Computer techniques for studying biologic rhythms:

Quantitative chronobiology

CHARLES F. STROEBEL, *INSTITUTE OF LIVING, Hartford, Connecticut 06102*

Chronobiology is the quantitative study of biologic rhythms—those biologic phenomena that fluctuate periodically over time. These rhythms, sometimes called biologic clocks, can vary in their period of oscillation from milliseconds (e.g., biochemical reactions or unit nerve activity) through the entire time domain to hours, days, years, or longer. By specifying the periods of individual rhythms along a continuum, a spectrum of bio-periodicities may be envisioned, as shown schematically in Fig. 1. Some regions of the spectrum have been more fully studied than others, either because of prominence (the sex cycles) or ease of study and demonstrable clinical relevance (EKG or EEG). Comparatively recent demonstration of the importance of other domains in the bio-periodicity spectrum (Halberg, 1969), argues strongly for the development of practicable measurement and computer techniques to permit large-scale quantitative analysis of their relevance in normal and abnormal human functioning. Examples are the activity-sleep cycle, the dream cycles, the times of maximum and minimum susceptibility to pharmacologic and infectious agents, rhythm adjustment to intercontinental jet and space flights, and various abnormal rhythms associated with emotional illnesses (Stroebe, 1969).

This paper will discuss techniques for studying long and short period rhythms with a LINC-8 class computer. Several of the applications should be of general interest because of their flexibility in permitting this relatively small computer to operate simultaneously in the following modes in a relatively automatic fashion: batch, process control, and interactive in a dedicated experiment.

PROBLEM

Because of inherent or superimposed noise, which is common in most biologic signals, several or many cycles must be observed to permit quantitative estimation of a rhythm's period, amplitude, and variability. While this sampling requirement poses relatively few problems in studying ultradian rhythms where many cycles occur over a short period of time, it may require full dedication of a LINC-8's capability for the period of data collection and analysis (e.g., EEG spectrum analyses, average evoked response studies, analysis of

operant behavior for periodicities) (Weiss, 1967). Measurement of slower circadian (circa, about; dies, day) or infradian rhythms requires less frequent sampling over longer time intervals—an uneconomical application for a dedicated LINC-8; a more economical approach would collect data off-line to be batch-processed when the computer is not dedicated to more demanding tasks. Our specific problem, however, stemmed from

a desire to use the computer as an interactive component in the longer rhythm experiments, collecting and analyzing data on-line to make decisions as to when a behavioral trial should be presented or when and how much of a medication should be presented or infused based upon the S's own biologic clock time.

To summarize our requirements, we sought a means to accomplish the following objectives concomitantly in a relatively automatic, flexible fashion using the LINC-8: (1) To commit the computer to "full-time" interactive experiments (capable of brief interruptions) such as average evoked response studies. (2) To

Fig. 1. Spectrum of biologic periodicities.

Fig. 2. Diagram of the general system.

Fig. 3. Control components of system diagrammed in Fig. 2.

sample a varying number of human and monkey Ss for a varying number of telemetered physiological variables four to five times each hour, testing incoming data for artifacts and against limits established from previous days of data for a given S, to appropriately store the data, and to make decisions as to when to deliver behavioral trials or medications. (3) To service interrupt device alarms using the external sense lines. (4) To automatically queue and

process various lengthy batch jobs (e.g., CalComp plotting of data when computer time becomes available).

METHOD

The foregoing objectives were met by writing a software monitor [called MONTOR (Tuttle, Pavel, Stroebel, 1968)] for the LINC-8 which executes GUIDE filed programs automatically in a sequence specified by typing job programs and

control programs into the monitor index via the Teletype. The control programs permit flexibility by providing the following generalized functions: (1) Repeat the above program. (2) Jump the next program on a (specifiable) external line level change. (3) Jump the next program after previous programs on the list have been executed XX times. (4) Interrupt this program and save it for restart after the interrupt is processed. (5) Halt.

Variables to be sampled with slow rhythm changes (e.g., core, temperature, heart rate) are sampled and evaluated once every 12 min by an interrupt presented by an external clock. All programs likely to be interrupted by the external clock contain skips at logical points in the program flow where the program, counters, and appropriate registers are saved in a storage area on tape, the sampling interrupt serviced, and the interrupted program restarted.

Figure 2 shows a diagram of the general system, whose control components are illustrated photographically in Fig. 3. During a typical 24-h period, core temperature rhythm data is collected, analyzed, and stored, requiring 30 sec once every 12 min, day and night. For the remaining of the 11½-min intervals during the day, the computer tests and measures behavioral performance of the Ss or is used for program development; the 11½-min intervals at night are used to accumulate average evoked response data by stage of vigilance and circadian phase for a single S and/or to analyze and plot data previously collected on the CalComp plotter. Once the monitor has been initialized, no further console interaction is required. Redundant error-detection programs, both internal and external to the computer, provide emergency notification by telephone to a

Fig. 4. Vertically isometric LINC-8 scope display, showing de-synchronization of brain temperature rhythm in monkey developing psychosomatic symptoms.

Fig. 5. Vertically isometric LINC-8 scope display of brain temperature rhythm in monkey developing more disturbed regressed behavior.

laboratory staff member on call when a failure occurs.

RESULTS

Our LINC-8 has been operating 24 h daily under MONTOR control for over a year. Failures attributable to minor "anomalous" computer malfunction have occurred on the average of once every 2½ weeks. Hardware failures requiring field maintenance are less frequent. Because disk storage has not been installed, MONTOR performance can be optimized by giving careful attention to location of programs and data on LINC-tape; otherwise, time spent in tape searching can be considerable.

During the year, considerable data has been collected to document two kinds of biologic rhythm abnormality associated with disturbed behavior in the rhesus monkey. Figure 4 is a vertically isometric LINC-8 scope display showing desynchronization of the brain temperature rhythm in a monkey developing psychosomatic symptoms (asthmatic breathing, neurogenic skin lesions, gastrointestinal disturbances) during the period of desynchronization. The figure shows 48-h brain temperature

records with samples every 12 min; the vertical dotted lines indicate the onset of a 12-h light period each day. The desynchronization of the rhythm becomes apparent in the seventh curve from the bottom; resynchronization with the light cycle is evident in the fifth curve from the top. During the interim, the S's body slowly becomes prepared for night functioning during the day and day functioning during the night, a phenomenon that would manifest itself clinically as insomnia.

Figure 5 shows a vertically isometric LINC-8 scope display of the brain temperature rhythm in a monkey developing more disturbed, regressed behavior (despondency, movement stereotypy, loss of appetite) as a result of the behavior frustration-stress. The vertically displaced 48-h records show an increased amplitude of the first 24-h peak, with suppression of the peak on the second day of each record. Power spectrum analyses (Fig. 6, Panel 2) of these data suggest that the S has developed 48- and 96-h rhythm components in response to the behavioral stress. Comparable rhythm abnormalities have been observed in

Fig. 6. Power spectrum analyses.

psychiatric patients. The remainder of Fig. 6 illustrates a further finding, that 6 weeks of treatment with a phenothiazine medication serves to suppress the "abnormal" longer-than-24-h rhythms and to restore relatively normal behavior and circadian functioning. Other experiments suggest that the recovery process may be accelerated by phasing drug administration with the S's own biologic clock time (as determined by the LINC) rather than by administering the drug in the usual clinical fashion at the convenience of staff. The evidence further suggests that appropriate timing of such medication can maximize the active drug principle and minimize undesirable side effects that are common with psychiatric medication. We are currently impressed that correction of the biologic rhythm disturbance using the interactive computer approach inevitably seems to precede behavioral improvement, suggesting a potentially important new role for computers in the psychiatric treatment process (Stroebe, 1967).

The techniques discussed here for using a LINC-8 in a chronobiology research environment represent only the initial steps of a complex data analysis sequence (Stroebe, in press). Similar approaches for data collection using a different computer have been developed with considerable ingenuity by Runge (in press) at the University of Minnesota, where Halberg (1968) has developed sophisticated statistical programs for subsequent analysis referenced to international biologic rhythm standards.

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