SESSION V

COMPUTER-BASED RESEARCH AND APPLICATIONS IN CLINICAL AND SOCIAL PSYCHOLOGY: A SYMPOSIUM

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A microprocessor-controlled clinical tremometer

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A microprocessor-controlled clinical tremometer has been developed to permit routine monitoring of disease processes where tremor is a principal sign and in behavior studies where tremor may be used to index anxiety, stress, or response to ethanol. Emphasis is placed on the measurement technique and the design and construction of the device. The important role played by the microprocessor in providing for human factoring of the instrument to make it compatible with the clinical setting is examined.

Tremor is a series of involuntary, small variable movements involving a part or parts of the body moved by skeletal muscles. Limb tremor can be subdivided into two broad categories (Brumlik & Yap, 1970), as shown in Figure 1. Both normal and abnormal tremor can in turn be subdivided into one of three types according to the nature of skeletal muscle activity present during tremor generation. Rest tremor, frequently measured during the time that the limb is left free to hang without voluntary muscle involvement, is commonly increased in diseases involving the extrapyramidal system, such as Parkinson's disease. Intention tremor is manifested when the limb is moved voluntarily from one position to another and is exacerbated in disease states where there is a degeneration of the cerebellum and basal ganglia, such as multiple sclerosis, Parkinson's disease, and Wilson's disease.

The most common and widely researched type of tremor, and the one to which this paper principally addresses itself, is postural, or physiologic. Postural tremor is present any time a limb is maintained voluntarily in a position other than rest. Abnormal postural tremor is present in alcohol withdrawal, Naloxone-induced narcotic withdrawal, and barbiturate withdrawal. The tremor is of interest in psychiatry since it is frequently associated with anxiety states and can be an undesirable side-effect of lithium treatment of manic-depressive illness. Normal postural tremor is increased

during fatigue, anxiety, and stress and, as such, may be a useful index in a psychological testing battery. Normal postural tremor is reduced by ethanol and may provide an involuntary behavioral measure of alcohol effects.

In the Human Responses Laboratory at the Addiction Research Foundation of Ontario, tremor is an important clinical parameter in assessing the efficacy of drug treatments in ameliorating the signs and symptoms of the alcohol withdrawal syndrome. Tremor is also used to provide an objective measure of narcotic withdrawal in addicted patients following intravenous administration of the narcotic antagonist, Naloxone. In addition, tremor is being measured as an involuntary

Figure 1. A classification scheme for tremor.

behavioral parameter in a clinical study investigating the development of tolerance to ethanol in a nonalcoholic population.

In the clinical environment or the behavioral research situation, it is typical that large numbers of tremor measurements are required to ensure sufficient time resolution for the assessment of treatment effects or an adequate description of the clinical or behavioral state. Measurements must often be made quickly and routinely by hospital and research personnel. The need to reduce the amount of information and to simplify the measurement procedure has led to the development of a microprocessor-based tremor measurement system.

TREMOR MEASUREMENT

In order to understand something of the problems associated with quantitating postural limb tremor, it is important to describe the measurement procedure.

In our laboratory, a single tremor measurement is performed when the subject sits comfortably in a chair with his right forearm supported up to the wrist joint at the height of the xiphoid process. A 33-g piezoelectric accelerometer (Brüel and Kjaer Model 4332) affixed to a Velcro strap is secured to the right index finger such that the most sensitive axis of the device is in the vertical plane when a subject maintains his hand outright in a horizontal plane. The fingers of the right hand are firmly taped together to reduce independent motion of the fingers at the metacarpophalangeal joints. With this arrangement the vertical motion of the hand is measured when the arm muscles are counteracting torque on the hand about the wrist joint against the force of gravity. Typical hand tremor frequencies range from 6 to 10 Hz.

The accelerometer arrangement above was chosen because of its ease of placement on the subject, its inherent ruggedness [maximum shock acceleration = 6,000 G (1 G = 9.81 m/sec²)], and high sensitivity (65.5 mV/G). For a single observation of tremor the subject is required to maintain his hand outstretched for approximately 25 sec. The subject is encouraged to watch his hand to maintain the same position over the observation period.

The Tremor Signal

The parameter selected for quantitation of tremor size is the variance or mean square value, since clinically it is frequently most important to know the intensity of shaking. Tremor variance has been shown (Sellers, Zilm, & Degani, 1977; Zilm, Sellers, MacLeod, & Degani, 1976) to be a sensitive measure in the clinical situation.

The tremor signal has a considerable dynamic size range. Tremor in withdrawal can be more than 100 times the size of normal postural tremor. Normal postural tremor is typically 10 times as large as resting tremor.

Figure 2. Two samples of tremor amplitude probability distribution functions. Dashed line is a Gaussian distribution with the same variance.

Treatment is frequently associated with a 10- to 100-fold decrease in limb tremor.

Postural tremor does not have a constant amplitude over time. Instead, its amplitude probability distribution function approximates a Gaussian distribution, as shown in the example in Figure 2. From a series of tremor recordings obtained from alcoholics in withdrawal and nonalcoholics, a total of 22 records were selected at random, 12 from the alcoholic population and 10 from the nonalcoholic population. The records were digitized and submitted to a Kolmogorov-Smirnov test of Gaussianity. In 8 of the 12 alcoholic and 7 of the 10 nonalcoholic recordings, the differences were not significant statistically. For records where the null hypothesis could be rejected ($p > .05$) the amplitude probability density functions were more "peaked," indicating that, at worst, the signal is best modeled as "narrow-band" random.

In addition to the amplitude variability of the tremor signal, there is a variability in the size (as measured by the variance or mean square of the tremor observation) of repeated tremor observations. Figure 3 illustrates the relation between the mean size of five sequential tremor measurements and the standard deviation of those measurements from records selected from 20 normal healthy volunteers. Standard deviation increases with tremor size. A similar relation exists for alcohol with-

Figure 3. Mean of five consecutive tremor observations vs. the standard deviation (20 subjects).

drawal tremor. This figure demonstrates that the coefficient of variation increases with tremor size; multiple observations of tremor must then be made if true tremor size is to be ascertained with any degree of certainty, particularly if the tremor is large. An analysis of variance on a number of the above records was computed to determine whether there was any major ordering effect on tremor size due to the sequence of repeated observations. The analysis demonstrated no significant order effect ($F = .47$, $df = 4,124$).

THE TREMOMETER

Description of Operation

Because of the nature of the tremor signal, there are special problems of automatic gain control, calculation of tremor size, computation of summary statistics for multiple observations, presentation, and logging of results. These problems are best solved by designing the tremor measurement system around a dedicated microprocessor. A block diagram of the hardware for the system is illustrated in Figure 4. A general schematic of the software is illustrated in Figure 5. The tremometer is designed to simplify and minimize operator interaction, thereby fulfilling an important criterion for human factoring the device for clinical and research purposes (Zilm, in press).

The signal generated by the movement of the accelerometer due to motion of the hand is initially amplified by a high-impedance MOSFET preamplifier. Initiation of a single measurement by the operator depressing a front-panel START switch causes the microcomputer to begin

executing a program stored in PROM (programmable read-only memory). Under program control, the gain of the variable gain amplifier (VGA) is initialized and the signal is shunted to a stand-alone hardware peripheral rectifier-integrator counter (RIC). The RIC rectifies the tremor signal and integrates the result. When the integral reaches a critical level, the integrator is reset and the integration begins again starting at zero. The number of times the integrator is reset is tallied on a 12-bit binary counter. At the end of a 5-sec period, the 12-bit counter is read by the microprocessor. The microprocessor uses

Figure 4. Schematic of hardware configuration for tremometer.

Figure 5. Brief flowchart of microprocessor software.

this 12-bit count to make an estimate of the signal size. From a look-up table in the memory, the microprocessor selects the gain based on the RIC count at which the VGA should be set according to the signal size. The appropriately amplified signal together with a 3-bit digital number indicating one of eight possible gains are made available for recording at the back of the instrument. Once the amplifier gain is selected, the signal is directed to a 12-bit analog-to-digital (A/D) converter. For the following 20 sec each 12-bit sample (11 bits magnitude, 1 bit sign) of the signal is squared, and the sum is cumulated in memory as a 40-bit number. During the 20-sec computation period, the signal is also shunted into a peripheral zero-crossing detector which detects and counts the zero crossings of the tremor signal. While a measure of tremor frequency is of less importance in postural tremor analysis, it can be of use in assisting the diagnosis and treatment of tremors resulting from diseases of the extrapyramidal system.

At the end of the measurement period, the mean of the sum of squares is calculated (ac coupling of the tremor signal at the input removes dc or the mean) using an appropriate scale factor to account for the sensitivity of the accelerometer and the amplifier gain; then tremor variance is displayed in units of $10^{-4}G^2$. The 12-bit counter that stores the number of zero crossings is read and the mean frequency is calculated.

The computer software stores the number of A/D converter overflows (indicating the signal has exceeded the input voltage limits of the converter) and displays tremor variance as a flashing number in the event the error threshold is exceeded. Following display, the operator has the option to disregard the measurement (ERASE), accept the measurement and take another (START), or compute the mean and standard deviation of observations cumulated to that point (COMPUTE). If a measurement is accepted, the signal variance and frequency are printed out on a thermal printer together with the observation number. Following COMPUTE, the means of tremor variances and frequency are printed. At any point the operator may terminate a tremor measurement by depressing the RESET switch.

Principle of Operation

The estimation of signal size by the microprocessor is based upon a knowledge of the characteristics of the tremor signal. The RIC peripheral returns a count to the microprocessor which is proportional to the mean absolute value (MAV) of the first 5 sec of the tremor sample. If the tremor signal is stationary over a 25-sec period, then the variance of the first 5 sec is a good predictor of the variance of the following 20 sec. In addition, if the tremor signal is Gaussian, then:

$$MAV = .798\sigma \quad (1)$$

where σ equals the standard deviation of the signal.

Thus, the MAV of the first 5 sec can be used to estimate the standard deviation or variance of the following 20 sec. Furthermore, knowing the crest factor (peak/ σ), it is possible to predict the peak value of the signal and therefore the gain required to provide a sufficiently large signal that the quantization error in the A/D conversion is minimal, but not sufficiently large to saturate the input of the A/D converter in 99% of all cases.

To test the above assumptions, 204 tremor recordings were selected at random from 12 individuals, half of whom were receiving treatment for elevated tremor. The MAV and variance (V_5) were calculated for the first 5 sec of each tremor signal, and the standard deviation (SD_{20}) and variance (V_{20}) of the subsequent 20 sec were computed. A linear regression of V_5 against V_{20} was computed, as was a linear regression of MAV vs. SD_{20} .

As shown in Table 1, the variance of the first 5 sec predicts the variance of the last 20 sec, confirming the assumption that the signal is stationary. In addition, the MAV predicts the standard deviation, and the slope (.76) is close to that expected if the signal is Gaussian (see Equation 1). The mean crest factor for the 5- to 25-sec period was 3.8 for the records.

Table 1
Regression Analysis of First 5 Sec of Tremor
With Following 20 Sec

	Slope	Y Intercept	r
V_s vs. V_{20} *	1.02	$.13 \times 10^{-4} G^2$	.81
MAV vs. SD_{20}	.76	.9974 G	.88

* V_s = signal variance, 0-5 sec; V_{20} = signal variance, 5-25 sec;
MAV = mean absolute value, 0-5 sec; $SD_{20} = \sqrt{V_{20}}$.

The Microprocessor

The choice of the microprocessor for this application was an Intel 8080. The decision to base the tremometer system on the 8080 involved four considerations: (1) availability of local support for the 8080 system, (2) availability of a microprocessor cross-assembler, (3) ability of the microprocessor to perform the necessary operations on 12-bit numbers at speeds compatible with the data rates required by the tremometer, (4) transferability of microprocessor technology to other laboratory projects.

The 8080 satisfied the first three criteria. Local support and experience was greatest for the Intel system. In addition, an 8080 cross-assembler was readily available for the Varian V76, the Human Responses Laboratory's computer. The fact that the 8080 architecture and instruction set permit a limited number of 16-bit operations was a strong point favoring its implementation in the tremometer. The most time-critical task in the tremor measurement system is the 12-bit square and sum that can be performed in less than .8 msec, well within the interval between conversions (5 msec).

The transferability of laboratory-generated technology to other laboratory projects was less important, since nearly all microprocessor systems offer an extraordinary degree of flexibility. However, with the Intel system no special problems were associated with interfacing with the Varian.

Minicomputer Interface and Programming the 8080

While the capital investment for microprocessor systems is frequently small, the investment for program development facilities can be large. The development of microprocessor software is often underestimated by the novice seeking to avail himself of the advantages of microprocessor-based systems. Without a proper program development facility, the task of bringing a microprocessor-based instrument to a successful conclusion can be enormous.

Program development for the tremometer and other 8080-based systems was greatly facilitated by a specially

designed 8080/Varian V76 interface and V76 driver (see Figure 4). Programs are initially loaded into and executed in 8080 random access memory (RAM). When programs have been debugged and perform according to requirement, they are loaded into a PROM from the Varian using a specially designed PROM programmer which is controlled by the V76.

The present 8080-V76 hardware and software interfaces are designed so that 16k words (8 bits) of 8080 RAM are mapped into Varian memory. The standard 8080 monitor was modified so that the microprocessor could accept data in parallel mode from a 16-bit buffered digital input-output port on the V76. With the 8080 RAM-Varian mapping, the 8080 monitor can be used to transfer code from the Varian to specific locations in RAM for program execution. The 8080 programs can be entered in a standard way to the Varian, cross-assembled, and set up for transfer to the microprocessor. Debugging of programs is facilitated by transferring registers and contents of memory locations to the Varian for examination.

A modified form of the 8080 monitor has recently been coded and made to execute in the Varian. With this facility, programming of any abbreviated 8080-based system can proceed with a minimum of effort.

SUMMARY

A microprocessor-based clinical tremor measurement device has been described. The microprocessor performs the difficult task of automatic gain control for a narrow-band random signal with a wide dynamic size range. The processor computes both the variance and mean frequency of a 20-sec sample of limb tremor and displays and prints the result following the measurement; the unit simplifies and minimizes operator intervention in the measurement process.

REFERENCES

- BRUMLIK, J., & YAP, C. *Normal tremor: A comparative study*. Springfield, Ill: Charles C Thomas, 1970.
- SELLERS, E. M., ZILM, D. H., & DEGANI, N. Comparative efficacy of propranolol and chlordiazepoxide in alcohol withdrawal. *Journal of Studies on Alcohol*, 1977, 38, 2096-2108.
- ZILM, D. H. The man-machine interface in the clinical research environment. In *Proceedings of the 10th Annual Meeting of the Human Factors Association of Canada*, September 1977 (in press).
- ZILM, D. H., SELLERS, E. M., MACLEOD, S. M., & DEGANI, N. Propranolol effect on tremor in alcoholic withdrawal. *Annals of Internal Medicine*, 1976, 83, 234-236.