
- specify nonlinear analysis parameters (start from defaults from above)
- provide patient information
- start data acquisition and analysis (start execution of NAS code)
- stop data acquisition and analysis (terminate execution of NAS code)
- archive patient information and summary of EEG data to NBI database/log (examples of summary information: minimum and maximum EEG amplitude, dataset length)
- display/edit patient information and summary from database/log
- display patient information and summary from database on CD-ROM
- write EEG data to CD-ROM for archive (to be determined later)
- read archival EEG data from CD-ROM or from 8-h archival VHS tape (to be determined later)

Output from NAC to CD-ROM: archival multichannel EEG (to be determined later)
Graphical User Interface: result to user
- measures of condition change (plots, plus file archive)
- data quality diagnostics (e.g., constant signal, excessive noise)
- status of nonlinear analysis (not running, running, initializing, expect a wait of at least 10 min)

Remote Access to NAC: via Internet
- real-time monitoring/control of NAC
- update nonlinear analysis code
- download patient dataset(s) to ORNL or NBI
- download patient database to ORNL or NBI

These functional requirements lead to specific requirements for the computer hardware for the NAC, the commercial software for the NAC, the GUI, and the NAS. Table B1 shows further detail about the GUI-NAS interaction. An outline of the NAC hardware requirements to implement these functional requirements is shown in Table C1. The computer hardware, in turn, drives the choice of commercial software to support the project as shown in Table C2. The NAS is presently in the form of research-class FORTRAN, which will be revised to work with the GUI as described below.

Internet Access

CD-ROM Archive

Graphical User Interface

Prototype of **N**onlinear **A**nalysis **C**omputer (NAC)

EEG

Present NBI **D**ata **A**cquisition **C**omputer (DAC)

EEG

Patient

OUTPUT FROM GUI:

- Data quality diagnostics

- Nonlinear measures (plots)

INPUT TO GUI:

- Analysis parameters
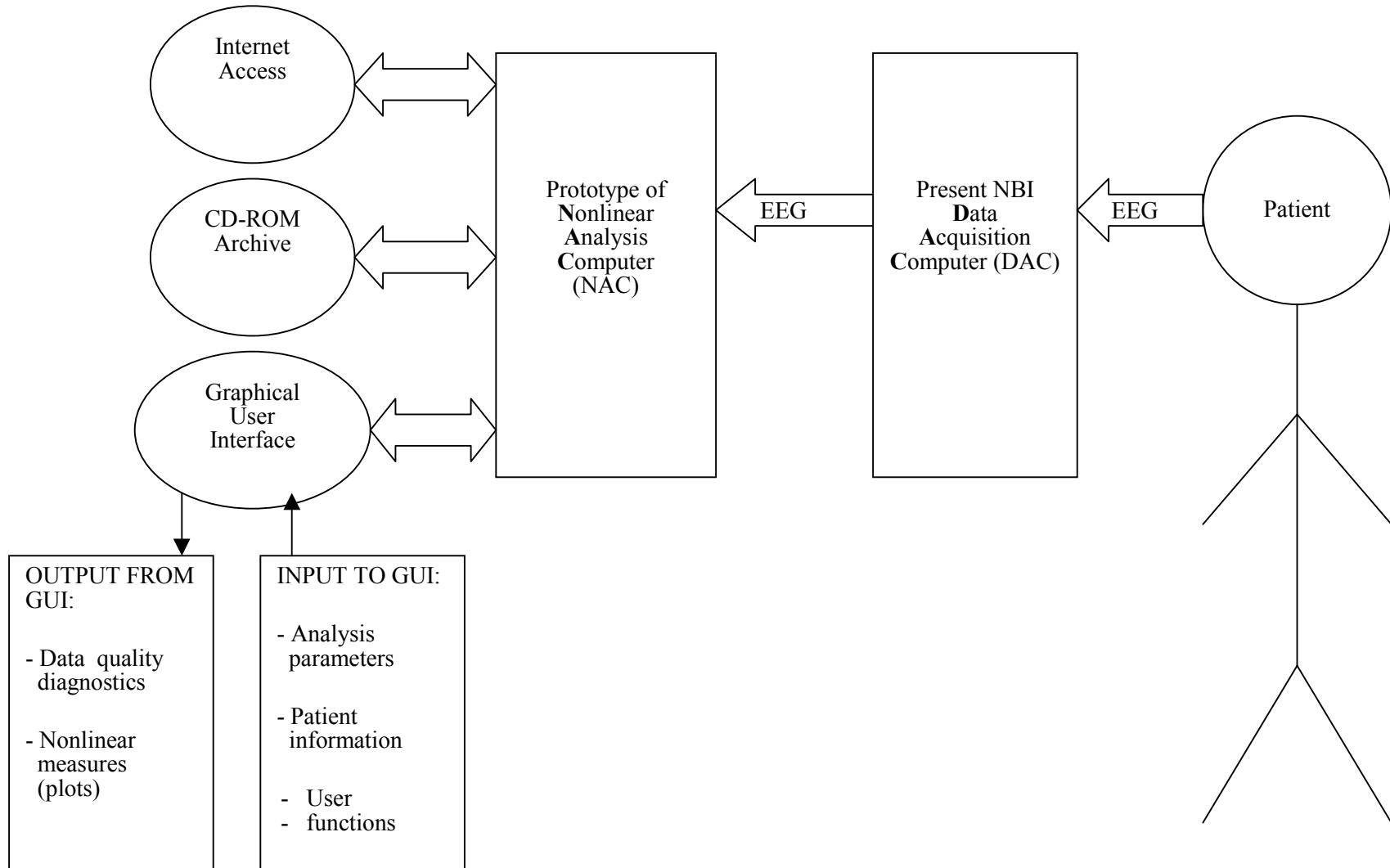
- Patient information

- User
- functions

Fig. B1: Schematic diagram of system interactions.

Table B1. Details of GUI-NAS Interaction

Data input	To analysis module	Data output(s)
1. Real-time EEG from patient	DAC	Analog multichannel EEG
2. User	GUI on NAC	Initiate execution of GUI and NAS on NAC (proceed to Step 3)
3. Nonlinear analysis parameters	NAS on NAC	Use FORTRAN-callable C-code to read parameters by call to INIC
4. Analog multichannel EEG from 1	GUI on NAC	Single channel of digital EEG written continuously to buffer
5. Single channel of EEG from 4	NAS on NAC	Use FORTRAN-callable C-code to read EEG by call to READVIAC
		Use FORTRAB-callable C-code to GUI via call to VFROMF2C
6. Read nonlinear measures from 5	GUI on NAC	Display of nonlinear measures, and user alert(s) for inadequate data quality append nonlinear and data quality measures to database summary
7. User	GUI on NAC	Terminate execution of NAS on NAC

Notes:

Cutset = window of 22,000 time sequential EEG data points;

DAC   = Data Acquisition Computer;

NAC   = Nonlinear Analysis Computer;

NAS   = Nonlinear Analysis Software for preseizure indication.

The multichannel cutset from the DAC includes a date/time stamp, which the GUI should compare to its own current date/time. The operator can easily synchronize the clocks on the DAC and NAC with free Internet software from NIST at :

http://www.bldrdoc.gov/timefreq/javaclck.htm .

With synchronized clocks and this date/time stamp, the GUI can verify that the current data has been provided in near-real time. If not, the GUI can alert the user to perform corresponding checks of the clock synchronization and check the systems for data loss. If the user selects data from archival media, then no such date/time check is needed. The above definition for a cutset uses 10,000 points, sampled at 200 Hz, corresponding to 50 s of real time data. This number of points is in fact a variable, which may be changed later (e.g., to 20,000, 30,000, or 40,000) as the nonlinear algorithm is improved.

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APPENDIX C: FUNCTIONAL FEATURES OF THE
SEIZURE FOREWARNING SOFTWARE

The algorithm includes a data quality check, recognizing that poor quality data into the NAS will certainly yield poor quality results for seizure forewarning. The NAS data quality measures will allow the GUI to issue meaningful diagnostic messages to the user for problem resolution. For example, two pre-CRADA NBI-provided EEG datasets had time intervals with a constant signal, which arose from loose electrodes. For this kind of problem, the GUI diagnostic message to the user could include suggestions about checking the electrode attachment(s) and continuity of electrical leads. The NAS data quality check has the following features with user alerting messages in bold type:

1. *If the number of data points in the time window (w) is not 22,000, then alert the user: <u>NAC is not receiving the proper number of EEG data points</u>. Please contact NBI.

2. *Determine the maximum (x_{max}) and minimum (x_{min}) in the artifact-filtered EEG signal (x_i). If $x_{max} = x_{min}$, terminate further analysis and alert the user: EEG <u>signal is flat</u>.   Please check scalp electrode and leads.

3. Compute the average number of time steps per cycle (T_c) in the artifact-filtered signal. If T_c < 4 timesteps/cycle, then alert the user: EEG <u>sampling rate is too low</u>. Please contact NBI.

4. Compute the first minimum (M_1) in the mutual information function of the artifact-filtered EEG. If $M_1 < 4$ timesteps, then alert the user: EEG <u>sampling rate for nonlinear analysis is too low</u>. Please contact NBI.

5. Obtain the first difference, $\Delta x_i = x_{i+1} - x_i$, over the entire artifact set of artifact-filtered data. Obtain the maximum (Δx_x) and minimum (Δx_n) values of Δx_i. If $\Delta x_n > 0$, then alert the user: EEG <u>data increase monotonically</u>. Please check the data acquisition system or contact NBI.

6. If $\Delta x_x < 0$, then alert the user: EEG <u>data decrease monotonically</u>. Please check the data acquisition system or contact NBI.

7. If the signal power in the first two peaks of the Fourier spectrum exceeds half of the total spectral power, then alert the user: EEG <u>data has excessive periodic content</u>. Please check grounding and potential oscillator sources.

8. Calculate the number of active bits (B) of data precision in the artifact-filtered EEG signal. If B<5, then alert the user: EEG <u>data has excessive noise</u>. Please increase EEG amplification factor to improve resolution.

9. Discretize the values of x_i into equality spaced bins between x_{min} and x_{max}. Tabulate the one-dimensional occurrence frequency of the discretized data in these bins. If the population at the bottom or top 10% of the distribution exceeds w/10, then alert the user: <u>EEG saturates at high/low limits</u>. Please decease EEG amplification to avoid saturation.

10. Tabulate the number of occurrences (N_z) of $\Delta x_i = 0$. If $N_z > w/10$, then alert the user: EEG <u>signal is intermittently flat</u> for >10% of samples. Please check scalp electrode and leads.

The underlined portions are a brief user description of each data quality check. Starred items (*) denote quality problems for which further analysis of the cutset is prohibited and for which control is returned to the GUI with a corresponding warning diagnostic. Other problems produce a warning, but the analysis continues. Details are provided in U.S. Patent #5,815,413 [6].

TheNAS is presently implemented as research-class FORTRAN. The analysis algorithm for archival EEG follows the protocol below:

1. set the analysis parameters and initialize the computation;

2. read a file that specifies the filename that contains the EEG data;

3. read the EEG data from this second file;

4. remove low-frequency artifacts (eyeblinks, etc.) from the EEG via a zero-phase, quadratic filter;

5. compute measures of EEG data quality;

6. if data quality is inadequate, then provide user warning and terminate the analysis;

7. otherwise, compute the first minimum in mutual information function of EEG;

8. convert time serial data into a multidimensional phase space representation;

9. tabulate the occurrence frequency (distribution function) in a discretized form of the phase space;

10. save the distribution functions for each of ten basecase time intervals;

11. repeat this process for each testcase time interval;

12. compare the distribution functions for testcase and basecases via four nonlinear measures;

13. output the nonlinear measures for postprocessing visualization.

The present NAS performs these calculations for a long set of contiguous archival data. The analysis on an ORNL dual 400 MHz PII computer required ~30 min to process 34.4 h of EEG data at ~50% processor usage (equivalent to a single 400 MHz processor). This speed corresponds to more than 60-fold faster than real time. Thus, we do not anticipate any problem in the adequacy of processing power to provide near-real time analysis of EEG. Presently, renormalization of the nonlinear measures is performed by the visualization analysis (via MATLAB). Details of the nonlinear analysis of EEG are described in recent ORNL publications [7–10, 12].

The near-real-time analysis begins by reading EEG for nonoverlapping time-sequential windows (cutsets), each with 22,000 points of data. This number of data points may change as the forewarning methodology is improved. The method next analyzes EEG data, as discussed below, waits for a new EEG cutset, and then repeats the process. After the analysis of each cutset, the results are provided to the GUI for display to the user. The revised algorithm for the near-real-time analysis mode is as follows:

1. set the analysis parameters and initialize the computation;

2. wait for the next cutset, then read the time-sequential EEG data;

3. apply the zero-phase, quadratic filter to the data from step 2;

4. compute the measures of data quality (as described above) for data from step 3;

5. if data quality is inadequate, then output alerting information to the GUI and go to step 2;

6. otherwise, compute the first minimum in mutual information function of the data from step 3;

7. obtain three-dimensional phase space representations of the data from steps 3–4;

8. tabulate the discrete phase-space distribution functions from step 7;

9. save the distribution functions for each of ten nonoverlapping base-case cutsets from step 8;

10. obtain nonlinear measures between each unique pair of nonoverlapping basecases from step 9;

11. save the average and standard deviation over the basecase nonlinear measures from step 10;

12. repeat steps 2–8 for each testcase cutset;

13. obtain nonlinear measures between the phase-space distributions for testcase and each basecase;

14.   compute the renormalized forms of the average nonlinear measures from step 13;

15.   output the results from step 14 for visualization by the GUI;

16.   wait for the next cutset of EEG data;

17.   repeat the methodology from step 12.

We previously analyzed <u>archival</u> data with the minimum and maximum in the signal amplitude over the <u>entire</u> dataset with 34 discrete amplitude symbols. <u>Near-real-time</u> analysis only has access to the minimum and maximum amplitude in the <u>basecase</u>. Fewer amplitude symbols (22) are appropriate when using the basecase extrema. This latter approach does not degrade the forewarning sensitivity, because both approaches uniquely capture the basecase dynamics against which the testcase dynamics are subsequently compared. In addition, many potential failure paths are possible in this algorithm. Examples involve the handshaking between the two computers (DAC and NAC), acquisition of the next window of EEG data, and the handshaking between the NAS and the GUI. Ample internal diagnostics are essential to understand and resolve such problems. Remote access to clinical NACs via the TIMBUKTU commercial software will be essential for diagnosing problems remotely. According to CRADA Task 2.3, ORNL will have an initial NAS implementation by March 1, 2000. Table C1 summarizes the handshaking between the GUI and the nonlinear analysis (FORTRAN) code to accomplish these tasks.

Table C1. Handshaking conditions between graphical user interface and FORTRAN

FORTRAN fault condition	Specific fault type	FORTRAN resolution	GUI resolution	Interface routine(s)
NCUTSETT $\leq$ 0	FORTRAN stops	Issue warning to GUI	Verify parameter	INIC
NCUTSETT > 22000	Out-of-bounds array ref	Issue warning to GUI	Verify parameter	INIC
NARTFLTR $\leq$ 0	FORTRAN stops	Issue warning to GUI	Verify parameter	INIC
NARTFLTR > 1000	Nonrobust results	Issue warning to GUI	Verify parameter	INIC
D=NDIMENSN	FORTRAN stops	Issue warning to GUI	Verify parameter	INIC
NDIMENSN > 10	Nonrobust results	Issue warning to GUI	Verify parameter	INIC
S=NPARTITN $\leq$ 1	FORTRAN stops	Issue warning to GUI	Verify parameter	INIC
NPARTITN > 100	Nonrobust results	Issue warning to GUI	Verify parameter	INIC
NPARTITN = odd number	Nonrobust results	Issue warning to GUI	Verify parameter	INIC
NBSCSCUT $\leq$ 5	Nonrobust results	Issue warning to GUI	Verify parameter	INIC
NBSCSCUT > 10	Out-of-bounds array ref	Issue warning to GUI	Verify parameter	INIC
NBSCSCUT*NCUTSETT > 220001	Out-of-bounds array ref	Issue warning to GUI	Verify parameter	INIC
SAMPFREQ < 200	Nonrobust results	Issue warning to GUI	Verify parameter	INIC
S**(2D) > 2**53	Wrong results	Issue warning to GUI	Verify parameter	INIC
# Outliers in basecase $\geq$ 5	Meaningless results	Return control to GUI	Return new basecase	READVIAC
Constant signal in raw EEG	FORTRAN stops	Return control to GUI	Return new cutset	VFROMF2C

APPENDIX D: COMMERCIAL HARDWARE AND
SOFTWARE REQUIREMENTS FOR NAC

Table D1:. Commercial computer hardware specification for NAC

Feature	Specification
Manufacturer	Dell
Model	Dimension L
Processor	500MHz PIII processor
Memory	384 MB SDRAM
Hard drive	6.3 GB
Monitor	15-in. viewable
Video card	Intel 3D AGP graphics
CD-ROM drive	Sony CD-RW
Mouse	Two button
Keyboard	Standard
Floppy drive	1.44 MB
Network adapter	Ethernet or ISDN
Operating system	Window NT 4.0/SP4
A/D board	Needed if data to NAC is in analog form

The choice of a PIII processor, rather than a Celeron, is based on higher floating-point speed in the former for nonlinear analysis. The processor speed (500 MHz) is the slowest for which the PIII is available to reduce cost. The computer memory (384 MB) is based on the "peak commit" memory that ORNL observed (310 MB) when running nonlinear analysis of NBI data on a 400 MHz PII WinNT PC. This memory allows for modest increases when running the GUI and other utilities on the NAC. The choice of Ethernet or ISDN network adapter is driven by fast Internet access, which a standard phone modem cannot provide. This choice will be dictated by the network access available at the clinical sites. We also recommend an uninterruptable power supply and spike suppressor. According to CRADA Task 2.2, NBI implemented the GUI and data conversion interface on the NAC early in the 2000 calendar year.

TABLE D2: Commercial computer software specification for NAC

Commercial product	Functional features that drive specification
TIMBUKTU	File transfer to and from NAC via Internet
	Remote observation to NAC
	Remote control of NAC
Digital Visual FORTRAN	Remote code modifications
	Remote debugging of source code
	Remote compilation of source code

    ORNL presently uses these commercial software products and has found them to be excellent for code development. We note that local debugging, code modifications, and compilation of executables at ORNL are preferable. However, hardware and software peculiarities at the initial clinical sites may require remote debugging, modifications, and compilation. In this latter case, a version of DVF at least on the NBI NAC will be necessary. Moreover, file transfer of the ~3.7 MB executable code will require >8-fold more wait time than the FORTRAN source code (~440 KB).

APPENDIX E: FEATURES OF PATIENT DATABASE

The database assures patient confidentiality by using a unique number for each patient and event. The clinical site retains the original file name (which at times is created from the patient name) but will not publish those original names. This data is useful for interpretation of an event, in which case the interpreter can use the original data file/patient name to obtain the raw data set. The GUI requires completion of specific database fields before beginning the monitoring session. The database fields will include the following:

- Patient information
    - Unique data file identification number
    - Original data file name
    - Sex
    - Age
    - Notes (e.g., whether light, sounds, temperature changes induce a seizure)
    - Medical history (other relevant medical conditions)
    - Interpretation report summary correlating testing (MRI, SPECT, etc.)
- Monitor information
    - Acquisition system used
    - Clinical site used
    - Number of channels recorded
    - Input channel used
    - Sample rate
    - Begin date/time of monitoring (from NAS clock)
    - End date/time of monitoring (from NAS clock)
    - Surface scalp recording (Phase I) or cortical depth recording (Phase II)
- Brain activity
    - Activity prior to seizure (e.g., sleeping, eating, talking, reading, watching TV, trembling, etc.)
    - Approximate times of these activities to correlate with EEG changes
    - Interpreted seizure time/day
    - Diagnosed seizure type
    - Clinical seizure duration
    - Electrical seizure duration
    - Other channels for which significant seizure electrical activity is observed
    - Clinical postseizure duration
    - Electrical postseizure duration
- Nonlinear analysis
    - NAS threshold, above which nonlinear features in the data are significantly different
    - Number of successive indications above this threshold for an indication of condition change
    - NAS indicated seizure time/day
    - NAS indication onset (s/min)
    - NAS forewarning time (s/min)
    - Summary of nonlinear analysis results

APPENDIX F: GRAPHICAL USER INTERFACE FUNCTIONALITY AND APPEARANCE

This appendix exclusively addresses the interface and functions presented to the clinical user. This document does not address any technical issues or functionality that is currently unknown to the user. Within this document the following definitions apply:

NAS/Forecast   Refers to the <u>N</u>onlinear <u>A</u>nalysis <u>S</u>oftware (algorithm)
NAC   Refers to the <u>N</u>onlinear <u>A</u>nalysis <u>C</u>omputer
FAP   Forecast Algorithm Parameters Screen
MIS   Main Interface Screen
EQI   Electrode Quality Indicator

Clinical User Sequence to activate the NAC:

Step #1   Boot up the NAC to the Windows Desktop Screen
Step #2   Click on the Forecast icon (TBD) on the desktop
Step #3   Display the Forecast Algorithm Parameters (FAP) dialog
Step #4   Within FAP, the user must complete the following fields:

Patient Name: Clinical user's entry is used for data file management and future file tracking.
Patient ID: User enters a unique ID number for data file management and future file tracking.
Patient Information: Free form field that allows the user type in specific entries regarding the study, patient demographics, diagnosis, etc. This will be a separate entry task from the database entries.
Threshold: The system defaults to a threshold level. In the future, the user selects from a predefined list to achieve the most appropriate threshold. (Graphics TBD)
Sampling Rate: The system will default to 250 Hz. In the future, the user selects from a predefined list.
Number of Channels Acquired: User enters the number of inputs being used during the monitoring study.
Electrode Input: User enters the electrode <u>and</u> amplifier input number to be used for the Forecast analysis.
Number of Sequential Occurrences Above Threshold: The system will default to two. In the future, the user will select from a predefined list of choices.
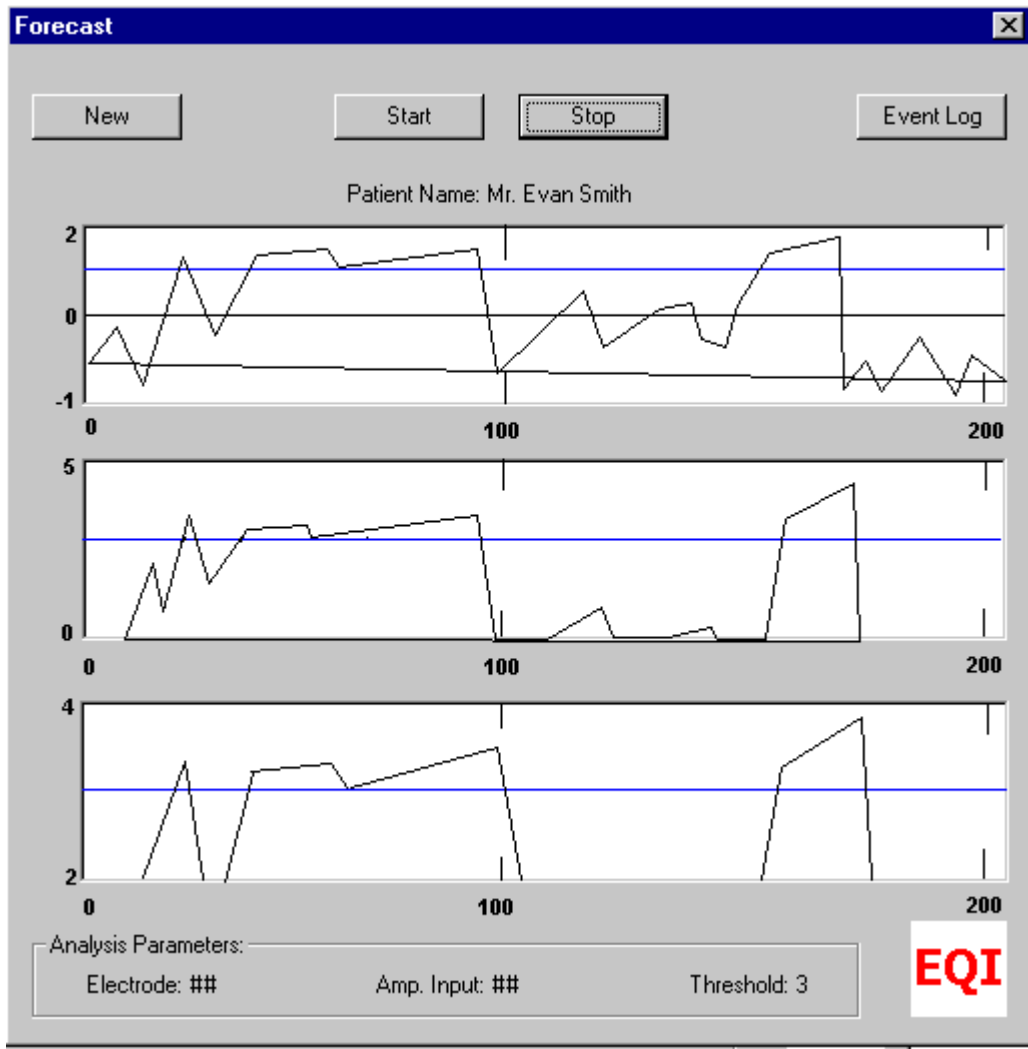**Electrode Quality Indicator:** System defaults to activation of this function with a default interface (TBD). In the future, the user may be able to select from a predefined list of options for interface and activation.
OK: Clicking this icon will remove the FAP screen and display the message stating, "Analysis has begun—please wait for initial results to be displayed." The screen will display a "progress bar" that shows a visual progression and time indicator in minutes. See below for typical GUI screens. <u>Cancel:</u> Clicking this icon removes the FAP screen and the Windows Desktop. No information is saved.

Step #5   After the initial data has been entered, the MIS is displayed with the following options:

1.   Selecting the <u>Stop</u> icon after the analysis had begun will prompt a message that confirms the user wants to stop the Forecast software. *Do you want to stop the Forecast Software? Yes_No* (The data will continue to be analyzed until the user makes a choice.)

- Selecting <u>Yes</u> will stop the analysis process and the trended and settings information will be saved to disk. The message screen will be dismissed, and the MIS screen will be displayed with the most recent trended information.

- Selecting <u>No</u> will continue the analysis process and dismiss the screen.

2.   Selecting the <u>New</u> icon will display the FAP dialog (no previously selected parameters will be saved.). This icon is only accessible if the algorithm is stopped-otherwise the icon is grayed out.

3.   Selecting the <u>Start</u> icon will begin the algorithm analysis on the most recently acquired data. After the analysis has begun, the Start icon will not longer be accessible; otherwise the icon ID grayed out.

4.   Selecting the <u>Event Log</u> icon will display any information currently entered into the log such as start times, stop times, software entries (TBD), etc. The log will allow the user to dismiss the screen when finished viewing. This log screen cannot be edited by the user but is designed to be accessed by Nicolet or ORNL staff (i.e., via networks).

5.   The MIS will display the <u>electrode label and amplifier input</u> that was selected within the FAP dialog box (currently being used for analysis) in the lower left hand corner.

6.   The MIS will display the <u>threshold</u> that defaulted (and is being used) within the FAP dialog box in the lower left hand corner.

7.   <u>EQI</u> icon will indicate to the user when the software detects poor electrode quality/contact. The icon will flash (duration .5 s) to the user one time per 3 s. The flash will be displayed in a gray color. The flash activity will continue until the software detects the contact/quality has improved.

Forecast

New   Start   Stop   Event Log

Patient Name: Mr. Evan Smith

Analysis Parameters:

Electrode: ##   Amp. Input: ##   Threshold: 3

EQI

Forecast Parameters

Name: _____   Electrode   Amp Input #

Patient ID: _____

Threshold: _____

Sample Rate: _____

# of Electrodes: _____

Indicator Settings
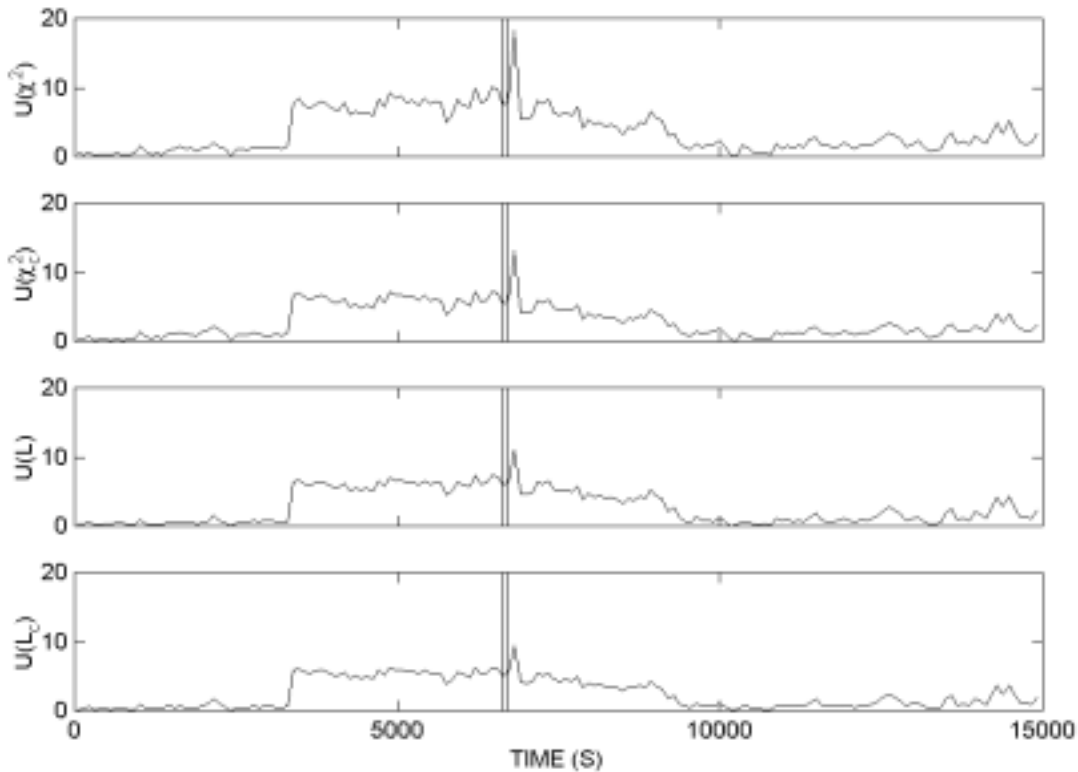☐ Electrode Quality Indicator (EQI)

Patient Information:

Cancel

OK

**APPENDIX G: PUBLIC RELEASE ON ANALYSIS OF THE FIRST CLINICAL DATASET**

These plots show nonlinear measures from the first clinical dataset that was acquired via the prototype seizure forewarning device. The vertical bars show the seizure duration from 6644–6705 s. All four measures show a clear change in the sample channel at 3520 s, giving 52 min of seizure forewarning. The prototype gave no false-positive warnings prior to this event, which occurred on the seventh day of continuous EEG monitoring. The forewarning technique first removes eyeblinks and other artifacts that are superimposed on the brainwave activity. The method then converts the artifact-filtered data to a geometrical (phase-space) representation. A distribution function (DF) tabulates the location and occurrence frequency in a discrete form of this multidimensional phase space. The nonlinear measures show the dissimilarity between nonseizure DFs and DFs for subsequent time windows.

The prototype was developed jointly by NBI and ORNL under a CRADA collaboration that began on October 1, 1999. The first prototype was installed at the epilepsy monitoring unit of the University of Wisconsin in Madison on April 28, 2000. Subsequent installations were at Strong Memorial Hospital in Rochester, New York (installed June 15, 2000); Henry Ford Hospital in Detroit, Michigan (installed June 23, 2000); Parklawn Hospital in Dallas, Texas (installed June 29, 2000); and Med City Dallas in Dallas, Texas (installed June 30, 2000). EEG data from these five clinical sites will be provided to ORNL for subsequent analysis.

The team members at NBI are Dr. Jon Joseph (principal investigator), Todd Lucht, and Char Merican. The ORNL team members are Ned E. Clapp (Engineering Technology Division), Dr. Lee M. Hively (principal investigator in the Engineering Technology Division), and Dr. Vladimir A. Protopopescu (Computer Science and Mathematics Division).

**APPENDIX H: TWO-PAGE DESCRIPTION OF FOREWARNING TECHNOLOGY**
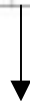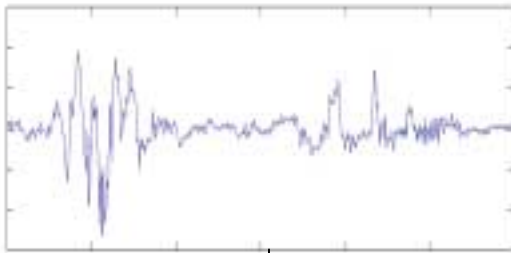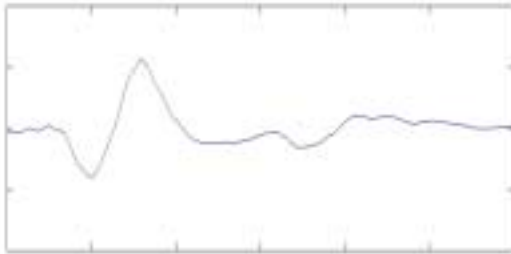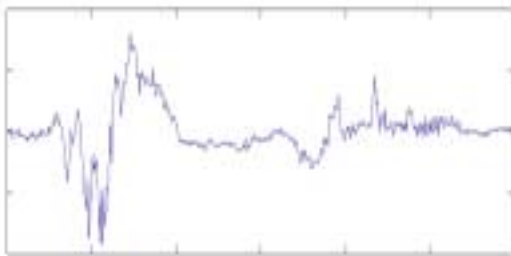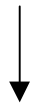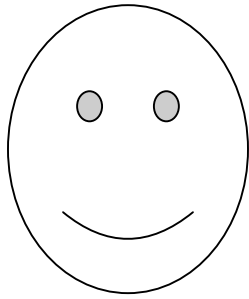
Noisy multichannel scalp EEG data is acquired from human patients. An alphanumeric designation uniquely identifies each dataset to preserve patient anonymity. For example, the data in this example is from SZ13IN.

EEG data contains information about the brain dynamics. This figure shows raw EEG from channel C3 in the 10–20 International System at a sampling rate of 250 Hz. Tick marks are spaced at intervals of 0.5 s.

Low-frequency activity in scalp EEG is associated with eyeblinks and related muscular movements. This figure shows such an artifact below 2 Hz that is removed via a zero-phase, quadratic filter. This ORNL technology is covered by U.S. Patent #5,626,145, dated May 6, 1997.

This figure shows the EEG signal after removal of the low-frequency artifact from the raw data. This method of artifact filtering retains the high-frequency nonlinear amplitude and phase information about the brain activity.
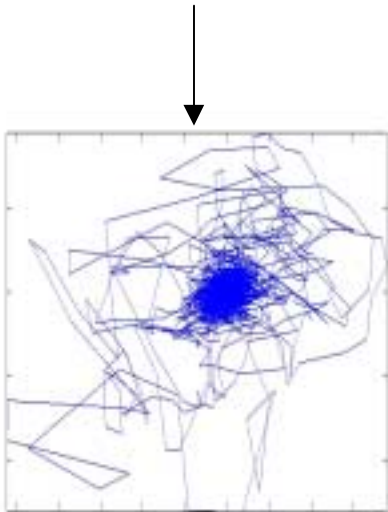
Artifact-filtered data (x_i) is converted to a phase-space (PS) form. This figure illustrates a two-dimensional version, showing lines between successive PS-points, (x_i, $x_{i+\lambda}$). The lag (λ) is chosen to best "unfold" the dynamics in this PS representation. The lag corresponds to the first minimum in the mutual information, which is the nonlinear analog of the autocorrelation function. This PS plot displays the structure of the nonlinear brain dynamics for 20,000 data points from dataset SZ13IN.
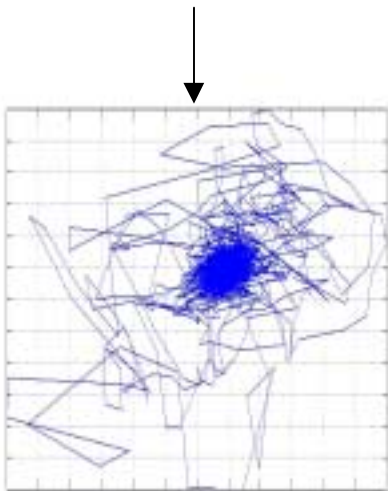
The phase-space is partitioned into bins in each dimension as depicted in this figure. The method tabulates the number of PS states that fall into each bin. The result is an invariant distribution function that statistically describes the occurrence frequency of brain activity over the phase space.
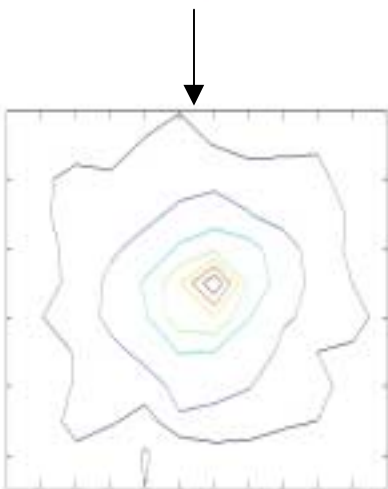
This figure illustrates logarithmically-spaced level contours of the PS distribution function (DF) that characterizes the artifact-filtered brain activity. A sufficiently high-dimensional PS captures relevant brain dynamics within the limits of noise and sensor accuracy. Typically, three dimensions and 5-40 bins are sufficient for such data. The PS-DF method is covered by U.S. Patent #5,815,413, dated September 29, 1998.

APPENDIX I: SAMPLE PUBLICATIONS FROM PUBLIC RELEASE

ORNL-Nicolet partnership promises help for epileptics (front page of the *Oak Ridger*, Monday, July 24, 2000, by Paul Parson, *Oak Ridger* staff).

What if an epilepsy seizure sufferer could be forewarned of an impending seizure? It's not a far-fetched idea. In fact, it's what a joint project between Oak Ridge National Laboratory researchers and Nicolet Biomedical Inc. is trying to accomplish. Epileptic seizures affected 2.3 million Americans in 1995, and approximately 181,000 new cases of epilepsy occur each year, according to statistics from the Epilepsy Foundation of America. People with epilepsy experience recurrent seizures, which strike when there is an abnormality in the brain's electrical activity. Symptoms of these seizures include twitching, muscle spasms, hallucinations, intense feelings of fear or deja vu, peculiar sensations such as seeing flashing lights and loss of consciousness.

Depending on when or where these seizures occur, a person could suffer humiliation or harm. But that could one day be a thing of the past. Lee Hively with ORNL said the project's goal is to devise a system to provide a "reliable" 8- to 50-minute warning of a looming seizure. "This will give the patient enough time to stop doing something that could cause something bad ... having the person stop doing hazardous activities such as swimming, climbing on a ladder or handling boiling water," Hively said.

Although the formal collaboration between ORNL and Nicolet began in October 1999, the actual research started in 1994. The research indicated nonlinear techniques could be used to identify properties of a seizure as well as giving researchers some forewarning indications. "At this time we saw forewarnings 8 to 15 minutes prior to the seizure," Hively said. "But, as research continued, the time period of those warnings increased."

New life was breathed into the research in January 1999 when a patent from the 1994–95 research was published and seen by Nicolet officials, who then contacted the ORNL scientists about a possible collaboration. Nicolet, located in Madison, WI, manufactures and distributes medical instrumentation systems for neurophysiological diagnosis and monitoring. This unified effort led to the development of a prototype, known as Forecast, that began being clinically tested in five U.S. hospitals earlier this year. It utilizes dime-size scalp electrodes that relay electroencephalographic signals from patients, who are tested 24 hours a day for a week, to a computer for analysis. A warning alert occurs when the computer detects a significant nonlinear change from nonseizure brain waves.

The forewarning technique first removes eye-blinks and other artifacts that are superimposed on the brain wave activity. The method then converts the artifact-filtered data to a geometrical (phase-space) representation. A distribution function tabulates the location and occurrence frequency in a discrete form of this multidimensional phase space. The nonlinear measures show the dissimilarity between nonseizure distribution functions and distribution functions for subsequent time windows.

The first prototype to be installed was at the epilepsy monitoring unit of the University of Wisconsin in Madison on April 28. The first person tested at this site experienced a seizure on the seventh day of the study. "We were provided a video of that first patient and you can see that the patient is sitting in bed at 9 a.m. ... watching TV and, suddenly, he goes into a seizure," Hively said. "If the physician knew the seizure was going to happen he could be at the bedside. He could watch to see if there was any initial trembling that might be a precursor. He could look at the severity of the seizure."

Data from all five clinical sites will be analyzed by ORNL researchers. And ongoing research is set to begin in October between the parties with a specific objective in mind. "Hopefully what we're going to do is develop it into something ambulatory, something that could move around with the patient," said Char Merican, project manager of seizure prediction for Nicolet. "We're very excited in the direction this could go. It could help a lot of people."

The team members at Nicolet are Jon Joseph, prinicpal investigator, Todd Lucht and Char Merican. Current ORNL team members are Ned E. Clapp, Engineering Technology Division; Hively, principal investigator in the Engineering Technology Division; and Vladimir A. Protopopescu, Computer Science and Mathematics Division.

And, while ORNL officials are working to help predict seizures, their research is proving to be beneficial in several other areas. Hively said the technique is being used in studies with heart attack victims and people who are paraplegic or quadriplegic as well as to test stress and strain data of a structure.

Early warning of epileptic seizures (page 17 of *New Scientist*, July 29, 2000) by Ian Sample

For many people with epilepsy, the biggest fear is that a seizure will catch them by surprise and cause an accident. A new alarm system aims to prevent this by warning when a seizure is about to strike.

The system, called Forecast, starts by recording its user's brain activity via EEG electrodes. It then monitors the brain's activity and compares this with the stored data. The software it uses to do this was developed by Lee Hively at the Oak Ridge National Laboratory in Tennessee. Sustained large differences can indicate that an epileptic seizure is imminent, says Hively.

"It seems that before a seizure, there's a warming-up period in brain activity that this algorithm picks up," says Char Merican of Nicolet Biomedical in Madison, Wisconsin, which is carrying out clinical tests of Forecast. The firm plans to build the technology into a wearable unit.

Forecast can detect seizures more than eight minutes before they strike, which could make a big difference, says Hively. "The person could immediately stop doing what they're doing – like get out of the swimming pool or get off the ladder—and go and lie down," he told *New Scientist*.

APPENDIX J: PRELIMINARY RESULTS OF EEG EPILEPSY FOREWARNING ANALYSIS

By September 22, 2000, ORNL had received 208 different EEG datasets (65.5 GB total). NBI intentionally included 17 duplicate data files. In each case, ORNL verified that the duplicate was identical to the earlier copy as a validation of the file transport protocol. The duplicate file ID numbers are: {10 12 13 15 16 18 20 184 219 258 269 274 277 293 297 390 398}.

On September 27, 2000, ORNL completed a preliminary analysis of 194 datasets for which both data and seizure characterizations were available. The results are based on the union of analyses for EEG data in the monopolar and bipolar montages. This analysis is only for the first seizure in each dataset, because the methodology for multiple seizures in one dataset has not yet been determined. ORNL made no attempt to optimize the variable parameters in the forewarning methodology for this analysis.   The number of true and false positives and negatives varied as the forewarning window was changed as shown in the following table.

```
            ------------FOREWARNING WINDOW IN MINUTES------------
                 10 - 30        5 - 36        5 - 45         1 - 60
FOREWARNINGS     74  (38.1%)  89  (45.9%)  99  (51.0%)  111   (57.2%)
TRUE NEGATIVES   11  ( 5.7%)  11  ( 5.7%)  11  ( 5.7%)   11   ( 5.7%)
FALSE NEGATIVES   2.5( 1.3%)   1.5( 0.8%)   1.5( 0.8%)    1.5( 0.8%)
FALSE POSITIVES 106.5(54.9%)  92.5(47.7%)  82.5(42.5%)   70.5(36.3%)
```

The entries of 0.5 under false positives and false negatives arise because a false negative occurs for the monopolar analysis, and a false positive occurs for the bipolar analysis (or visa versa). Consequently, that occurrence was tabulated as one-half for each (increment total of false positives by 1/2 and false negatives by 1/2). Work under CRADA Task 1.3 is pursuing further analysis to reduce the rate of false positives and false negatives.

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24. T. L. Lucht, Nicolet Biomedical Inc., 5225 Verona Road (Building 2), Madison, Wisconsin, 53711.
25. C. E. Merican, Nicolet Biomedical Inc., 5225 Verona Road (Building 2), Madison, Wisconsin, 53711.