

— INSTRUMENTATION & TECHNIQUES —

A computerized system for monitoring and controlling intracranial electrical self-stimulation behavior

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An automated system for measuring intracranial self-stimulation behavior is described. The system consists of two Commodore 6502 microcomputers interfaced with a constant-current generator and a standard operant chamber. The system hardware allows sine- and square-wave stimulation. Stimulus intensity can be varied in 256 steps between 0 and 100, 0 and 500, or 0 and 1,000 μ A. The system programs, which are written in machine language, allow the control of various schedules of reinforcement, the counting of operant responses and reinforcements, the measurement of interresponse intervals, and the storage of the data on disk. The software is designed for the determination of the threshold of reinforcement, on the basis of the titration of postreinforcement pauses caused by changeover in schedule control between concurrent continuous reinforcement and fixed ratio schedules.

In this paper, an automated system for controlling and assessing intracranial electrical self-stimulation behavior is described. The system hardware allows the manipulation of different stimulus parameters, such as waveform, frequency, intensity, and duration. The software permits the counting of operant responses, the measurement and storage of interresponse intervals (IRIs), and the presentation of different schedules of reinforcement such as FR, CRF, and combined FR/CRF.

Figure 1 shows an overview of the complete system, which consists of several components. The Skinner boxes, the oscilloscope, and the cumulative recorders are readily obtainable standard devices, whereas the constant-current generator was designed and constructed in our own laboratory. Two inexpensive home computers are interfaced to the current generator: One is used for controlling the stimulus parameters and the reinforcement schedule; the other is used for measuring IRIs. The current generator and the interface make up the most important unit of the system. It is equipped with two constant-current outputs for one electrode each and one input (with 48 lines) for computer control. The stimulus parameters, such as waveform, frequency, and intensity, can be manipulated independently for each electrode. Any controlling computer can be used, but it must have at least 48 I/O channels.

The system was developed to provide an automated method for measuring the threshold of reinforcing brain

stimulation according to psychophysical requirements. A problem facing the psychophysical threshold measurement of reinforcement is that subthreshold stimulus intensities must be presented to the subject. To prevent extinction of operant behavior when subthreshold (nonreinforcing) stimulus intensities are presented, two stimuli are presented concurrently, according to two different schedules of reinforcement. Reinforcement on one schedule is used to maintain behavior, while the other schedule is used to measure the reinforcing effects of a second stimulus. The schedule used to maintain behavior is an FR schedule, under which the animal is reinforced for every n th response with an intensity that is held constant throughout the experiment. The second schedule is a CRF-schedule under which stimulation is provided after every response. Varying the intensity of the CRF stimulus allows the experimenter to observe changes in the animal's behavior. As intensity is decreased below a critical value, pauses in bar-pressing behavior occur after the FR reinforcement. These postreinforcement pauses (PRPs) (Felton & Lyon, 1966) gradually disappear when the intensity of the CRF stimulus is increased. The presence of PRPs as criteria for changeover from CRF to FR schedule control and vice versa can be used to calculate a psychophysical threshold of reinforcement by the method of limits (Cassens, Actor, Kling, & Schildkraut, 1983; Huston & Mills, 1971; Phelps & Lewis, 1982; West & Michael, 1987) or by the method of constant stimuli (Buscher, Wagner, & Huston, 1990). Thus, a special feature of the software described here is the presentation of concurrent schedules of reinforcement. Software for this particular application is described, in order to illustrate the use of the system hardware.

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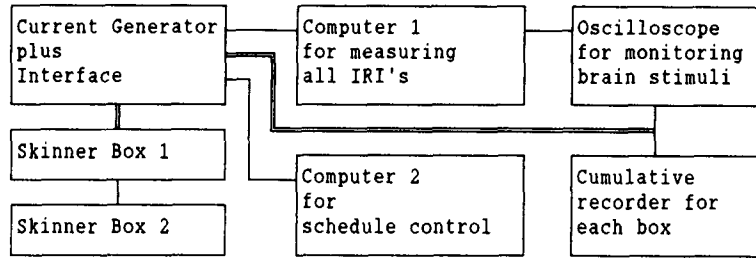


Figure 1. Schematic drawing of self-stimulation system. The constant-current generator as the central unit is interfaced with two computers. The connection with Computer 1 consists of input and output lines; the connection with Computer 2 includes only output channels. Computer 1 controls the reinforcement schedule and allows the manipulation of all experimental parameters. Computer 2 receives the information regarding FR or CRF reinforcement of responses. It measures all interresponse intervals and displays them graphically. The oscilloscope is connected with the constant-current generator and serves for monitoring the brain stimuli. The use of two cumulative recorders, which are connected with the interface, is optional. The operant lever in the Skinner box is connected with the interface with an input line, and an output line connects the interface with a commutator.

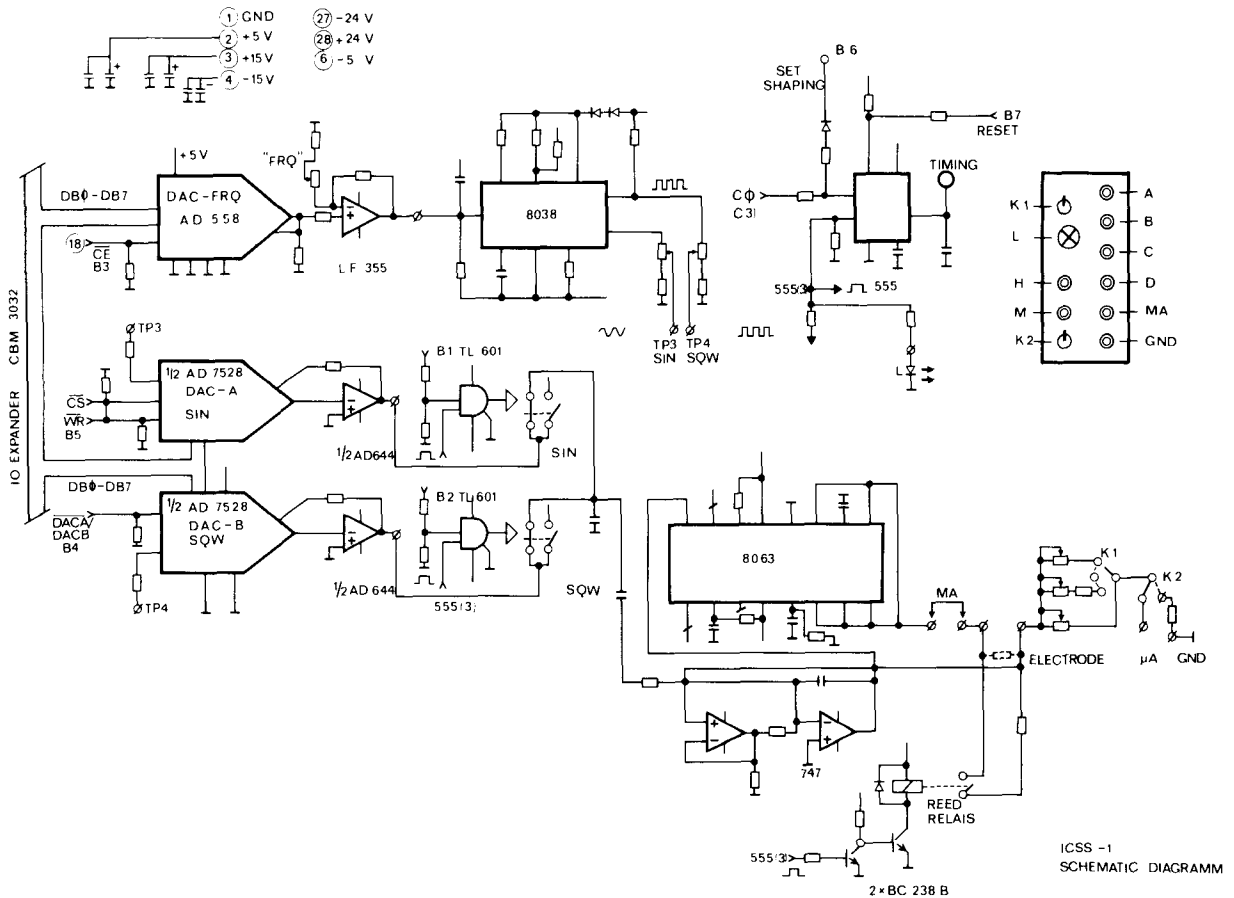


Figure 2. Constant-current generator. See text for further details.

HARDWARE

Figure 1 shows an overview of the complete system as a schematic drawing. The Skinner boxes (Coulbourn Instruments, E 10-10), the oscilloscope (Hameg, HM 205), the computers (Commodore CBM 3032 and Commodore C-64), and the cumulative recorders (Campden Instruments, 654) are easily obtainable standard devices, whereas the constant-current generator and the interface were designed and constructed in our own lab.

The unit containing the constant-current generator and the interface included four electronic boards. Two boards are needed to control waveform, frequency, and amplitude of stimulation for 2 animals with one electrode each or for 1 animal with two electrodes, respectively (Figure 2). The third board (Figure 3) is needed to control train duration, and the fourth (Figure 4) is used for experimenter-induced stimulation during the shaping period. Six functional parts can be distinguished on the circuit diagram in Figure 2. They illustrate how the unit works.

1. The most important part of Unit 1 consists of a microprocessor-compatible 8-bit D/A converter (Analog Devices AD 558) with latch. It is used to set the stimulation frequency.

2. Unit 2 contains a waveform generator (ICL 8038), which generates sine and square waves with the frequency that is set by Unit 1. The frequency is determined by the voltage, which is provided by the AD 558. The waveform generator (ICL 8038) is set to generate a waveform

with an amplitude of 1.2 V (rms). Different amplitudes between 0 and 1.2 V can be adjusted in Unit 3.

3. Unit 3 contains an 8-bit double D/A converter (Analog Devices AD 7528) with latch. One half of this chip controls (attenuates) the amplitude of sine waves; the other half controls the amplitude of square waves. The controlling signal (also voltage) at this point contains the information about frequency, waveform, and amplitude, which is set by the user. The signal is then sent to the constant-current generator via Unit 4.

4. Unit 4 enables the user to switch between sine waves and square waves. The current generator receives only one signal, which can be used to generate stimuli with the appropriate waveform.

5. Unit 5 contains the power driver amplifier (ICL 8063) and the operational amplifier (747). A feedback system is used to keep the current constant; any variation of tissue resistance is sensed by the operational amplifier and applied to the power driver amplifier. During the interpulse interval, a gate opens and short-circuits the electrode tips to avoid the accumulation of current charge at the tips.

6. Unit 6 controls the train duration. It contains a timer chip (555), which is regulated by another board (Figure 3).

The timer board (Figure 3) contains one CMOS four-channel flipflop 4175 and one CMOS analog multiplexer 4051 for each Skinner box. One 8-bit port (VIA 3, Port B) is sufficient to control this board, since 2 bits (Bit 0 and Bit 4) are needed for both clocks and 3 bits are needed

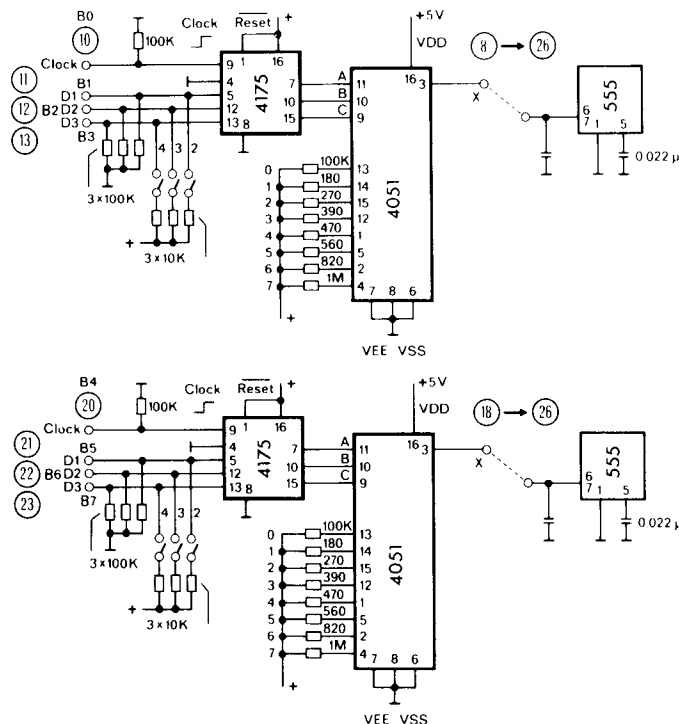


Figure 3. Board for controlling train duration. See text for further details.

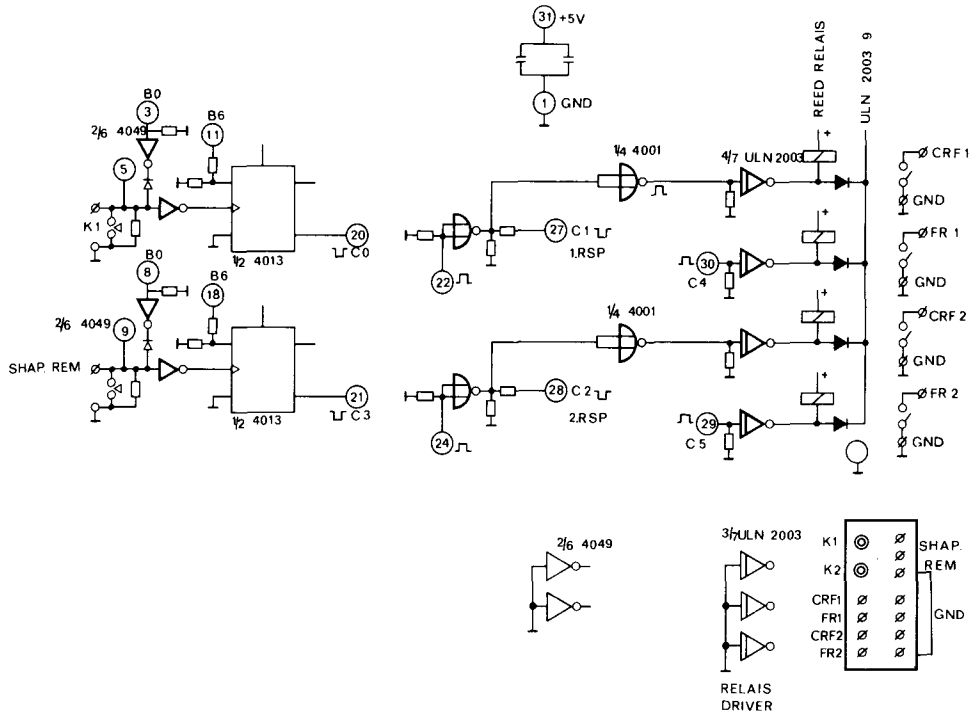


Figure 4. Shaping board. See text for further details.

for each Skinner box in order to select one out of eight possible train durations.

The shaping board (Figure 4) is used for computer-induced stimulation and for managing the cumulative recorder. Two bits are sufficient for computer-induced stimulation (Bit 0 of Port B from VIA 1 and 2), and 4 bits are needed to control the cumulative recorder. One bit per Skinner box indicates a barpress, and a second bit is needed to signal whether the last reinforcer was an FR or a CRF reinforcer.

The CBM 3032 computer is equipped with an I/O expansion in order to control all chips of the interface. The expansion includes three versatile interface adapters (VIAs, 8255). This chip is also known as a programmable peripheral interface, or PPI, with each VIA containing three 8-bit ports: Port A, Port B, and Port C. Each bit of Port A and Port B can be used as an input or output, whereas in Port C, the upper or the lower 4 bits can be used as inputs or outputs. The following ports are used to control the constant-current generators:

- VIA 1, Port A Data bus to set frequency, waveform, and amplitude.
- VIA 1, Port B Control port for the first electrode.
- VIA 2, Port B Control port for the second electrode.
- VIA 1, Port C Cumulative recorder and computer-controlled shaping. Four bits of this port are used as inputs and 4 as outputs.
- VIA 3, Port B Programmable timer-controller.
- VIA 2, Port C Checks the external keyboard. For this purpose, four bits are used as input.

Port B of VIA 1 and VIA 2 is the most important register for the control of the current generator. It is used to set the frequency, waveform, and intensity of the stimulation. The function of each bit is as follows:

- Bit 0 Starts/stops experimenter-induced stimulation.
- Bit 1 If this bit is set, sine wave is generated.
- Bit 2 If this bit is set, square wave is generated.
- Bit 3 Sets frequency; the data from Port A are written into Chip AD 558.
- Bit 4 Selects half of the AD 7528. If Bit 4 equals 0, then the sine-wave half is set; if Bit 4 equals 1, then the square-wave half is set.
- Bit 5 When this bit is set, the data from Port A are written in the half of the AD 7528 that is selected with Bit 4.
- Bit 6 When this bit is set, the lever of the corresponding Skinner box is checked. This bit becomes 0 when the animal is stimulated; no new stimulation can be initialized during a stimulus train.
- Bit 7 Timer-enable bit. When this bit is set, a leverpress is followed by a stimulation of a preset duration. If this bit is not set, the train duration is 0 (e.g., during extinction, when leverpresses are counted, but not reinforced).

The 8 bits above are used in the following way:

To set the frequency, the corresponding value is written in Port A. When Bit 3 of Port B is set, the value is written into the AD 558 and the frequency is set.

To select a waveform, Bit 1 or Bit 2 of Port B must be set. To set the stimulation intensity, the correspond-

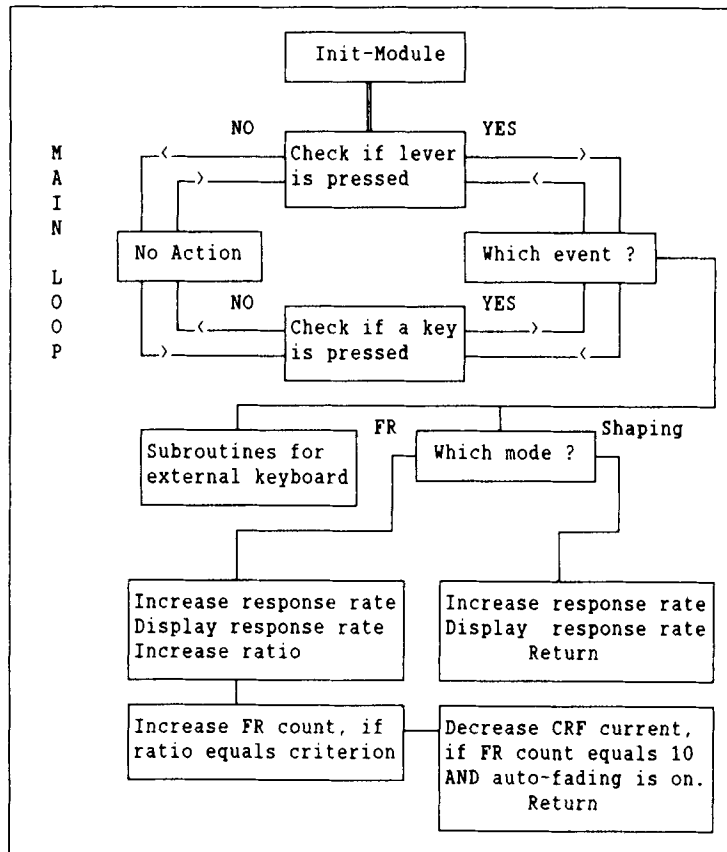


Figure 5. Flowchart of the program, which controls different schedules of reinforcement. After the initialization of all system components, the program checks the operant lever in the Skinner box as well as the buttons on the external keyboard. Depending on which event has occurred, different subroutines are called.

ing value must be written in Port A, and Bit 5 must be set to 1.

Port B of VIA 3 must be manipulated to set the train duration. The duration for the first Skinner box is set in the low byte of Port B; the duration for the second one is set in the high byte of Port B. The first bit of both nibbles serves as the clock, and Bits 1, 2, and 3 receive the information about one of eight possible train durations. When the clock bit is set, the train duration is selected.

SOFTWARE

Here, we will describe a program that demonstrates how the system hardware can be used. In a sample experiment (Buscher et al., 1990), animals were electrically stimulated simultaneously in the lateral hypothalamus (LH) of the left and right hemispheres. They were trained to self-stimulate under a fixed ratio (FR) schedule of reinforcement in one LH and under a superimposed continuous reinforcement (CRF) schedule in the other LH. Self-stimulation was controlled by one lever only.

Two current generators were required for this experiment for 1 animal: one for stimulation on the FR schedule in one LH, and one for stimulation on the CRF schedule

in the contralateral LH. Figure 5 shows a flow chart of the program, which controls the reinforcement schedules.

In the init module, all interface registers are set to 0, the I/O expansion is initialized, all stimulus parameters are set to their default values, and finally the screen is built up. The program contains two different screen masks, one for the shaping mode and one for the FR mode. The program always starts in the shaping mode. (See Figure 6 for the parameters displayed on the screen with two different masks.)

In the main loop, the program checks the operant lever and the external keyboard in an alternating fashion. If the program detects an event, it checks to see whether it is in the shaping or the FR mode and continues with the corresponding action. After the program has returned from the subroutines, the lever is checked if the event has occurred on the external keyboard, and the external keyboard is checked if the event occurred on the operant lever. Nothing happens if no event is detected.

If the program detects a leverpress, the leverpress counter is incremented and displayed on the screen. If the shaping mode is set, the program then returns to the main loop. In the case of a leverpress, the program has to perform

Shaping-Mode		FR-Mode	
Lever	: Enabled	Lever	: Enabled
Response Rate	: 0000	FR-Crit.	: 20
Current	: 000	Response Rate	: 0000
Hemisphere	: Left	FR Run	: 00
		FR Count	: 000
		FR Current	: 000
		CRF Current	: 000
		Auto-Fading	: Off

Figure 6. Screen display of the computer, which controls the schedule of reinforcement. When the program is in the shaping mode, the total number of responses and the intensity of stimulation are displayed. In addition, the display shows which side of the brain is stimulated and whether a response is followed by a brain stimulation or not. When the program is in the FR mode, additional information is supplied. In this mode, the program shows the FR intensity and the FR criterion, how many responses have been emitted since the last application of an FR reinforcer, as well as the total number of FR reinforcements. Finally, the display shows whether or not the autofading option is set.

more tasks during the FR mode. First, the program increments the ratio and compares it with the user-defined FR criterion. If the ratio equals the criterion, the program delivers FR reinforcing stimulation into the appropriate LH. If the autofading option is set and the number of FR reinforcers equals 10, the program decreases the intensity of the stimulation given on the CRF schedule and sets the FR counter to 0. If the autofading option is not set, CRF intensity will not be changed by the program, and the FR counter displays the total number of FR reinforcers.

All parameters can be manipulated using the external keyboard. All choices available on the external keyboard are summarized in Figure 7.

When the program is in the shaping mode, only the keys that are underlined have a function; the others are disabled. During the shaping mode, the experimenter can terminate the session. If the program detects the corresponding buttonpress, it sets the current intensity to 0 and returns to the system. The lever can be enabled or

disabled. If the lever is disabled, the animal's responses are counted, but a response is not followed by brain stimulation. The experimenter can choose between self-stimulation in the right or in the left LH. The screen indicates through which electrode a stimulus is applied. The experimenter also can apply stimuli to the chosen electrode manually. The intensity of the CRF stimulation can be increased and decreased. The actual value of current intensity is always displayed on the screen. Finally, the program can be switched to the FR mode. If the corresponding button is pressed, the screen display will be changed. In this mode, all keys on the external keyboard are functional: The autofading option can be toggled on and off, the FR current and the FR criterion can be increased and decreased, and experimenter-induced stimulation can be applied to both electrodes.

When the program is in the FR mode, the screen display shows the actual FR criterion, the stimulated side of the brain, and whether the response is followed by a

<u>End of Session</u>	<u>Lever Enable/Disable</u>	Auto-fading On/Off
<u>Stimulus in left hem.</u>	<u>Stimulus in right hem.</u>	<u>Set Counter to Zero</u>
<u>Switch to FR mode</u>	<u>Change side of stimulation</u>	Switch to Shap. mode
<u>Increase CRF current</u>	Increase FR current	Increase FR criterion
<u>Decrease CRF current</u>	Decrease FR current	Decrease FR criterion

Figure 7. Keymap of the external keyboard. All functions are available when the program is in the FR mode. Only the functions that are underlined are available when the program is in the shaping mode. See text for further information.

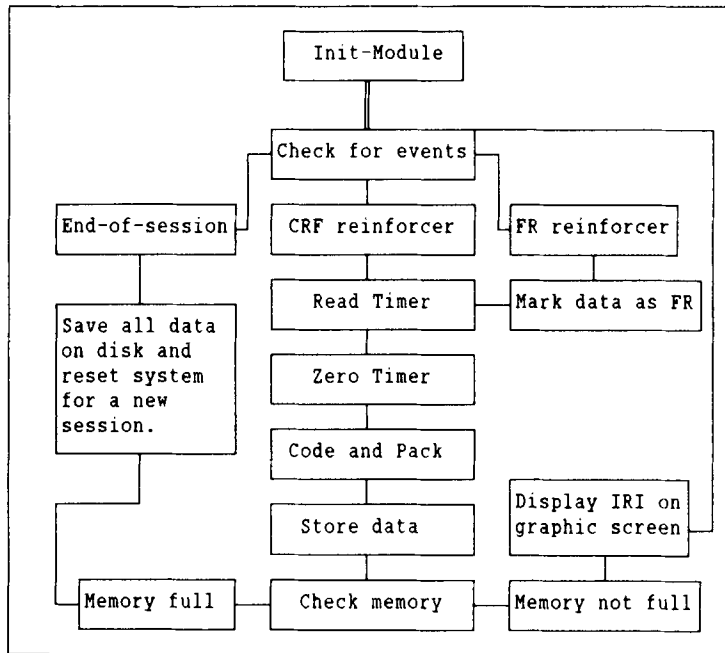


Figure 8. Flowchart of the program, which measures and stores all interresponse intervals. In the main loop, the program checks the port register, which contains the information regarding FR or CRF reinforcement. When the program registers a response, it reads the time since the last response. This interval is coded, stored in memory, and displayed on the screen in graphic fashion. All data are stored on disk when the testing session is finished by the experimenter or if the memory is full.

stimulation or not. It also displays the total number of responses, the number of responses since the last FR reinforcement, the total number of FR reinforcers, and FR as well as CRF stimulation intensity. Autofading in this experiment is understood as an automated procedure for training behavior under FR schedules of reinforcement by the method of reinforcement fading (Huston, 1968). In this method, training starts with a CRF schedule. The intensity of the reinforcing stimulation following the terminal response in the FR run is kept constant, whereas the intensity of the stimulation presented after all other responses is gradually faded out.

When the autofading option is set on, the CRF stimulus intensity is decreased automatically by the program after the application of every 10th FR reinforcer, while the intensity of the FR reinforcing stimulus is kept constant. If the animal does not stop responding, the CRF intensity is decreased to 0—that is, until the animal performs barpressing behavior under a pure fixed ratio schedule of reinforcement.

Since the capacity of the CBM 3032 is just sufficient to keep the program code for controlling the reinforcement schedule, the IRIs are measured and stored with a second computer. In each test session, it is necessary to measure all IRIs in order to decide whether or not the IRI following FR reinforcement is taken as a PRP. In the sample experiment, an IRI is counted as a PRP if it appears between FR reinforcement and the third response following FR reinforcement and if it is longer in duration than 95% of all IRIs since the last PRP. The PRP itself is taken

as an index for changeover in schedule control; as long as the animal does not show PRPs, its behavior is under the control of the CRF schedule of reinforcement. The time at which PRPs appear is the point when the animal's behavior comes under the control of the FR schedule of reinforcement. With this method, the point of changeover in schedule control is defined as "threshold of reinforcement." Figure 8 shows a flow chart of the program, which measures all interresponse intervals.

In the init module, the display mode of the C-64 is switched to graphics display, the user ports data-direction register is set on INPUT, and both CIAs are switched to 50 Hz (otherwise the clock would run too fast).

In the main loop, the port register is checked for events. The three possible events are: application of a CRF reinforcer, application of an FR reinforcer, and end-of-session button pressed by experimenter. The only exit from this loop is the end-of-session button or full memory. If any kind of response is registered, the hardware registers, which contain minutes, seconds, and tenths of seconds, are read and set to 0, so that they contain the actual duration of interresponse interval when the bar is pressed the next time.

In the code and pack module, the information concerning the event and duration of IRI is packed in the following way:

EASS SSSS MMMM TTTT

Each letter represents one bit and can have one of two values. Bit E contains the information about the event (FR

or CRF). Bit A was used in another experiment in which stimulation was presented only in one LH and 2 animals were run simultaneously (Buscher et al., 1990). It contained the information of whether Animal 1 or 2 pressed the lever. This bit has no meaning in the present experiment, since only 1 animal was tested per session. The following 6 bits (S) contain the seconds. The high nibble of the second byte contains the minutes (M) and the low nibble contains the tenths of seconds (T). These two bytes of information can represent a maximum interresponse interval of 16 min and 1 sec (15 min + 60 sec + $10 \times .10$ sec). In the next module, the information is stored in memory and the memory pointer is increased. If the memory is full, the program stops and saves the data automatically; otherwise, the routine, which displays the IRIs on the graphics screen, is called.

In the save data module, the complete memory block containing the data is stored on disk. When the routine is finished, the system-reset routine is called, and the program can be started again by calling it with its starting address. Another program is used to decode the coded data on disk for a statistical analysis. This program produces an ASCII file containing all interresponse intervals. This file is ready for processing by other programs. Three programs are needed to run the sample experiment: one for controlling the reinforcement schedule, one for measuring the IRIs, and one for preparing the saved data for statistical analysis. The source code of these programs is available from the authors on request. If the measurement of IRIs is not required for a given experiment, the second computer can be omitted.

The price for the complete system is about \$1,200—about \$600 for the constant-current generator, including power supply and interface, and about \$300 per home computer with disk drive. If it is not necessary to measure and store all IRIs, the system can be controlled with one computer, since the only reason for integrating the

second computer was the limited RAM capacity of the CBM 3032 (32K). The current generator can be controlled by any other computer (e.g., an IBM-compatible computer) that has at least 48 I/O channels. Control over the stimulus parameters is achieved by manipulating single bits of the interface as described above. If a fast machine (10 MHz or more) is available, and if no more than 2 animals are to be tested at the same time, there is no need to write the programs in machine language.

When the system is installed—when routines are developed for controlling the current generator—it can be used for controlling most kinds of reinforcement schedules. If all IRIs are measured by the system, the user has access to much more information than simple cumulative recorders can provide, allowing a sophisticated analysis of behavior controlled by different kinds of reinforcement schedules.

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