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Epilepsy Forewarning Using a Hand-Held Device

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ABSTRACT

Over the last decade, ORNL has developed and patented a novel approach[1-40] for forewarning of a large variety of machine and biomedical events. The present implementation uses desktop computers to analyze archival data. This report describes the next logical step in this effort, namely use of a hand-held device for the analysis.

1. INTRODUCTION

ORNL staff have developed and patented technology for forewarning of machine and biomedical events. Six U.S. patents and two patents pending have resulted from this work, as follows.

IP1) L.M. Hively, "Methods for Improved Forewarning of Critical Events Across Multiple Data Channels," Patent pending (ORNL ERID# 1300) submitted to US Patent Office (22 Sept. 2003).

IP2) L.M. Hively, P.C. Gailey, V.A. Protopopescu, "Condition Assessment of Nonlinear Processes," *U.S. Patent #6,484,132* (19 Nov. 2002).

IP3) D.E. Welch, L.M. Hively, and R.F. Holdaway, "Nonlinear Prediction of Fatigue Failure," *US Patent #6,460,012* (1 Oct. 2002).

IP4) L.M. Hively, "Methods for Consistent Forewarning of Critical Events Across Multiple Data Channels," Patent pending (ORNL ERID#0885) submitted to US Patent Office (12 July 2002).

IP5) L.M. Hively, N.E. Clapp, C.S. Daw, W.F. Lawkins, "Epileptic Seizure Prediction by Nonlinear Methods," *U.S. Patent #5,857,978* (12 January 1999).

IP6) L.M. Hively and E.G. Ng, "Integrated Method for Chaotic Time Series Analysis," *U.S. Patent #5,815,413* (29 September 1998).

IP7) 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* (28 April 1998).

IP8) N.E. Clapp, L.M. Hively, "Method and Apparatus for Extraction of Low-Frequency Artifacts from Brain Waves for Alertness Detection," *US Patent #5,626,145* (6 May 1997).

Section 2 provides background on the specific biomedical and machine applications of this patented technology. Section 3 describes the analysis methodology for implementation on the hand-held device. Section 4 discusses the hardware and software implementation on a prototypical hand-held device, and corresponding validation results. Section 5 presents potential future applications of this work.

2. BACKGROUND

The present work leverages nonlinear technology developments that have grown out of several recent projects. One project was sponsored under a Cooperative Research and Development Agreement (CRADA) collaboration in 1996 - 1998 at approximately $350K with Y-12 (lead), ORNL, and Cincinnati Milacron Incorporated (CMI) in Ohio, a premier manufacturer of machine tools. The bellows coupling on the Z-axis of a Magnum machining center at Y-12 (B9303) broke in the middle of July 1997. ORNL analyzed the motor current data, and found clear predictors of this failure. This work was the earliest implementation of patented technology for machine events and was published in the 1997 MAintenance and Reliability CONference (MARCON) proceedings.[2]

A second project involved a funds-in CRADA collaboration with Nicolet Biomedical Incorporated (NBI). Dr. Jon Joseph of NBI contacted Lee Hively in the spring of 1999, because NBI's literature search found ORNL's US Patent on epilepsy forewarning (IP5). Dr. Joseph met with the ORNL team in March 1999 to discuss a CRADA collaboration, which began in October 1999. The amount of funds-in from NBI for this CRADA was $247K in FY00 and $190K in FY01. DOE's Laboratory Technology Research program (through Terry Payne at ORNL) provided additional funding of $47K in FY00 and $47.5K in FY01. Detailed results have been published and presented at various conferences[2-19] While most other groups use invasive intracranial data, these results are based on non-invasive, scalp brain waves, using two novel technology components: (1) removal of eye blinks (and related muscular artifacts that are superimposed on the scalp brain waves), and (2) multi-channel nonlinear analysis for seizure forewarning.

This and other recent analyses of biomedical data have demonstrated the nonlinear technology for a variety of biomedical applications, as follows:

- forewarning of epileptic seizures from scalp human brain wave data[1-19];
- forewarning of ventricular fibrillation events from human heart waves[14-15, 18-19];
- detection of inhaled-endotoxin-induced septic shock from rat heart waves[14-15, 18-21];
- condition change due to increasing breathing difficulty from pig chest sounds[14-15, 18-19];
- forewarning of fainting (syncope) from human heart waves[12, 18-19];
- deception detection from polygraph data[22].

A third project was sponsored by the U.S. Department of Energy (DOE/NE-20) under their Nuclear Energy Research Initiative (NERI). ORNL was funded at $157K in FY2000, $481K in FY01, and $479K in FY02 to develop an advanced prognostic for machinery faults of progressively increasing severity, and to forewarn of uncontrolled failures. The NERI project results are thoroughly documented in various technical reports and conference papers[26-35]. The ORNL technology detects and predicts a rich variety of equipment faults (e.g., drill-bit wear, tool chatter, bellows coupling failure, imbalance, misalignment, offset, cut rotor bars, turn-to-turn short) in motors and motor-driven components (e.g., pump, bearing, gearbox, cracked blade, structural failure) via analysis of process-indicative, time-serial data (motor current, voltage, power, acceleration, torque, stress and strain)[23-38]. Success for this large array of diverse processes gives confidence that the paradigm may work for any nonlinear system.

The present laboratory-class technology uses analyst-intensive, off-line analysis of archival data on desktop computers. The left column of Table 1 summarizes the features of the present research-class technology, as read from top to bottom. A prototypical device for potential commercialization needs to provide analyst-independent, on-line analysis of (near-)real-time data via a hand-held device. The right column of Table 1 shows the features of a practical prototype device, also as read from top to bottom. In response to a call for proposals from ORNL's Office of Technology Transfer (OTT) early in 2004, we proposed development of a prototype for a specific application (e.g., forewarning of epileptic seizures) to

bridge the gap between today's research-class technology (left column of Table 1) and a practical prototype (right column of Table 1), as shown in the center column of Table 1. OTT provided $50K for the proposed work. We anticipate subsequent use of the same technology infrastructure for other applications in the biomedical (e.g., forewarning of ventricular fibrillation) and machinery (e.g., forewarning of structural failure, forewarning of bearing failure) fields of use. The present work addresses near-term items (a') – (b') in Table 1, as the minimal set for a prototypical device.

Table 1: Summary of Improvements for Commercialization

Current laboratory-class technology	Bridge	Need for commercializable prototype
(a) off-line use of …	now	(a') on-line use of …
(b) a desktop computer for …	now	(b') a held-held device for …
(c) analysis of archival data …	≥1 year	(c') analysis of (near) real-time data …
(d) that is analyst-intensive …	≤3 years	(d') that is analyst-independent …
(e) giving binary forewarning that is …	>3 years	(e') to give remaining time to failure, …
(f) machine- and fault-specific, after which …	>3 years	(f') independent of the machine or fault ...
(g) failure occurs in an uncontrolled fashion …	>3 years	(g') allowing failure avoidance or control …
(h) using high-cost laboratory resources …	≥5 years	(h') at reasonable cost …
(i) that depend on laboratory infrastructure	≥5 years	(i') reliably/independently for years

Task 1 of this project involved specification of the basic hardware and software for real-time data acquisition and analysis of data on a hand-held device (HHD), such as a digital signal processor or personal digital assistant. Modern HHDs have ≥64 MB of memory and a CPU speed of 624 MHz, which are not incompatible with the computational requirements for the nonlinear analysis of Sect. 3.

Task 2 of this work involved conversion of the present research-class FORTRAN nonlinear-analysis software into code for the HHD. This task included a graphical user interface to (i) control the data acquisition, (ii) perform forewarning analysis, and (iii) display the results. This work began with an existing student-developed MatLab[34] GUI to display the research results. This task also involved verification of the forewarning of epileptic events on the HHD against the results of our most recent work[17] via real-time playback of existing archival data. The research-class software was developed and used on a variety of computers and operating systems over the past decade: IBM RISC/6000 under IBM's version of UNIX, DEC-alpha under DEC's version of UNIX, Intel-PII under Windows NT and Windows 2000, and AMD-Athlon™ and Intel Pentium-4™ under Windows2000™ and Windows-XP™. The software required little, and usually no, change to move from one computer and/or operating system to the next. Thus, we anticipated no problems with implementation on a HHD. Further improvements in speed and the memory requirement are possible by reducing unnecessary arrays and subroutines.

Task 3 of this effort entailed the project management, including work coordination, documentation of the results, and formulation of any patent application(s).

3. ANALYSIS METHODOLOGY

After initializations, we read the stream of time-serial data and divide it into contiguous, non-overlapping windows of N data points. This step is labeled (A) in Fig. 1. Subsequent steps are noted below and labeled sequentially in Fig. 1. Each step operates on one window of data points, unless otherwise noted.

The artifact signal is removed from each cutset with a novel zero-phase quadratic filter[39], using a moving window of data points, e_i, with the same number of data points, w, on either side of a central point [step (B) in Fig. 1]. We fit a quadratic curve in the least-squares sense over this window, taking the central point of the fit as the best estimate of the low-frequency artifact, f_i. The residual value, $g_i = e_i - f_i$ (artifact-filtered data), has essentially no low-frequency artifact activity.

We convert each artifact-filtered point into a discrete symbol, s_i, as one of S different integers in the range, $0 \le s_i \le S-1$. For this purpose, we obtain the minimum, g_{min}, and maximum, g_{max}, in the data of the first baseline cutset [step (C) in Fig. 1]. We use contiguous, non-overlapping partitions to obtain uniform symbols: $s_i = \mathrm{INT}[S\,(g_i - g_{min})/(g_{max} - g_{min})]$ for $g_i < g_{max}$, and $s_i = S - 1$ for $g_i = g_{max}$ to maintain exactly S discrete symbols [step (D) in Fig. 1]. The function, INT, converts a decimal number to the next lowest integer [e.g., INT(3.14) = 3].

The analysis assumes that the complex, high-dimensional brain dynamics evolve over a bounded, low-dimensional region, called an "attractor" in the parlance of nonlinear dynamics. Thus, the symbolized data can be converted into a phase-space (PS) representation [step (E) in Fig. 1] by standard reconstruction of the dynamics via the time-delay vectors[41]. The single-channel form is:

$$y(i) = [s_i, s_{i+\lambda}, \ldots, s_{i+(d-1)\lambda}] \tag{1}$$

Eq. (1) converts the time-serial data into a sequence of discrete locations (phase-space states) within a d-dimensional geometric object to extract event forewarning on the basis of a local time delay, λ, dimensionality, d, and signal precision, S. Moreover, information exchange in the brain connects local processes, implying that a multi-channel PS vector of C channels[42] may extract additional information:

$$y(i) = [s(1)_i, s(1)_{i+\lambda}, \ldots, s(1)_{i+(d-1)\lambda}, \ldots, s(C)_i, s(C)_{i+\lambda}, \ldots, s(C)_{i+(d-1)\lambda}]. \tag{2}$$

Here, $s(k)$ denotes symbols from the kth channel, $1 \le k \le C$. Symbolization in this more general case divides the multi-channel phase-space into S^{Cd} bins. The present analysis uses two channels (C=2).

We next tabulate the number of points that occur in each PS bin, $y(i)$, to obtain the distribution function (DF) of the PS points on the attractor [step (F) in Fig. 1]. We denote the population of the ith bin of the DF, Q_i, for the base case, and R_i for a test case, respectively. An (un)changing DF indicates (un)altered dynamics. We save the DFs from first B cutsets as baseline DFs [step (G) in Fig. 1] to represent non-seizure dynamics, with B=10 to capture sufficient variability.

The baseline DFs are exhaustively compared to one another in pair-wise fashion [step (H) in Fig. 1] via the dissimilarity measures (DM) of Eqs. (3) - (6), to obtain [step (I) in Fig. 1] the mean baseline dissimilarity, $\underline{V}$, and a corresponding standard deviation, σ, for each DM from the set, $V = \{L, L_c, \chi^2, \chi_c^2\}$.

In a similar fashion, we obtain the dissimilarity[3-7, 9, 16-17] [step (H') in Fig. 1] between DFs for the baseline, Q_i, and test case, R_i, respectively. One set of dissimilarity measures (DM) is:

$$\chi^2 = \sum_i (Q_i - R_i)^2 / (Q_i + R_i), \tag{3}$$

$$L = \sum_i |Q_i - R_i|. \tag{4}$$

These summations run over all populated phase-space states. These measures account for the geometry and visitation frequency of the attractor. A second DM set represents the dynamical flow[43] by connecting successive PS points, $y(i) \rightarrow y(i + 1)$. This extended form of the PS reconstruction is a $2Cd$-dimensional vector, $Y(i) = [y(i), y(i + 1)]$, which is obtained by adjoining two vectors at successive time steps from the Cd-dimensional PS of Eqs. (1-2). We call $Y(i)$ the connected phase space (CPS), which is divided into S^{2Cd} bins by the symbolization. As before, Q and R denote the CPS DFs for the baseline and test cases, respectively. The PSDM compare these two CPS DFs via the L_1-distance and χ^2 statistic, as before[7]:

$$\chi_c^2 = \sum_{ij} (Q_{ij} - R_{ij})^2 / (Q_{ij} + R_{ij}), \tag{5}$$

$$L_c = \sum_{ij} |Q_{ij} - R_{ij}|. \tag{6}$$

The subscript c denotes connected PS measures. The first index in (5)−(6) labels the initial PS state, $y(i)$; the second subscript, j, labels the sequel PS state, $y(i+1)$. The CPS DM have higher discrimination than their PS counterparts by satisfying the following inequalities[7]: $\chi^2 \le L$, $\chi_c^2 \le L_c$, $L \le L_c$, and $\chi^2 \le \chi_c^2$.

The disparate range and variability of these measures are difficult to interpret, so we need a consistent means of comparison. Thus, we renormalize the dissimilarity measures[3-7, 9, 16, 35] by comparing each of the B baseline cutsets to each (ith) test case cutset, and then computing the corresponding average dissimilarity value, V_i, of the ith cutset [step (J) in Fig. 1]. The renormalized form is: $U(V) = |V_i - \underline{V}|/\sigma$, as the number of standard deviations that the test case deviates from the baseline mean. This renormalized dissimilarity is used to test for statistically significant change in the dynamics.

Further analysis [step (K) in Fig. 1] uses the renormalized DM from the beginning of the data file, proceeding forward in time until a forewarning occurs, as defined next. A true positive ($TP = 1$ in the sum below) is a correct forewarning of a seizure event. This forewarning occurs when a specific number, N_{SIM}, of PSDM simultaneously exceed a threshold, U_C, for a number of sequential occurrences, N_{OCC}, within a preset forewarning window, $T_1 \le T_{SZ} - T_{FW} \le T_2$, before the seizure onset time, T_{SZ}. This analysis uses a value of $T_1 = 1$ minute, based on input from a physician collaborator that with even one minute of forewarning, useful things could be done to help the patient medically[44]. The corresponding forewarning time is T_{FW}. Recent work by Litt *et al.*[45] found precursors that occur up to several hours before epileptic events. Consequently, this work uses a forewarning window out to $T_2 \le 8$ hours before the epileptic event to obtain ≤5.5 hours of forewarning before the seizure event. A false positive (FP) is a seizure forewarning in a non-event dataset, or when $T_{SZ} - T_{FW} < T_1$ or $T_{SZ} - T_{FW} > T_2$. A true negative ($TN = 1$) corresponds to no forewarning in a non-event dataset. No forewarning in an event dataset is a false negative (FN). This analysis is repeated for each additional window of time-serial data [step (L) in Fig. 1].

We tabulate the occurrence of forewarning for each dataset via the above algorithm, and then combine the results for all of the datasets. The algorithmic flow for this portion of the methodology (not in Fig. 1) involves loops over N_{SIM} , N_{OCC} , U_C , each of several data channels, and over datasets. We determine channel-consistent forewarning[16] in the ith dataset for the jth channel of the kth patient by summing the number of true instances, $T_{jk} = \Sigma_i [TP_{ijk} + TN_{ijk}]$. The sum over datasets runs from i=1 to $M(k)$ = number of datasets for the kth patient. The occurrence of $T_{jk} \ge 2$ indicates consistency in more than

one dataset for the same patient, while $T_{jk} \leq 1$ means that the jth channel provides no such consistency. The best channel consistency is $c_k = \max(T_{jk})$, for $T_{jk} \geq 2$ and k fixed; $c_k = 0$, if $T_{jk}=1$; and $c_k = 1$ for patients with only one dataset. The channel-consistent total-true rate then becomes $f_T = [\Sigma_k\, c_k]/[\Sigma_k\, M(k)]$. Here, k runs over all P of the patients, weighting each dataset equally. Steps (K)-(L) are very fast and are not presently implemented on the prototypical HHD; they are described here for completeness and clarity.

4. IMPLEMENTATION ON A HAND-HELD DEVICE

The analysis of Sect. 3 was converted from existing research-class FORTRAN code to C/C++ using Microsoft Visual C++ version 6.0, and then to C# (Microsoft Visual .Net version 1.0). The majority of the work involved conversion of the programming commands and array syntax from one language to another. Standard functions (e.g., square root) were replaced with the appropriate language-specific functions. The basic code structure, procedures, and algorithms were retained. Table 2 summarizes the FORTRAN subroutines that were retained in the C/C++/C# versions with the same names, except for capitalization. The only object-oriented classes in the C/C++ version were for data input, data output, and error messages. The C# version also uses object-oriented classes for the GUI and for the sort method, as described in the next paragraph. Two versions of the C# implementation exist. One is a single executable version. The second is a client/server version, which consists of a server program that runs on a laptop or desktop (to emulate acquisition of data and to receive the PocketPC results) and a client that runs the forewarning analysis on a PocketPC (400-MHz Compaq iPaq PocketPC, Model 3970 with 64 MB of memory, running PocketPC 2002 version 3.0.11171 and .Net Compact Framework version 1.1).

Table 2: Summary of Routines in Forewarning Implementation

Subroutine	Brief Description	Step in Fig. 1	Comment
aaaanal2	high level routine	----	choose type of data analysis
analysis	call steps in Fig. 1	A-J	
artfiltr	artifact filter	B	
chisquab	baseline dissimilarities	H-I	
chisquar	test-case dissimilarities	H'-J	
concpsdf	construct DF	E-F	
datasett	extract data for analysis	A	
mcphssp0	setup of PS analysis	E-F	
mcphssp1	perform PS analysis	E-F	
quiksor1	sort (next paragraph)	F	C/C++ version; C# version uses built-in function
readdata	input data	A	
savebscs	save baseline DFs	G	
statistc	linear statistics	C	
symbunif	uniform symbols	D	
writesum	output results summary	J	

Each phase-space state, $y(i)$, is uniquely represented by an integer via modular arithmetic:

$$\mathrm{ID}_i \equiv \mathrm{ID}[y(i)] = \sum_{k=0}^{k=d-1} s_{i+kd}\, S^k;\ \mathrm{CID}_i \equiv \mathrm{ID}[Y(i)] = \mathrm{ID}[y(i)] + S^d\, \mathrm{ID}[y(i{+}1)]. \tag{7}$$

Thus, the EEG dynamics are represented by a sequence of identifiers for the phase-space state, ID_i, and the connected phase-space state, CID_i. The analysis sorts this sequence of identifiers from the smallest to largest value. Then, the method tabulates the distribution function by counting the number of occurrences of each (rank-ordered) identifier. The FORTRAN version uses the QuickSort algorithm from the book, Numerical Recipes in FORTRAN[46];the C/C++ version also uses the QuickSort algorithm from a companion book, Numerical Recipes in C[47]. The FORTRAN and C/C++ QuickSort routines are algorithmically equivalent. The C# version uses the built-in Array.Sort method that is provided by the

.Net Framework Class Library, also based on the QuickSort algorithm. This analysis is part of step (F) in Fig. 1 (Table 2).

Further changes were required for the PDA platform to accommodate restrictions in memory (64 MB) and software emulation of floating-point arithmetic. First, the FORTRAN, C/C++, and C# compilers each handle memory allocations in different ways. Second, the FORTRAN version apparently places all (or most) of the data in virtual memory, because most of the variables are in common blocks. This allocation results in the FORTRAN code using 2.82 MB of random access memory and 1.07 GB of virtual memory; see Table 3 for typical values. The C/C++ version will not run in the Microsoft Visual Studio environment if these large data arrays are allocated statically. Rather, the large data arrays must be allocated dynamically via the "new" or "malloc" operator. The C# version does not have this limitation. Third, all of the large data arrays in the C/C++/C# versions were reduced in size using the minimum array indices for the best EEG analysis parameters[17]. Several of the FORTRAN double precision arrays were converted to single precision without affecting the accuracy of the results in the C/C++/C# versions.

Table 3: Summary of Validation Results

Language	Program	Platform	Compiled	CPU Time (h:mm:ss)	Wall Clock Time (h:mm:ss)	Peak Memory Usage (Mb)	Virtual Memory Size (Mb)
FORTRAN	stand-alone	1.8 GHz PC	Release	0:00:14	0:00:15	2.82	1069.27
			Debug	0:00:15	0:00:16	2.924	1073.16
		400 MHz laptop	Release	0:00:54	0:01:00	2.732	1069.24
C/C++	stand-alone	1.8 GHz PC	Release	0:00:16	0:00:17	6.244	5.748
			Debug	0:00:42	0:00:45	6.308	5.748
		400 MHz laptop	Release	0:01:27	0:01:37	6.168	5.728
C#	stand-alone	1.8 GHz PC	Release	0:00:26	0:00:27	11.292	9.916
			Debug	0:00:27	0:00:28	11.912	10.216
		400 MHz laptop	Release	0:01:36	0:01:43	13.36	12.176
C#	server	1.8 GHz PC	Release	0:26:00	0:01:56	23.464	20.184
	client	1.8 GHz PC	Release	0:01:04		16.796	14.456
C#	server	1.8 GHz PC	Release		2 hours	13.152	11.088
	client	PocketPC emulator	Release			11.16	
C#	server	400 MHz laptop	Release	0:02:34	7-8 hours	12.936	11.028
	client	400 MHz PocketPC	Release			15.88	

Table 3 shows test results for the FORTRAN (first row). The "Debug" form has extra code and print statements for debugging, which the FORTRAN compiler automatically inserts. The "Release" form excludes the extra code and print statements. The times in Table 3 are in a format of hours, minutes, and seconds [h:mm:ss], unless otherwise noted. The results are for the EEG dataset, DAT.F00163, which spans 5,000 wall-clock seconds (1 hour and 24 minutes). The output was a single line with the four PSDM values for each analysis window of *N* data points.

Subsequent work involved conversion of the FORTRAN to a stand-alone Windows™ application in C/C++ (second row in Table 3) on a 1.8-GHZ Pentium-4 PC with 2 GB of memory, under the

Windows XP SP2 operating system. (The release mode of C/C++ only compiles if the optimizer is disabled under project settings.) The C/C++ results duplicate the FORTRAN results to 7 digits for representative datasets[17] (DAT.F00163, DAT.F00308, and DAT.F00207).

Further revisions provided a stand-alone C# code (third row in Table 3), which was tested on the same 1.8-GHZ Pentium-4 PC. These analyses show that the processing (wall-clock) time for the stand-alone versions (14 – 28 seconds) is much faster than real-time (5,000 seconds of EEG data). Execution of the same stand-alone C# code on a 400-MHz Pentium-2 laptop (384 MB of memory under Windows™ XP SP2) yielded a processing (wall-clock) time of 103 seconds, which also is much faster than real-time. The C# version duplicates the FORTRAN results to 6-7 digits, when run on the 1.8-GHz Pentium-4 PC. Consequently, the stand-alone C/C++/C# software duplicates the original FORTRAN results, in terms of accuracy and much-faster-than-real-time processing.

The C# software was next divided into two components (fourth row in Table 3). The server component emulates data acquisition, transmission of that data to the client, and receipt of the analysis results from the client. The client component provides the forewarning analysis, as described in Sect. 3. The processing time for this case (6,960 seconds) is 39% more than the 5,000-second length of the dataset. The fifth row in Table 3 shows the results for software emulation of the PocketPC on the 1.8-GHZ Pentium-4 PC, giving a processing time that is 44% more than the dataset length. These two simulations clearly show a dramatic decline in processing speed, arising from the server-client interactions.

Finally, the client software was installed and tested on the PocketPC hardware (sixth row of Table 3), with the server code on a 400-MHz Pentium-2 laptop with 384 MB of memory under Windows™ XP SP2. The processing time (7-8 hours) depended on network variability. The C# client on the PocketPC uses integer arithmetic to emulate floating-point analysis, and duplicates results only to 3-4 digits for DAT.F00163. Further work (beyond the scope of the present project) is needed, as follows. Use of a faster-CPU HHD will improve the interaction efficiency between the server and client software. Improvements in the wireless network link should yield a faster, more stable client-server communications. A HHD with a floating-point arithmetic unit will improve the analysis precision.

5. FUTURE POTENTIAL APPLICATIONS

Implementation of the EEG-epilepsy forewarning analysis on a hand-held device provides an initial bridge between the research-class version and a prototype for practical use of the technology, as discussed in Sect. 2. This success also provides a personal monitor for a wide variety of potential biomedical applications. An advanced version of the HHD might include a mobile phone and global-positioning system (GPS) in severe cases for an automatic request of emergency responders to the patient's location. We briefly discuss these future potential applications below.

1. **Epilepsy Diagnosis** for inpatients in an EEG monitoring unit. Wireless forehead electrodes initially would send data to the hand-held device for analysis. After receipt of a seizure forewarning, a full set of scalp electrodes could be installed by hospital staff for acquisition of complete, multi-channel EEG data. This approach would eliminate tethering to a monitoring station, and would reduce the potential for accident or injury by alerting staff (and the patient) to an impending seizure event;

2. **Pre-surgical epilepsy evaluation** for outpatients undergoing 24-hour monitoring. After receipt of a seizure forewarning, the patient could report to the hospital monitoring unit for pre-surgical evaluation, including video and EEG capture of the seizure activity. Use of outpatient monitoring could dramatically reduce inpatient hospital cost;

3. **Refractory epilepsy monitoring** for outpatients undergoing 24-hour monitoring. After receipt of a seizure forewarning, the patient could follow the physician's pre-arranged protocol. Examples include: stop dangerous activity (e.g., operating a motor vehicle, climbing a latter, handling hazardous material), lie down until the seizure event passes, take medication, and/or call an emergency responder;

4. **Child epilepsy monitor** that would alert the care-giver of the impending event for appropriate action;

5. **Vagal nerve stimulation** only after receipt of a seizure forewarning, which we conjecture would improve the present 30% event suppression rate under continual simulation. The forewarning device could be programmed to automatically activate the vagal nerve stimulator. Further research is needed to confirm this conjecture;

6. **Functional imaging studies** (e.g., fMRI, PET, SPECT) of an epilepsy outpatient after the receipt of a seizure forewarning. Use of outpatient monitoring would dramatically reduce the medical costs and increase the likelihood of imaging studies during the pre-ictal and/or seizure period;

7. **Epilepsy drug discovery** that would be enhanced by 24-hour, ambulatory monitoring during trials of candidate drugs to screen for those worth pursuing in multi-center trials;

8. **Stroke detection** that would be based on ambulatory EEG and electrocardiogram (ECG) monitoring of high-risk individuals. This approach would enhance the recognition of stroke onset for prompt application of clot-dissolving therapies prior to irreversible brain damage (currently ~5% of patients receive such therapy due to delays). The patient and medical personnel could be alerted;

9. **Early diagnosis of Parkinson's Disease and other dynamical brain disorders** via advanced analysis of EEG dynamics for early treatment to slow or halt the deterioration. Tremor monitoring (e.g., 3-axis acceleration, electrical activity of the muscles) and scalp EEG monitoring could provide indication for clinical diagnosis of Parkinson's or other neuromuscular pathologies;

10. **Diagnosis of CNS pathologies** that would be based on analysis of sensory-evoked potential changes in EEG. Present analysis uses (for example) EEG changes immediately after (e.g., within 300 milliseconds) presentation of sensory input (e.g., a computer image or sound);

11. **Hands-free computer control**, which is hampered by the presence of confounding eye-blink (and other facial muscular) activity in scalp EEG. We conjecture that removal of these artifacts via ORNL's patented artifact removal filter (IP8) could greatly enhance hands-free computer control via scalp EEG. Specific applications include computer control by paraplegics and quadriplegics (e.g., wheelchair, prosthetic devices), rapid/complex operations by airplane pilots, gamers, etc. Present approaches use invasive intracranial electrodes in paraplegics and quadriplegics to avoid these EEG artifacts;

12. **Head trauma diagnosis** via EEG changes (e.g., intracranial pressure or bleeding);

13. **Cochlear-implant monitor** via analysis of EEG and imposed sounds to evaluate the brain's processing of signals if hearing is not restored;

14. **Drug/chemical effects diagnosis** via EEG changes to identify drug overdose/abuse or chemical exposure with central-nervous-system (CNS) toxicity;

15. **Motion disorder management** by EEG analysis for onset detection, followed by deep brain stimulation and/or trans-spinal drug infusion;

16. **Detection of brain ischemia** (loss of blood flow) during brain surgery, which is not possible with present technology;

17. **Drowsiness** monitor, using extraction of the eye-blinks (an indicator of sleepiness) from scalp EEG via ORNL's patented artifact filter (IP8) coupled with EEG analysis. This application could alert the operator, supervisor, or others as appropriate. Typical users include long-haul commercial truck drivers, airplane pilots on long flights, patients with sleep disorders, guards, operators of critical/heavy equipment, medical and military personnel, and shift workers;

18. **Fitness-for-duty** monitor for key personnel in high stress situations via EEG analysis. Typical users include air traffic controllers, reactor operators, military personnel, soldiers, physicians, and astronauts;

19. **Automated sleep staging** of nighttime polysomnogram data in outpatients to reduce the physician's time (and cost) for interpretation of a sleep study;

20. **Daytime sleepiness** in ambulatory outpatients for a sleep disorder. This approach would be more accurate than personal recall, and would be much less expensive than inpatient monitoring;

21. **Cardiac diagnosis** of ambulatory outpatients via ECG monitoring using an augmented or "smart" Holter monitor. An advantage over current Holter monitor technology is forewarning of cardiac events;

22. **Forewarning of cardiac events** in ambulatory outpatients after a heart attack or with other high-risk indicators for ventricular or atrial fibrillation. After receipt of an event forewarning, the patient could immediately follow the physician's pre-arranged protocol, as in item 3. A more advanced device

could incorporate event forewarning into pacemaker/defibrillators to allow intra-cardiac injection of therapeutic agent, followed by preemptive shocks if drug injection does not prevent the event;

23. **Forewarning of cardiac events** during transport by an emergency responder to enable appropriate in-transit care;

24. **Fetal ECG monitor during labor and delivery**, allowing the mother more comfort and enhancement of labor by walking and maintenance of an upright position;

25. **Monitor for premature and newborn infants** with an elevated risk for cardiovascular events or sudden infant death syndrome (SIDS). The analysis could include ECG, EEG, and/or chest sounds;

26. **Heart valve monitors** via ECG or chest sounds to forewarn of an impending failure;

27. **Fainting (syncope) monitor** via ECG analysis for susceptible patients (e.g., orthostatic hypotension, Shy-Draeger syndrome, and cardiac pathologies). Syncope also occurs in healthy people (e.g., astronauts after many days in a micro-gravity, military aircraft pilots after a long flight) when they attempt to stand and/or walk. Syncope forewarning would avoid falls and concomitant injuries;

28. **Shock monitor** via ECG analysis for trauma patients (e.g., surgery, accident);

29. **Abdominal aortic aneurism (AAA)** to forewarn at-risk patients of impending or incipient rupture via analysis of ECG, abdominal sounds, and/or aortic stress-strain data;

30. **Diagnosis of lung disorders** via analysis of chest sounds for breathing difficulty. Shortness of breath may also be an indicator of a cardiac pathology (items 20-22). The ability to distinguish cardiac and pulmonary pathologies clearly will require careful research;

31. **Forewarning/detection of an asthma attack** via chest-sound analysis to alert the patient, care-giver, or emergency responders. Current technology uses an exhalation peak-flow meter;

32. **Monitor for orthopedic implants** via analysis of joint sounds and/or muscle activity to detect wear, infection, bone degeneration, and related abnormalities;

33. **Artificial-heart monitor** via analysis of chest sounds and/or electrical activity to adjust pumping effort for metabolic demand and forewarn of mechanical failure;

34. **Continuous blood-glucose monitor** via skin-mounted optical-sensor data for automatic insulin infusion and/or other therapeutic agent to maintain tight blood glucose control;

35. **Personal monitor for dementia-sufferer at home**. Multiple sensors (e.g., EEG, ECG, and chest sounds) could provide early detection of illness and/or forewarning of catastrophic health events (e.g., items 1-34) in cognitively impaired people, who have difficulty sensing, evaluating, and/or communicating health-related symptoms to caregiver(s). An embedded GPS and mobile phone could alert the caregiver to unanticipated excursions and could preclude the patient from becoming lost;

36. **Multi-purpose monitor for nursing home and assisted-care residents**. Typical data could include EEG, ECG, pulse oximetry, body temperature, and geographical location via GPS. Caregivers could then respond promptly to cardiac, or breathing events. Prevention of wandering-related falls (particularly in dementia patients) would be highly cost-effective by alerting staff as early as possible;

37. **Multi-purpose soldier monitor** via clothing-embedded sensors with wireless transmission to the HHD for assessment of the physiological and battle readiness via multi-channel analysis. Typical data could include EEG, ECG, body temperature, pulse oximetry, and chest sounds. Typical battlefield endpoints include exposure to chemical/biological/radiological agents, fatigue, stress, alertness, injury, unconsciousness, breathing difficulty, and septic shock from an infected wound. An embedded GPS and mobile phone could request a medical responder for prompt care as in Item 3;

38. **Sports/fitness monitor** via ECG and chest sounds to assess training results in terms of healthy variability (e.g., as a function of jogging speed, distance, and effort level).

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, Tenn. (April 1995).

[2] L.M. Hively, "Data-Driven Nonlinear Technique for Condition Monitoring," *Proc. Maintenance and Reliability Conf.*, 1: 16.01-16.10 Knoxville, Tenn. (1997).

[3] L.M. Hively, P.C. Gailey, V.A. Protopopescu, "Sensitive Measures of Condition Change in EEG Data," *Proc. of Int'l Workshop Chaos in Brain* World Scientific Publ., Bonn (March 1999).

[4] P.C. Gailey, L.M. Hively, V.A. Protopopescu, "Robust Detection of Dynamical Change in EEG," in *Proceedings of 5th Experimental Chaos Conference*, Orlando, Florida (6/28-7/1/99).

[5] L.M. Hively, P.C. Gailey, and V.A. Protopopescu, "Detecting dynamical change in nonlinear time series," *Physics Letters A* 258: 103-114 (1999).

[6] L..M. Hively, N.E. Clapp, V.A. Protopopescu, J. Joseph, C.E. Merican, T. Lucht, *Epileptic Seizure Forewarning by Nonlinear Techniques*, ORNL/TM-2000/333, Oak Ridge National Laboratory, Oak Ridge, Tenn. (November 2000).

[7] L.M. Hively, V.A. Protopopescu, P.C. Gailey, "Timely detection of dynamical change in scalp EEG signals," *Chaos* 10: 864-875 (December 2000).

[8] L.M. Hively, N.E. Clapp, V.A. Protopopescu, "Forecasting epileptic seizures," *ORNL Review* 33(2): 21 (2000).

[9] V. A. Protopopescu, L. M. Hively, P. C. Gailey "Epileptic event forewarning from scalp EEG," invited review paper in *J. Clin. Neurophysiol.* 18: 223-245(May 2001).

[10] L. M. Hively, V. A. Protopopescu, J. Joseph, *CRADA Final Report for CRADA Number ORNL99-0559 – Epileptic Seizure Forewarning by Nonlinear Techniques*, C/ORNL99-0559, Oak Ridge National Laboratory, Oak Ridge, Tenn. (January 2002).

[11] L. M. Hively, "Forewarning of Medical Events," Invited presentation to ORNL/OTT Conference on Overcoming Barriers Facing Persons with Disabilities Through the Applications of Technologies, Roane State Community College (16 July 2002).

[12] L.M. Hively, "Nonlinear Analysis of Physiological Data for Event Forewarning," Invited presentation to weekly Biomedical Engineering seminar at University of Kentucky, Louisville, KY (16 Sept 2002).

[13] L. M. Hively, "Forewarning of Biomedical Events via Nonlinear Analysis of Physiologic Data," one page abstract to DOE Office of Medical Science for 2003 summary booklet (1/30/03).

[14] L. M. Hively and V.A. Protopopescu, "Detection of Changing Dynamics in Physiological Time Series," presentation and *Proc. ANS Conf. on Nucl. Math. Computational Sci.* (Gatlinburg, Tenn.) 6-11 April 2003.

[15] L. M. Hively and V. A. Protopopescu, "Need for High Performance Computing in Analysis of Biomedical Data," Invited Presentation to Cray Biology Workshop at ORNL (5/9/03).

[16] L. M. Hively and V. A. Protopopescu, "Channel-consistent forewarning of epileptic events from scalp EEG," *IEEE Trans. Biomed. Engr.* 50: 584-593 (May 2003).

[17] L.M. Hively, V.A. Protopopescu, and N. B. Munro, "Epilepsy forewarning via phase-space dissimilarity," submitted to *J. Clin. Neurophys.* (2004).

[18] L. M. Hively, V. A. Protopopescu, N. B. Munro "Detection of Changing Dynamics in Physiological Time Series for Biomedical Event Forewarning," Biomed. Engr. Soc. Mtg. (Nashville, Tenn.) (10/3/03).

[19] L. M. Hively, "Detection of Changing Dynamics in Physiological Time Series for Biomedical Event Forewarning," invited presentation to Biomedical Engineering Seminar at Univ. of Memphis (2/27/04).

[20] L. M. Hively, V.A. Protopopescu, N.B. Munro, "Prediction of Sepsis Onset in Trauma Victims Using Advanced Nonlinear Analysis," FY02 Progress report to ORNL LDRD Manager (03 Oct 2002).

[21] L. M. Hively, V.A. Protopopescu, N.B. Munro, "Prediction of Sepsis Onset in Trauma Victims Using Advanced Nonlinear Analysis," Final report to ORNL LDRD Manager (Sept 2003).

[22] L.M. Hively, N.E. Clapp, *Nonlinear Analysis of Polygraph Data*, K/NSP-351 Oak Ridge National Laboratory, Oak Ridge, Tenn. (March 1996).

[23] L.M. Hively, N.E. Clapp, C.S. Daw, *Nonlinear Analysis of Machining Data*, ORNL/TM-13157, Oak Ridge National Laboratory, Oak Ridge, Tenn. (January 1996).

[24] L.M. Hively, V.A. Protopopescu, N.E. Clapp, C.S. Daw, *Prospects of Chaos Control of Machine Tool Chatter*, ORNL/TM-13283, Oak Ridge National Laboratory, Oak Ridge, Tenn. (June 1998).

[25] S.C. Robinson, T.W. Ayers, H.D. Haynes, L.M. Hively, R.E. Pollard, R. Curless, and K. Ziegler, *CRADA Final Report for CRADA Number Y1295-0357 – High Throughput and Reliability (HiTaR)*, Y/DX-2365, Y-12 Plant, Oak Ridge, Tenn (15 July 1998).

[26] L.M. Hively, V.A. Protopopescu, and M. Maghraoui "NERI2000-109 Project Review," invited presentation to DOE/NE-20 at ORNL (25 July 2001).

[27] L. M. Hively, V. A. Protopopescu, M. Maghraoui, and J. W. Spencer, *Annual Report for NERI Proposal #2000-0109 on Forewarning of Failure in Critical Equipment at Next-Generation Nuclear Power Plants*, ORNL/TM-2001/195, Oak Ridge National Laboratory, Oak Ridge, Tenn. (November 2001).

[28] L. M. Hively, V. A. Protopopescu, "NERI2000-109 Project Review," invited presentation of FY02 project at US Department of Energy, Germantown Headquarters to NE-20 staff (16 Oct 2002).

[29] L. M. Hively, "Forewarning of Failure in Critical Equipment at Next-Generation Nuclear Power Plants," FY02 annual summary of NERI2000-109 project to DOE/NE20 (22 Oct 2002).

[30] V. Protopopescu, J. Barhen, Y. Braiman, and L. M. Hively, "Predictability and Control Issues in Complex Dynamical Systems," presentation to DOE/NSF/SIAM Workshop on Predictability of Complex Phenomena, Santa Fe (16-18 December 2002).

[31] L. M. Hively and V.A. Protopopescu, *Forewarning of Failure in Critical Equipment at Next Generation NPP*, Annual Report for NERI2000-109 project, ORNL/TM-2002/183, Oak Ridge National Laboratory, Oak Ridge, Tenn. (February 2003).

[32] L.M. Hively, "Forewarning of Failures in Critical Equipment at Next Generation Nuclear Power Plants," invited presentation to DOE/NE-20 and peer reviews at Rockville, MD (20 May 2003).

[33] V.A. Protopopescu and L. M. Hively, "Forewarning of machine failure via nonlinear analysis," *Proc. ANS* (June 2003).

[34] L.M. Hively, V.A. Protopopescu, K.M. Reichard, and, K. Maynard, *Failure Forewarning in NPP Equipment – NERI2000-109 Final Project Report,* ORNL/TM-2003/222, Oak Ridge National Laboratory, Oak Ridge, Tenn. (2003).

[35] L.M. Hively and V.A. Protopopescu, "Machine failure forewarning via phase-space dissimilarity measures," *Chaos* 14: 408-419 (June 2004).

[36] D.E. Welch, L.M. Hively, R.F. Holdaway, "Nonlinear Crack Growth Monitoring," *Proc. 2000 ASM Materials Solutions Conference and Exposition,* St. Louis, Missouri (11 October 2000).

[37] D.E. Welch, L.M. Hively, R.F. Holdaway, "Nonlinear Crack Growth Monitoring," *Proc. Int'l Mech. Engr. Congress and Exposition,* Orlando, Florida(5-10 November 2000).

[38] D.E. Welch, L.M. Hively, R.F. Holdaway, "Nonlinear Crack Growth Monitoring," *Proc.* 33rd *National Symp. On Fracture and Fatigue,* Moran, Wyoming(June 2001).

[39] L. M. Hively, N. E. Clapp, C. S. Daw, and W. F. Lawkins, *Nonlinear Analysis of EEG for Epileptic Seizures*, ORNL/TM-12961, Oak Ridge National Laboratory, Oak Ridge, Tenn. (April 1995).

[40] P. C. Gailey, L. M. Hively, and V. A. Protopopescu, "Detection of Condition Change in Nonlinear Times Series Using a Connected-Phase-Space PDF," presented at Amer. Phys. Soc., Atlanta, GA (March 1999).

[41] J. P. Eckmann and D. Ruelle, "Ergodic theory of chaos and strange attractors," Rev. Mod. Phys. 57: 617−655 (1985).

[42] S. Boccaletti, D.L. Valladares, L.M. Pecora, H.P. Geffert, and T. Carroll, "Reconstructing embedding spaces of coupled dynamical systems from multivariate data," *Phys. Rev. E* 65: 035204-1 to -4 (2002).

[43] H. D. I. Abarbanel, *Analysis of Observed Chaotic* Data, New York: Springer Verlag, 1996.

[44] M. L. Eisenstadt, private communication.

[45] B. Litt and J. Echauz, "Prediction of epileptic seizures," *Lancet Neurology* 1: 22-30 (May 2002).

[46] W.H. Press, S.A. Teukolsky, W.T. Vettering, and B.P. Flannery, Numerical Recipes in FORTRAN, Cambridge Univ. Press (2nd ed.) 1992.

[47] W.H. Press, B.P. Flannery, S.A. Teukolsky, and W.T. Vettering, Numerical Recipes in C, Cambridge Univ. Press (2nd ed.) 1992.

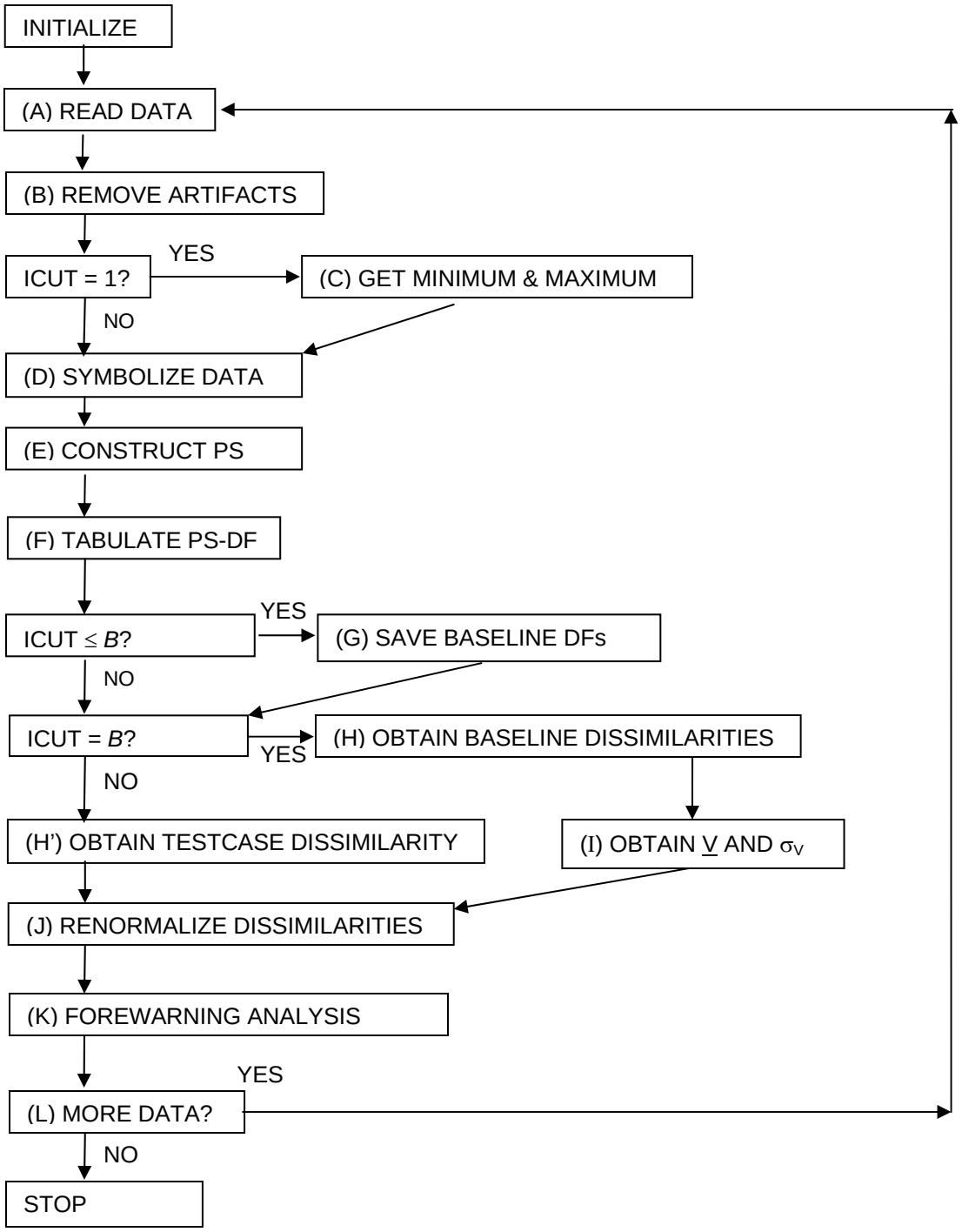

Figure 1: Flow diagram for nonlinear analysis. The letters in each box refer to the corresponding description in the text of Sect. 3.

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