Computer analysis of epileptiform EEG abnormalities

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PROLONGED multichannel electroencephalographic (EEG) recordings are required for the evaluation of an epilepsy surgery candidate in order to define precisely the epileptogenic areas, the patient's suitability for surgical treatment, and the extent of a proposed resection. An adequate sample of ictal and interictal EEG abnormalities must be obtained to make these important clinical decisions. The minimal monitoring period required to obtain the sample varies from patient to patient, but should be as short as possible.

Minimizing the time away from home is especially important when recording from pediatric patients. Children do not understand the importance of the diagnostic test, may be less patient in a restricted and boring setting, and are more likely to interfere with the apparatus. Nevertheless, a positive diagnosis and definite classification are more important at this stage of life than at any other. In patients of any age requiring intensive inpatient EEG monitoring, a computer system can serve to shorten the total time of confinement while maximizing the information yield from the diagnostic evaluation. The storage and data reduction capabilities of a computer system ease the interpretation burden on the electroencephalographer, making it possible to record long enough to acquire an adequate sample of EEG abnormalities.

Although a limited amount of continuous monitoring can be carried out with essentially manual methods, the large amount of EEG data soon becomes a practical concern. A 16-channel EEG recorded at the normal paper speed for 24 hours would generate 1.6 miles of chart paper, weighing 230 pounds. Even for a large computer system, this is not a trivial amount: digitized at 200 samples/second/channel, this same recording would occupy 553 megabytes.

An alternative semimanual scheme is to record the EEG continuously on magnetic media (such as videotape), then retrospectively review only those sections of the EEG known to contain a clinical seizure. Because children are less inhibited and exhibit a wider range of normal behavior, facial expressions, body movements, etc., the detection of a seizure or postictal state on clinical grounds alone can be more difficult than in adults. Although this method eliminates the need for continuous paper recording, it does not accomplish any data reduction per se. What is clearly needed is methodology which will not only reduce the paper requirement, but which will also reduce the interpretation time to a manageable level.

The fundamental purpose of a computer system designed for intensive monitoring is to make extended recording possible without generating an impossible workload for the electroencephalographer—to accomplish data reduction by identifying segments deemed "interesting" by the computer, for final confirmation or rejection by the electroencephalographer. The computer is not asked to make a diagnosis, but rather to assist the neurophysiologist by eliminating the majority of the repetitive normal data. Although the computer cannot be expected to be as accurate as a human reader, it will provide more objective and repeatable abnormality identification, in addition to being indefatigable. A byproduct of machine processing is the generation of numerical parameters associated with various aspects of the EEG. These can be correlated with other physiological measures and statistically com-

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pared, in order to study, for example, the effects of drug treatment or other therapeutic measures.

As the number of centers carrying out prolonged EEG monitoring has grown, various techniques have been developed to cope with the mountains of EEG data produced. Even without any abnormality detection, the amount of paper generated can be reduced or eliminated by storing the EEG on another medium. Commercial systems are now available which can store dozens of EEG channels onto videotape along with the video image of the patient. Relevant sections for review can be identified by recorded "markers" triggered by the EEG technologist or by the patient. Alternatively, a large amplitude band seen on a very slow paper speed EEG recording can pinpoint segments for detailed review; or conversion of rapidly replayed EEG signals into audio signals utilizes aural perception to supplement visual analysis for discriminating abnormal events. These noncomputer methods of data reduction are to a certain extent being combined with computer analysis, as microprocessors find their way into more instruments.

Continuous EEG analysis makes heavy demands on all components of a computer system. Although personal computers are now ubiquitous in many other applications, EEG analysis will usually require a substantial computer system, especially when large numbers of channels are needed for accurate localization. The magnitude of the difficulty is due, in part, to the requirement for *on-line* analysis. On-line analysis means that the data are processed as fast as they are acquired in *real-time*, i.e., essentially at the same time. Hence, when the recording period is concluded, the data analysis is also completed. *Off-line* analysis, on the other hand, is carried out on data which have been simply stored, then processed later. Although off-line analysis allows considerably more freedom and complexity in the detection algorithm design, it is unsuitable for patients undergoing continuous inpatient monitoring over several days.

Programs optimized to run in real-time are particularly complex, frequently requiring a Herculean development effort. The most successful real-time program to date was developed more than ten years ago at the Montreal Neurological Institute,[1] and has been modified only with respect to technology-dependent implementation details.[2] This system is based on a principle originally articulated by Ives et al[3] which (a) reduces the continuously acquired EEG to a series of short discontinuous segments considered to be of interest either because of a computer-detected abnormality or a push-button marker, and (b) employs the computer as a delay line to insure that EEG data preceding a segment of interest have been saved. The latter feature is especially important with respect to seizures where clinical manifestations (and hence push-button signalling) may not become apparent until well after the onset of electrographic seizure activity.

Mathematical analysis of the EEG has been carried out for many decades, and digital computers have been applied to the task since the advent of laboratory mini-computers in the late 1960s. The majority of this processing effort has been directed at characterizing the background or ongoing abnormalities. Routine frequency domain processing of many signals, including the EEG, was made possible by the discovery of the highly efficient Fast Fourier Transform (FFT) by Cooley and Tukey in 1965. Although the earliest spectral analysis of the EEG was carried out in 1938,[4] the FFT facilitated rapid, even real-time, analysis of the frequency components of the EEG. The FFT is, however, only a mathematical transformation, and its beauty is also a form of seduction: it encourages the belief that the EEG derives from a combination of sine waves. Although this is a useful concept in some research studies, it has not been of any proven clinical benefit. In the field of epilepsy, it is the transient events (where frequency spectral analysis is least sensitive) which are of paramount importance. These paroxysmal abnormalities may occupy only a fraction of a percent of the recording time, and so demand computer methods sensitive to brief interruptions of the ongoing activity.

Details of the various methods of spike detection can be found in several extensive reviews by Barlow,[5] Frost,[6] Gotman,[7,8] and Ktonas.[9] Essentially, these methods can be broken down into optimum filtering methods or heuristic analysis. The former (sometimes called parametric methods) are based on linear prediction or autoregressive modeling; they typically employ correlation, notched, inverse, and autoregressive filtering.[10] The heuristic methods, designed to mimic more closely the electroencephalographer's thought process, have generally yielded better results and exhibited more robust performance with respect to artifacts.[9] While it might seem that "artificial intelligence" approaches (such as "expert systems" methodologies) would be well suited to detection of epileptiform abnormalities, no significant progress has been made in this area, and current implementations of the technology cannot keep up with real-time data rates.

Despite numerous attempts, none of the systems currently in existence can reliably detect sharp waves or seizures in patients undergoing long-term EEG monitoring. The goal of the ideal EEG monitoring system is to improve efficiency so that recordings long enough to include all of the required diagnostic information can be carried out with a minimum amount of human review. To accomplish this, the ideal computer system should accurately detect all abnormalities, and store the important patterns for final physician review in a variety of display formats.

Although the computer can be programmed to detect sharp waves with amplitude, duration, and sharpness criteria equivalent to those used by electroencephalographers, the experienced human reader takes into account many contextual factors such as state of consciousness, spatio-temporal characteristics of the electric field, age-related variations, and other heuristics. As a result, EEG interpretation is highly dependent on training and experience, and correspondingly difficult to encode in software. For clinical purposes, however, it is not necessary that the computer detect every single spike in the record,[2] only that it provide us with accurate and usable diagnostic information in a form that presents a reasonable workload to the electroencephalographer.

SYSTEM FUNCTIONAL REQUIREMENTS

In order to carry out effective and practical long-term EEG monitoring, some form of automation is clearly required. While the noncomputer systems mentioned above conserve paper, they still require a high level of manual review or the acceptance of a large number of missed abnormalities. Computer-based systems can assist with data reduction, permitting a more thorough sampling of EEG events while minimizing manual intervention. A computer-based system for long-term monitoring must perform certain fundamental tasks; significantly enhanced capability can be added to the basic system with additional hardware and software. The remainder of this review describes the functional components required of the basic system, and some of the possible enhancements.

Data acquisition

In order to carry out any digital signal processing, the EEG must first be transformed into digital data by an analog-to-digital converter (ADC). The quality of the incoming signal, as determined by electrode application, analog filtering, and elimination of 60-Hz mains interference, will be the primary determinant of the computer's event detection accuracy. When preceded by a high-quality, low-noise EEG amplifier with an upper frequency cutoff of 70 Hz, waveform fidelity is preserved by an ADC resolution of 12 bits and a sampling rate of 200 samples per second for each channel. Many advanced analytic procedures depend on simultaneously obtained samples; therefore simultaneous or burst mode sampling is required. Close integration of the ADC and CPU is suggested, e.g., direct bus access by the ADC. Outboard ADCs communicating over a general-purpose interface, most often found as personal computer accessories, are generally not practical for continuous real-time EEG monitoring.

Intermediate storage

Once collected by the computer, the data must be stored in digital form for immediate access by the various programs composing the system. The computer must store ("buffer") the raw data long enough for the operator to retrieve an event, such as a seizure, that was not noted until some time later. Buffering the raw data also allows the system to apportion the computer's workload over time. Activity of the spike detection algorithm may be temporarily slowed by heavy use of the graphics processor, then accelerated later when the system activity is lower, in order to catch up. After the raw data have been analyzed by the abnormality detection programs, the reduced data ("interesting segments") must be stored on-line until reviewed by personnel, printed on paper, or archived to off-line digital storage. Extensive buffering increases computer efficiency but requires additional storage. The amount of time that the data remain accessible both to the computer's analysis programs for abnormality detection and to the clinical team for visual review is directly proportional to the available storage capacity.

Abnormality detection

Once the data have been acquired, the computer system can emulate a standard strip-chart recorder, i.e., permanently storing and displaying multichannel voltage *v* time data. This function is an essential part of the computer system for backup and verification. More importantly, the computer can manipulate the information with a set of extremely powerful tools which provide the capability to enhance the data, compress the data, or highlight important features. Highly developed over the last 20 years for use primarily in radar and communication, digital signal processing techniques can now be applied to physiologic signals by knowledgeable programmers. Although medical data vary tremendously and violate some assumptions of standard mathematical algorithms, our knowledge has now progressed to the point where we understand the limitations of EEG computer processing and can have confidence in the results. Algorithms should be built into the system to detect both sharp waves and seizures. Because these events will always be further reviewed by a technologist and/or electroencephalographer, the computer can be programmed to err on the side of detecting too many candidate epileptiform transients. Algorithms should be adjustable in order to "tune" them to a given patient's background. Adjustment by moving average or other continuously updating algorithms is desirable, because manual tuning leads to a lack of repeatability and the exclusion of sharp waves of a less-frequent type. Detections must also be triggerable by nonEEG events, such as a push-button marker.

Detection algorithms can be divided into those which attempt to sense deviation from a carefully characterized background and those which attempt to find a previously identified and fully characterized abnormal event. The first type of analysis is carried out by assuming that the background activity can be modeled by a random process and therefore described by its statistical parameters. While the level of consciousness and the stimulation level remain unchanging, these parameters can be assumed to be stable, or stationary in the mathematical sense. Departures from stationarity then imply a transient, possibly epileptiform, event[11] which can be detected by examining the predictive error.[12] The extreme form of the second type of analysis is template matching,[13] wherein the computer is provided with a sample waveform which is continuously cross-correlated with the incoming data to identify all subsequent occurrences of the same waveform. This matched filtering method has generally been unsuccessful because of considerable interpatient and intrapatient variability in spike morphology.[14] More often, sharp waves are less restrictively characterized by measures of the first derivative,[15] second derivative,[16] curvature at the apex of the spike,[17] and duration.

Detection algorithms are generally implemented a channel at a time, using one or a combination of filtering, wave analysis with descriptor extraction, and threshold comparison. Multichannel correlation significantly enhances accuracy of sharp-wave detection.[18] A filtering stage is frequently employed prior to detailed wave analysis in order to make epileptiform transients stand out from the background. Filtering per se is not a data reduction technique. Filtering simply transforms the data into another format; it remains as a continuous time representation with the same number of data points per unit time as before the filtering operation. Digital filtering within the computer can be employed to simply replicate a standard analog filter or to implement a filter design which is difficult to achieve in hardware. Even computationally simple finite impulse response filters can achieve reasonably good results.[19] The programmability of a digital filter affords the opportunity to adjust its parameters dynamically in order to adapt automatically to a given patient.

Wave analysis methods such as zero-cross analysis or peak detection[20,21] can be utilized to separate the EEG into a concatenation of half-waves which can then be individually analyzed as potential sharp-wave candidates. Zero-cross analysis is carried out by locating the points where the EEG signal crosses the zero axis, then approximating one-half cycle of the major wave by the time interval between two points. Each half-wave can be characterized by a series of descriptors, such as amplitude, duration, frequency, steepness, and sharpness at the apex. Even a seemingly simple measurement such as amplitude quickly becomes complicated when the various ways to measure amplitude are contemplated: peak to baseline, peak to preceding trough, peak to succeeding trough, peak to average trough, peak to inflection point, or RMS. Comparison of these descriptors to threshold values will then determine whether a candidate wave fulfills the criteria for a sharp wave. The software design chosen for setting the threshold and the comparator function will have a key influence on system operation.

The threshold level for a given descriptor can be defined on an absolute basis or may be set relative to the background activity. Manual alteration of thresholds is generally to be avoided because it introduces a detection bias which makes comparison between patients, or even at another time on the same patient, impossible. Entirely automatic threshold determination can also be fraught with hazard because of the circular procedure involved. For example, if the segment used by the computer to measure the normal level of a given descriptor contains an abnormality or artifact, the threshold is set too high. The threshold can alternatively be determined in an on-going fashion by continually updating it, based on the recent history of the signal. This continually varying threshold level may be an advantage or a detriment depending on the particular descriptor. For systems programmed to remove detected abnormalities from the background before computing the updated threshold, the threshold level will be directly dependent on the detection accuracy. This can induce an upward or downward spiraling of the threshold, leading to an ever-increasing or decreasing number of detections.

Because of finite memory limitations and to insure a degree of constancy within a segment, EEG data are processed in a series of "epochs," usually ranging from 0.5 to 10 seconds. The selection of a particular epoch duration will be determined both by practical hardware considerations and (more importantly) by the optimum time interval. This interval should be long enough to assure quasi-stationarity but short enough to prevent the inclusion of two markedly different states within the same epoch. To prevent loss of information which may occur when waveforms are divided at the boundaries of an epoch, some overlap of adjacent epochs may be desirable.

Effective abnormality detection programs will always consist of multiple operations. Programs may be executed in stages so that the output of each stage determines the function of the next. Since the process is designed to carry out a coarse screening followed by progressively finer screening procedures, detection criteria become more rigid with each succeeding stage. Because unsuitable waveforms will presumably have been rejected by earlier stages, this method allows the computer to carry out more sophisticated (and hence more time consuming) computations on fewer epochs. Alternatively, the outputs of each step of the process can be combined and weighted in a discriminant function.

Although programs which follow a step-wise procedure have generally performed better than those which determine several waveform descriptors in parallel followed by discriminant functions, the decision logic is often extremely sensitive to very subtle differences. Hence, very minor parameter changes or the empirical addition of a new test can lead to dramatic distortions in program operation. Computer abnormality detection methods which incorporate adaptive mechanisms are intuitively appealing because they conceptually have the capability to "learn" the difference between normal and abnormal in a given patient. Unfortunately, what usually occurs in practice is that the program concentrates on one particular abnormal waveform and becomes better and better at detecting it, to the exclusion of less obvious abnormalities.

Most EEG analysis systems reported in the literature have been developed and tested in a research setting where patient activity and instrumentation function are carefully monitored for relatively few hours by a technologist. Under round-the-clock recording conditions in an epilepsy monitoring unit, the major limitation to accurate abnormality detection is the very practical problem of artifacts. Although many artifacts formerly were instrumentation-related, preamplification equipment is no longer the weak link in the data-acquisition chain. The vast majority of the artifacts which confound the computer's analysis algorithms are related to movements: head movements causing EMG artifacts, eye movements generating electrooculogram artifacts, triboelectric interference from patient movement, and sudden potential changes caused by movement at the electrode/skin interface. These artifacts are represented in the extreme in recordings obtained from freely moving subjects utilizing cassette recorders.[22]

The electroencephalographer normally has little difficulty excluding artifacts from consideration because of employing a wide range of contextual clues. An electroencephalographer relies on the spatial and temporal properties of the discharge, level of consciousness of the patient, associated electrographic activity, the history of artifactual discharges during the recording, and a knowledge of what constitutes a physiologic discharge. This kind of information is extremely difficult to program, and all EEG analysis software suffers from marked degradation in performance during segments containing artifacts. Even advanced artifact rejection techniques are far less reliable than the most naive human interpreter. False-positive detections due to artifacts can be tolerated if a system of editing detected sharp waves is employed. Serial editing, first by computer detection of "interesting events," followed by technologist and electroencephalographer review of the relevant raw data segments, effects the desired data reduction.

EEG DISPLAY

Because of the longstanding use of ink-written z-folded strip charts, electroencephalographers have come to rely on a high-resolution multichannel data presentation which they can quickly flip through. When looking primarily for epileptiform abnormalities, an electroencephalographer will frequently scan 20 to 60 seconds of 16-channel data per second. Except for extremely high-end mainframe-level systems, the speed and resolution required for EEG review at this rate outstrip the capabilities of computer graphics. Video cassette recorder-based systems suffer to an even greater extent from these rapid review requirements. To overcome the frustrating limitations of display terminal review of high volume data, most systems resort to D/A output recorded on strip charts. This method facilitates the electroencephalographer's fast review in the traditional manner but precludes extensive textual annotation, interactive rescaling of data, scrolling up and down through more than 16 channels, and other desirable features characteristic of computer-generated cathode ray tube displays. Decreasing dependence on strip-chart paper awaits the development of special-purpose display subsystems and high-speed laser printers optimized for output in a strip-chart format.

Data archival

After the detected sharp waves and seizures have been reviewed and the relevant clinical information extracted, the data must be disposed of in some fashion. The practical limitation imposed by available on-line disk storage capacity will ordinarily force these disposition decisions to be made in an on-going fashion. Selection of a sufficient number of segments for printout via a graphics printer should provide permanent documentation of the results of the clinical neurophysiologic evaluation.

Saving additional segments on computer-compatible electronic media allows future comparison or detailed off-line reanalysis after treatment (e.g., correlation of spike frequency with plasma levels of antiepileptic drugs). With adequate samples, population-based studies can be carried out. The creation of an electronic library of sharp waves (and other relevant abnormalities) allows refinement and testing of new computer algorithms with a well-documented data base.

PERFORMANCE VALIDATION

A key requirement of signal processing systems is validation; unfortunately, this is much too often overlooked. There must be provision for manual (visual) evaluation of data integrity and quality at every stage. Validation encompasses two major areas: algorithm evaluation and run-time inspection. During the development of abnormality detection algorithms, it is the responsibility of the program developer (a) to carefully analyze the range of input data expected by the program module, frequently using statistical methods and histograms to characterize the distribution of the parameter under study; (b) to manually review printouts or displays at intermediate checkpoints within the program to confirm that the results are as anticipated and that they are appropriate for the next stage; (c) to undertake a worst-case analysis of the potential interactions and conflicts between program modules; and (d) to perform rigorous testing on data whose expected output is well known, including both artificial waveforms and thoroughly documented real data, e.g., from a "spike library." During program operation, there must be additional checks in order to provide routine raw data printouts at reasonable intervals so that some manual interpretation is always carried out; to enable viewing of "live" data at any time for spot-checking; and to indicate system status and alarm conditions from the program's self-monitoring software.

ADVANCED COMPUTER METHODOLOGY

During routine operation of an epilepsy monitoring unit computer system as outlined above, detection and display of the ictal and interictal events are usually sufficient for clinical purposes. Above and beyond this basic necessity of data reduction for improved efficiency, there are additional quantitative analytical tools which may have significant advantages. Research and clinical computing tasks which are too slow to perform in real-time can be put to use off-line on visually preselected segments. Montage reformatting,[23] for instance, can be helpful in localizing an unusual sharp wave, even though it is too computer-intensive for application on every epoch. Likewise, complex digital filtering algorithms can be retrospectively applied to digitized data to suppress unwanted activity or to enhance a particular waveform. These two techniques are used in combination when a reformatted noncephalic reference is coupled with an electrocardiographic subtraction algorithm.

Topographic displays can generally only illustrate the distribution of a single parameter, such as the electric field distribution of a spike or the frequency of spiking. If both intensity and color can be employed, then two parameters may be displayed with respect to spatial orientation. Cartooning (e.g., rapidly displaying a sequence of maps) allows the time dependence of a parameter to be shown as well. These techniques may help to summarize the information pertaining to localization of an epileptogenic area. In patients with focal epilepsy, the use of frequency analysis in combination with topographic mapping (as performed by several commercially available systems) has yielded results which are not consistent from one investigator to another[24–27] and cannot be considered a useful test at present.

Analyzing the propagation of a spike or seizure from one region to another with use of the paper record is sometimes difficult because it gives the visual impression of simultaneous occurrence at several locations. The computer's capability for improved time resolution and recognition of occult rhythmicities can provide a tool for detailed study of spike trajectory or seizure evolution. Gotman[28] has used "coherence" analysis (i.e., the measurement of phase difference between two channels over a range of frequencies) to distinguish patients with apparently bilaterally synchronous epileptic discharges.

Because of the magnitude of the task involved, systems for detection of EEG epileptiform abnormalities are usually built around large general-purpose computers. Once the computer is in place, it becomes tempting to shift many other related tasks to it and the personnel responsible for it. Data base applications are an obvious example. In institutions with hospital-wide medical information systems, it is technically possible to transfer results to and from other laboratories. Integration of all patient data such as imaging studies, results of intracarotid amytal testing, neuropsychology studies, follow-up visits, etc., is possible within the epilepsy monitoring unit computer. This tendency, however, should be guarded against, since it will very swiftly overload the computer. A computer system obtained on the basis of specifications for a high volume, real-time signal processing task will suffer degradation of performance if forced to fulfill other roles as well.

CONCLUSION

As prolonged inpatient EEG monitoring becomes available at an increasing number of centers, automated methods to deal with the avalanche of EEG data continue to be developed. Intensive monitoring is considerably different from recording a routine EEG, and the computer system for sharp-wave and seizure detection should not be viewed as if it were an EEG machine, an isolated piece of equipment. Design of the patient monitoring facility must be thoroughly integrated, and the computer system should be considered part of the total monitoring environment. Specification of the architecture, integration of the equipment (especially custom interfaces, e.g., computer/video time-code synchronization), and development of the software should all proceed in parallel.

An epilepsy monitoring unit can be automated by purchasing a "turn-key" computer system with integral software, or by buying the necessary hardware components and developing software customized to a particular clinical approach. Although the first path decreases the software development required, either course will lead to a substantial effort in the computer arena. The typical approach of contracting with an outside vendor or a data processing department within the institution for delivery of a finished product (such as an automated billing system) will usually not work.

Hardware capabilities are increasing exponentially, and costs are decreasing similarly. This trend permits increasingly greater performance and functionality than were possible with previous generations of equipment. Achievement of higher levels of capability, however, requires more complex and sophisticated software. Development of the software is not subject to the same economies of scale that drive the hardware advances. Software development is essentially a manual, interactive process, especially in the medical environment, where applications are highly specific and continually evolving.

The process of design, procurement, installation, and implementation is highly labor-intensive, requiring considerable interdisciplinary expertise and necessitating personnel dedicated to this task. A team approach with frequent regular contact between physicians, technologists, software developers, and hardware engineers is essential for a successful implementation. Recruiting personnel with the appropriate engineering skills, as well as training and integrating them into the medical environment, is not an easy task. Well-designed and fully integrated computer systems of today serve as adjuncts to visual analysis by showing to the human interpreter interesting EEG segments picked out by the computer. Future systems hold the promise of actually reducing the monitoring time required and extracting information not visible to the human interpreter.

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