Digital Computers in the Biological Laboratory

Computer processing of data during experiments facilitates biological research.

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The digital computer has a new and vital role to play in the biological laboratory when used to acquire data during the course of an experiment. In studies on animals or excised tissue the computer may program stimuli, detect and measure responses, store data, analyze and make calculations, display the results on a cathode-ray oscilloscope, or plot the graph on an X-Y recorder. The complexity of neurophysiological investigations and the precision of measurements made during them may thus be greatly extended. The data are analyzed during the course of the experiment, and results of the analysis are available to the experimenter within minutes, not weeks or months later, as with some methods of analysis. The biologist is alerted to novel and emergent phenomena when they occur. The use of a computer permits exploitation of opportunities; the whole procedure of an experiment may be changed with the flick of a switch.

A schematic representation of a computer-equipped biological laboratory developed by H. K. Hartline and his associates at the Rockefeller Institute for experiments on vision (*1*) is shown in Fig. 1. The presentation of stimuli and the collection of data are automated. The pattern and sequence of light stimuli are set by the experimenter on a digital programmer. The stimuli are then presented automatically during the experiment. The time intervals between nerve impulses are stored in the "memory" of a Control Data Corporation 160-A computer as they occur.

Up to 500 nerve impulses from each of three fibers can be timed simultaneously with a precision of 0.1 millisecond. The computer not only times the nerve impulses as they occur, it performs the required calculations, gives an immediate display of the results, and records the data on paper tape. In this form the data are accessible for later, more complete computer analysis.

The purpose of this article is to study the requirements for use of a digital computer as a valuable adjunct to analytical instruments used in the laboratory and also as an "on-line" instrument in biological experiments—that is, an instrument used in the course of the experiment.

An example of the use of the computer as an analytical instrument in the laboratory is its use for analyzing the output of the detector of an optical spectrophotometer. The ouput of the spectrophotometer may be recorded on punched paper or magnetic tape. The wavelength-dependence of the detector, recorded in the form of a table of measured values, may be fed into the computer. The data of a particular sample run may then be processed and the corrected spectrum plotted, all within a few minutes. Extensive calculations can be performed, and the analyzed results can be tabulated or plotted. No hand measurements or calculations are necessary. A single digital computer can be used as an adjunct to many different analytical instruments. Computer techniques have been used for data collection and processing in optical spectroscopy (*2*), gas-liquid chromatography, radioactive tracer measurements (*3*), x-ray dosimetry (*4*), nuclear pulse-height spectrometry (*5*), and for a number of other applications (*6*).

The digital computer is an ideal device for simulating biological and chemical systems (*7*). An instrument with a cathode-ray tube or an X-Y recorder display under computer control is advantageous for heuristic studies of mathematical models. It is possible also to combine analog with digital computer elements to permit hybrid computation (*8*). The capability of a small digital machine may be greatly extended by such techniques. Moreover, computer models of a physical process may be connected with isolated parts of the system for studying the adequacy of the model in action. This method has been used with analog computers for designing process-control mechanisms and clinical instruments. It was used to design a device for servo anesthesia in which the rate of drug injection during surgery is controlled by the measured characteristics of brain waves (*9*). Digital-computer simulation has been employed to study chemical kinetics (*3*), to study respiratory and circulatory dynamics (*10*), and to formulate statistical models of neuroelectric data (*11*).

For "on-line" use of the computer, digital techniques are particularly advantageous and justify their cost when the power and speed of the computer significantly enhances the experimental possibilities. It is possible, for example, to study the amplitude and the time of occurrence of bioelectric waveforms simultaneously, or to combine measurement with servo control of stimulus parameters (*8*).

When an analog-to-digital converter is used, sampled values of continuous voltages may be obtained in the digital form required by the computer. One may study the amplitudes of a number of simultaneous voltages by means of a "multiplexing" technique. The different voltages are sampled sequentially at a high enough rate so that the numerical samples taken represent each waveform accurately. This digital technique provides greatly increased resolution in the measurement of simultaneous biological events.

Computer facilities make it possible to control the experimental procedure on the basis of an ongoing analysis of the measured data. A computer may be programmed to adjust the intensity of the stimulus in accordance with the measured amplitude of response. The stimulus amplitude may be adjusted

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continuously to equal the threshold of response. Fluctuations in the threshold level may be measured concurrently by recording the stimulus amplitude. A computer may function as an adaptive process controller. The parameters of the control function, built into the computer program, accommodate different response modes of the system studied and are changed automatically to compensate for qualitative changes in the response.

In order that a digital computer may be used as an "on-line" instrument in the laboratory, a separate device or "interface" must be built so that the electronic system of the computer will be compatible with other equipment. The voltage and power levels of amplifiers, stimulators, and controllers in the laboratory must be made compatible with the voltage and power levels of the computer circuits. Usually the interface equipment also includes an analog-to-digital converter, a multiplexer, and one or more digital-to-analog converters. The analog-to-digital converter produces digitally coded samples of continuous (analog) electrical signals, such as those measured in biological preparations. The multiplexer allows the analog-to-digital converter to sample a number of different analog voltage sources sequentially, or as required by the computer program. The digital-to-analog converters produce continuous voltages for control purposes, voltages such as are necessary to generate an oscilloscope display. Each piece of equipment must be made compatible with the computer circuits.

In order to understand these requirements, a knowledge of the main aspects of computer structure and function is needed (Fig. 2). For a discussion of such structure and function, which is beyond the scope of this article, see chapter 2 of *Digital Computer and Control Engineering*, by Ledley (see *12*).

We begin our discussion with consideration of the input-output facilities needed for a laboratory computer as compared with other computers. Next we discuss the analog-to-digital and the digital-to-analog conversion processes in relation to the precision, rate, and speed of sampling of the signal waveforms being processed. Finally we consider the cost and availability of equipment and the advantages and disadvantages for biological work of instruments and installations of various kinds.

Input-Output Requirements

A computer used in extensive scientific or business computations requires a large memory capacity. It must be designed to perform multiplication, division, and logical operations rapidly. The registers and basic machine cycle must accommodate a word of large size in order to perform arithmetical

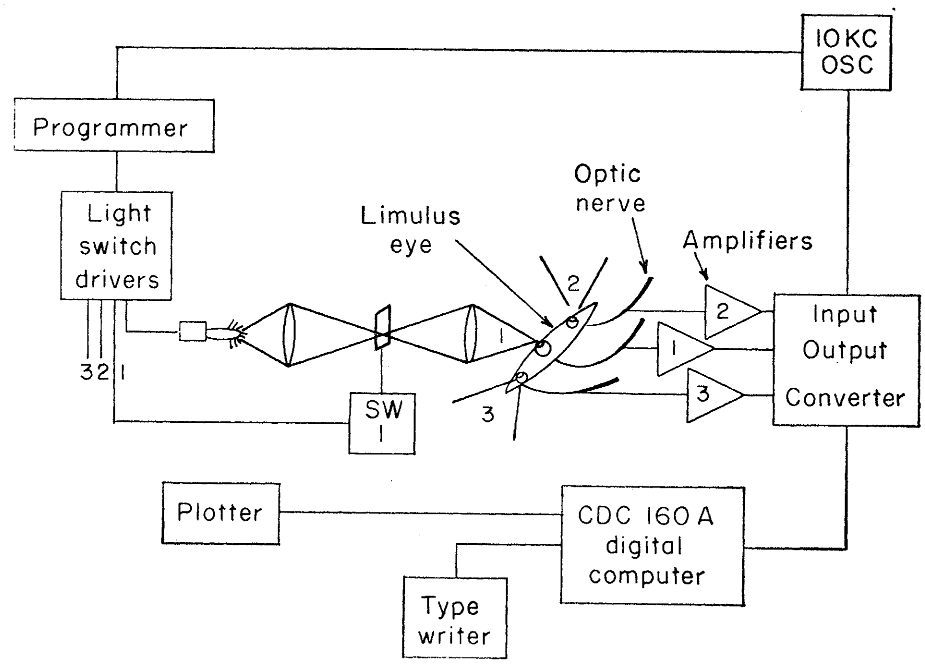

Fig. 1. Laboratory setup for research in vision. Three switched light beams are directed onto separate facets of the eye of *Limulus* (the horseshoe crab). Nerve impulses in associated fibers are picked up, amplified, and timed. The times of occurrence of the impulses are stored in the memory of a Control Data Corporation (CDC 160-A) computer during the course of the experiment. The processed data may be plotted or typed.

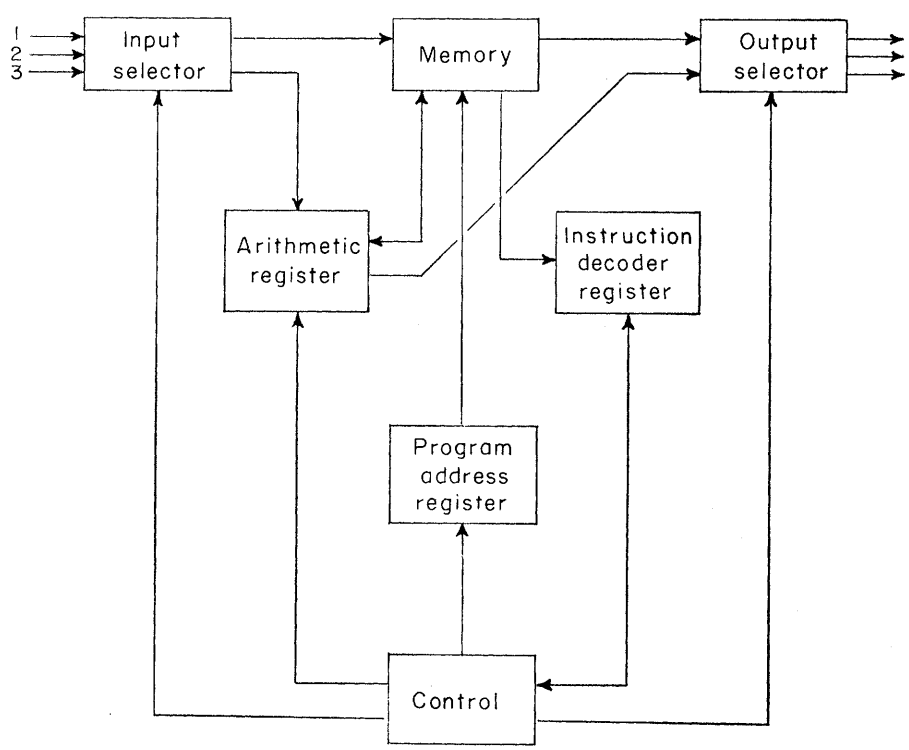

Fig. 2. Block diagram of a computer. Three peripheral devices, labeled 1, 2, and 3, are assumed for input and output. Arrowheads indicate signal flow directions. Arrowheads on both ends of the line indicate two-way flow—for example, between the control and the instruction decoder register and between the memory and the arithmetic register.

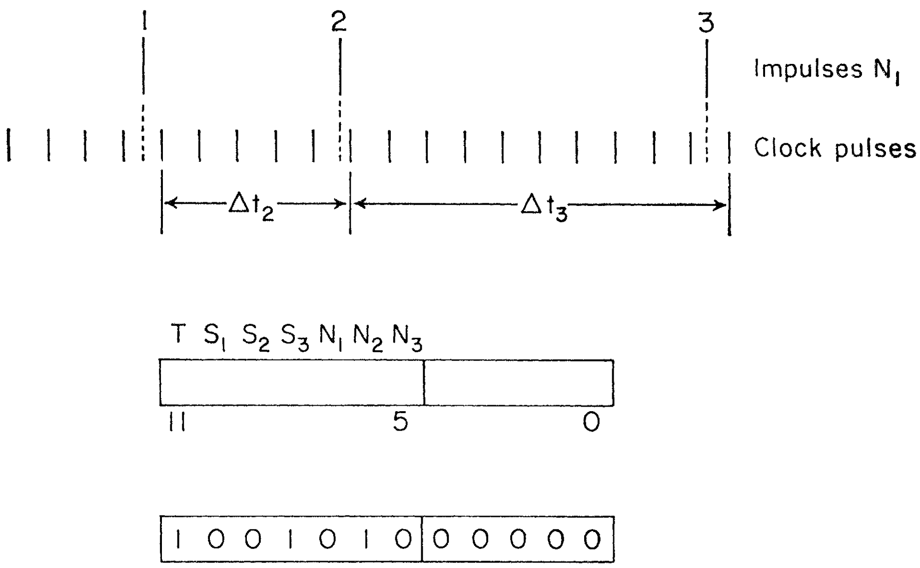

Fig. 3. (Top) Timing of nerve impulses. The time Δt_2 is measured from the clock pulse following nerve impulse 1 to the clock pulse following nerve impulse 2. (Middle) The makeup of the word register sampled by the computer. The bit labeled 0 is the 12th bit. Tag T is bit 11, signifying the start or end of the run. S_1, S_2, or S_3 are bits 10, 9, or 8, signifying the start or end of the light stimulus. N_1, N_2, or N_3 are bits 7, 6, or 5 signifying the occurrence of a nerve impulse. (Bottom) A binary word taken into the computer. The run has just started or ended. Stimulus S_3 has changed, and a nerve impulse has occurred in fiber 2.

calculation to an accuracy of ten or more decimal places. Requirements of this kind are much less severe for a computer used in the biological laboratory. The memory capacity can be relatively small, and an arithmetical accuracy to three decimal places is usually sufficient. The maximum word length may be of the order of 12 bits.

The data processed for bookkeeping and accounting purposes must be prepared in a form consistent with business needs. For example, magnetic-ink character readers are required in computers used by banks to process checks. Equipment such as typewriters, line printers, and punch-card readers is needed in computers used for commercial and general scientific work. These features are not essential for "on-line" work in the biological laboratory. On the other hand the computer used in the biological laboratory requires special input-output equipment not needed in these other machines. Devices for analog-to-digital conversion and for accommodation of a variety of electrical signals are also needed.

The required speed of input-output operations for business purposes is much lower than the speed of the internal cycle of the computer. The modern computer can read a single instruction from memory and execute it in 0.25 to 10 microseconds. On the other hand, it can read a single character from a typewriter, or "write" a character on a typewriter, in about 0.1 second. It can read an 8-bit character from devices such as line printers, punched paper tape, and punch-card handlers in from 1 to 10 milliseconds. It can read a 7- to 9-bit character from magnetic tape in 10 to 100 microseconds, depending on the tape speed and the density of character packing, and it can "write" an 8-bit character on magnetic tape in the same time. However, the entire exchange between the magnetic tape and the computer may take many seconds or minutes. The tape unit must reach operating speed, and the proper area, which may be at the end of the tape, must be located. Because of these time relationships it is efficient, for business purposes, to feed into the computer memory, or print out, words in large blocks rather than individual words.

In biological applications, however, it is desirable that the computer be able to feed one word at a time from a selected peripheral device into a specified memory location or arithmetic register at a rate compatible with the maximum rate at which the biological data can occur. The input rate can be made comparable to the rate of the basic computer cycle. If this is done, external signals may be sampled at very high rates to permit resolution of rapidly changing signals, or a number of slowly varying signals may be sampled sequentially by means of a multiplexer. In this way the computer may be used both to time events and to process the data in the intervals between the taking of samples.

An example is the use, by H. K. Hartline and his associates, of the Control Data Corporation 160-A computer to time nerve impulses (*1*). The occurrence of a stimulus or nerve impulse is stored in a one-word register in the input-output converter. The contents of this register are taken into the computer every 100 microseconds synchronously with pulses from a 10-kilocycle oscillator (Fig. 1). In the intervals between clock pulses the contents of the register are examined and the computer adds 1 unit to a time count. When a nerve impulse occurs, the time count and the identification are stored in the memory.

Each of the 12 binary places in the one-word register (Fig. 3, middle) is assigned a different significance. The lowest five places, or bits, are not used. The highest bit, T, is assigned a significance of "1" ("1" signifies the occurrence of an event) during the 100-microsecond interval following the start and following the end of the run. All clocked events, such as the start and end of the run and the light stimuli, are signaled to the computer exactly 100 microseconds after they occur. Asynchronous events such as nerve impulses are signaled to the computer at the next 100-microsecond clock pulse which follows their occurrence. The next lower three bits (S_1, S_2, and S_3) are used for signaling the onset or termination of light stimuli, and the next lower three bits (N_1, N_2, and N_3) are used for identifying the occurrence of nerve impulses. After the computer feeds the word into the arithmetic register, tests are made to determine whether or not the word has a significance of zero or whether bit 11 is "1" (the program starts and ends with the bit-11 identification). If the word is zero, the computer adds 1 unit to the time count and waits. When any one of bits 5 through 10 is "1," signifying the occurrence of an event, the identifying word and the time increment are stored in two separate lists in the memory, with correlated addresses. The time count is reset to zero, and the computer waits for the next input. All these tasks are accomplished in the 100-microsecond intervals between clock pulses. This computer program requires 14 computer cycles of 6.4 microseconds each. Another 4 or 5 microseconds are required for the exchange of control signals with the peripheral equipment. The 100-microsecond interval between clock pulses is ample for completion of the program.

Input-output operations such as those described may be carried out while the main computation cycle is in operation, if additional control circuits are used. With this type of equipment, words representing data may be taken into or sent out of one part of the memory automatically, independently of the main program, which is operating at the same time. This is called a buffer operation, and the equipment is called a buffer channel. A number of buffered channels are provided in very large machines.

Fast buffered operations considerably extend the computer's versatility and capacity. If the average rate of calculation and output exceeds the average rate of input and the fluctuations in input rate are not too severe, there is no limit to the number of data that can be processed. The results are not stored in the computer memory but are displayed, recorded, or stored on another medium, such as magnetic tape.

For example, a list of data may be used in a buffered output to provide an oscilloscope display during an experiment while new data are being taken into the computer. The time of occurrence of nerve impulses, registered on an external timer, may be taken into the computer memory through a buffered channel while the amplitudes of signals of slow potential are being sampled in another channel. Alternatively, two separate inputs may be taken in over the same path and the words representing the separate data sources put in successive alternating memory locations. In the continuous buffered mode, data are entered in sequential locations, in a prescribed section of the memory. After the last address in this memory section has been filled it is possible to repeat the buffer operation. Meanwhile the computer has worked on the data, so that the calculation and output process can be kept ahead of the storage of new data.

Analog-to-Digital Conversion

Signals measured in the laboratory vary continuously over a range of amplitudes. Such analog voltages must be converted into the digital language of the computer (*13*). They must be represented by discrete numbers signifying the amplitude by quantum steps. Conversely, the digital words or binary numbers treated within the computer must often be converted into continuously varying signals for control and display purposes in electronic equipment external to the computer.

Many problems are encountered in converting voltages to a digital form. The relative difficulty of the conversion depends on the time duration of the signal and the amplitude resolution needed. If statistical calculations are to be performed on an ensemble of voltages, the requirements may be more severe than if one signal is to be processed. In other applications it may be desirable to study the details of a single waveform such as that shown in Fig. 4 (top). The pulse may be a mammalian compound action potential of 1-millisecond duration. Alternatively, the signal may originate from a gamma-ray detector and be extremely rapid, with a duration of 1 microsecond. In this case the computer may be used to obtain amplitude statistics on the height of the main peak by

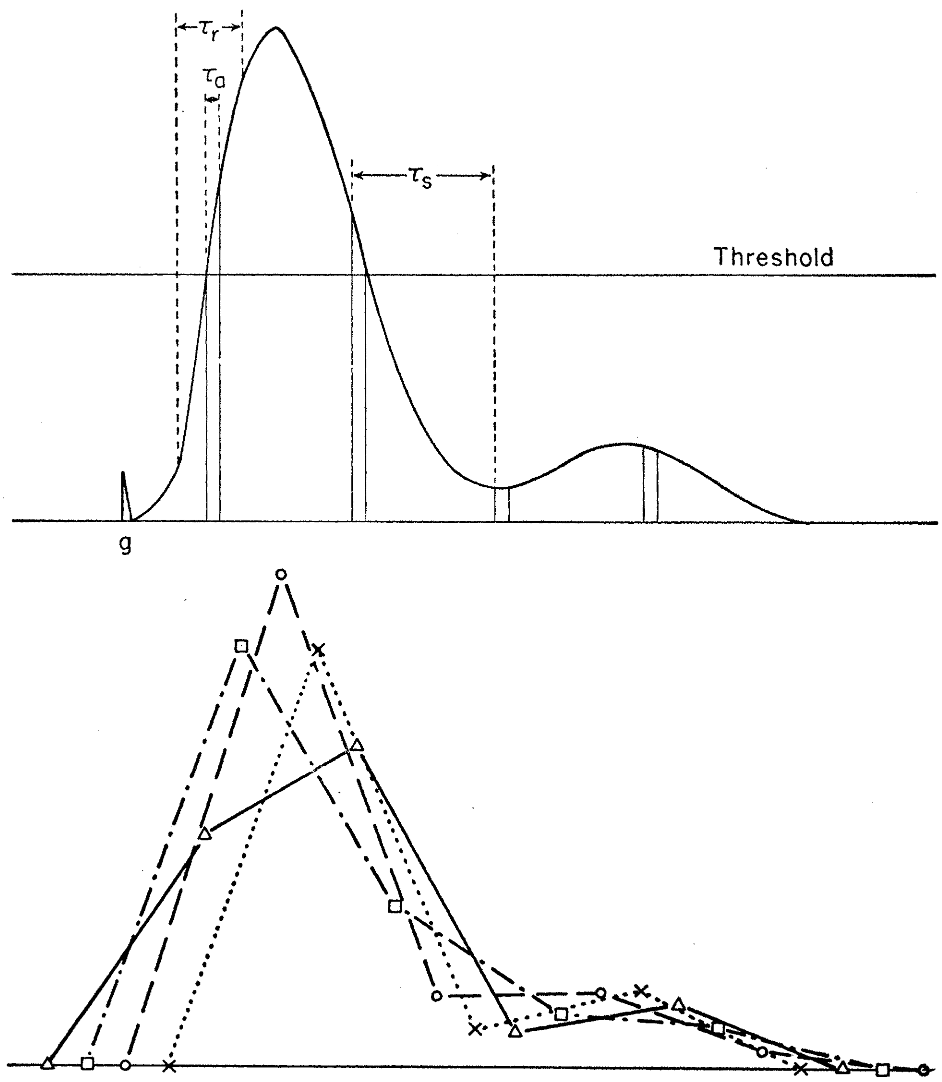

Fig. 4. (top) Bioelectric waveform evoked by a stimulus *g*. The peak amplitude exceeds a threshold indicated by the horizontal line. Pairs of solid vertical lines indicate times when samples are taken. τ_a, Duration of sampling, or aperture time; τ_s, time between beginnings of times of sampling, or sampling period; τ_r, time from 10 percent to 90 percent of maximum amplitude, or rise time. (Bottom) Waveforms formed by sampling the signal of waveform *a* at the indicated rate and interpolating between the sampled values. Different waveforms are formed by varying the phase of the samples with respect to the signal.

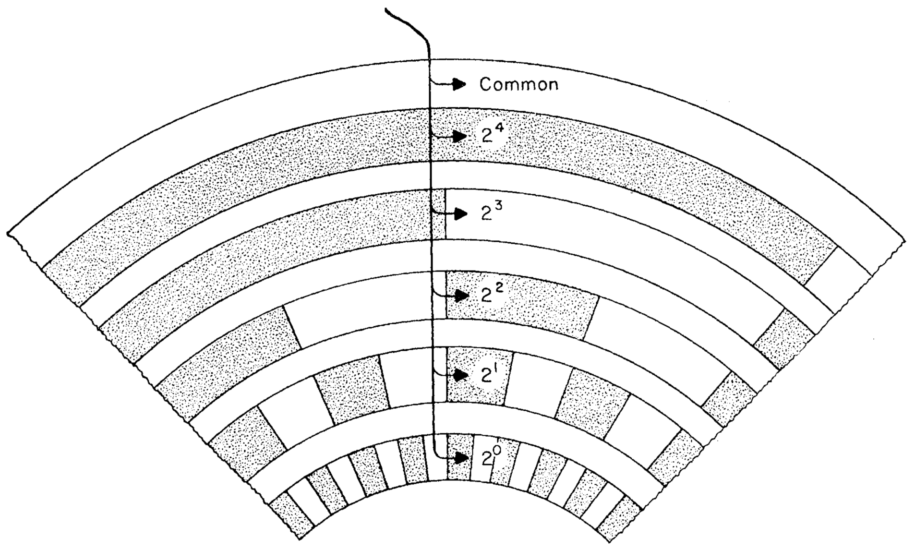

Fig. 5. A section of a shaft encoder. Arrows indicate brushes. The angular displacement of the brushes from the left edge is represented by a binary code in terms of conductive regions, shown in white. When the brushes are in the position shown, the code is 01000 and the brush labeled 2^3 is connected to the common, closing an external circuit. The "1's" in the code are represented by using the closed circuit to supply a voltage to the computer.

measuring many similar pulses. The pulse may be a 1-second portion of spontaneous variations in potential recorded from the surface of the cortex of an animal. The computer may then be used to determine a number of the waveform characteristics, such as the maximum slope and the time interval between peaks and valleys. In each case, both the nature of the waveform and the information sought determine what is to be done.

In measuring the time of occurrence of a nerve impulse, one wishes to know whether or not an amplitude threshold has been exceeded during a particular time interval. In Fig. 4 (top) the threshold exceeds the second peak. A comparator circuit is used to generate a signal when the threshold is passed. This signal may be used to store a single binary bit in a word register of a computer, as discussed in connection with Fig. 3. In effect, one has an analog-to-digital conversion with an amplitude resolution of 1 binary bit; that is, the amplitude of the signal is greater or less than that of the threshold.

Alternatively, one may wish to store a replica of the wave in the computer memory by taking successive amplitude samples of finer resolution. In Fig. 4, it may be seen that a rough estimate (bottom) of the characteristics of the waveform (top) can be obtained by interpolating amplitudes between four evenly spaced samples taken in arbitrary phase relation to the signal. The original voltage will be reproduced almost exactly if the number of samples is large enough. The maximum fractional error in estimating the amplitudes of the waveform will occur if the peak falls halfway between two sampling periods, indicated in Fig. 4 (top). The rate of rise during τ_r (see legend to Fig. 4), is approximately $1/\tau_r$. The time difference between the nearest sampling period and the peak is $\tau_s/2$, where τ_s is the time between beginnings of times of sampling. Therefore, the fractional error will be the product of this time difference and the rate of rise $\tau_s/2\tau_r$. A number of other formulas have been given for the sampling error (*13*). None of these should be taken too seriously; they give a rough estimate of the number of samples needed to reproduce a waveform to a specified accuracy.

However, even if the amplitude of the peak is sampled as it occurs, an error is implicit in the process of converting the amplitude to a digital form. For example, the amplitude might be given by numbers from 1 to 100. Peak amplitudes between any two integer values will be represented by the smaller number, so the error may be as much as 1 part in a hundred. For an analog-to-digital conversion in which the amplitude is represented by a binary number of n bits, the maximum possible error is $1/2n$.

A computer may be used to enhance signal amplitudes with respect to noise by an averaging technique. This method is effective if the signal, like that of Fig. 4 (top), has a fixed time relation to a stimulus g. For example, the waveform may be a cortical potential evoked by an auditory signal. It may be obscured by spontaneous fluctuations in potential from other parts of the brain and by noise from the amplifier. Since the signal amplitudes in successive runs are the same function of time in relation to the stimulus, the number stored at the address representing each sampling time is proportional to the product of the signal amplitude and the number of runs that have been made. On the other hand, it can be shown that the amplitude of the noise at each sampling point is proportional to the square root of the number of trials (*14*). Hence the ratio of the signal to the noise amplitudes increases as the square root of the number of trials.

In this application the aperture time τ_a (see Fig. 4, top) of the sample should be short compared to the interval between the beginnings of sampling periods, τ_s. The maximum error caused by the duration of sampling, τ_a, is

$$\frac{\tau_a}{2}/\tau_r.$$

If the number of runs over which data are averaged is N, the fractional uncertainty in the sum of signal amplitudes due to τ_a is

$$\frac{\tau_a N}{2}/\tau_r.$$

In each case the ratio of the average value for summed signal amplitudes to the noise is proportional to $N^{\frac{1}{2}}$. It may be seen that, as the number of trials increases, the effect of the error due to τ_a increases proportionately. No relative advantage occurs as with the ratio of signal to noise. The effectiveness of the averaging technique is thus critically dependent on the size of the error due to τ_a.

A number of conversion methods and circuit techniques have been evolved, dictated by the resolution, sampling speed, and computational purpose desired in different applications. In analytical instruments such as amino-acid analyzers or analyzers in gas-liquid chromatography, the analog signal is represented by the shaft position of a slide-wire potentiometer with a response time of the order of 1 second. One may encode the shaft position by arranging conductive bars or slots on a disk or cylinder mounted on the shaft (Fig. 5). Brushes or photocells in a fixed position with respect to the rotating member may signal the binary representation of the angular position. The encoding can be done in such a way as to effect a nonlinear transformation of the analog signal represented by the shaft position. For example, the coding may be the digital representation of the logarithm of a photocell voltage, to represent optical density. The rate of data acquisition is slow enough to permit storage of the encoded data on magnetic tape or storage through punching on paper tape or cards before the data enter the computer.

In nuclear pulse-height spectroscopy the essential requirement is that the error in pulse-height quantization be the same from the lowest to the highest pulse in order that statistically meaningful pulse-height frequency distributions may be obtained (*5*). In this case the peak of a 1-microsecond pulse is stretched, through storage on a capacitor, for as long as is necessary for the performance of an analog-to-digital conversion (Fig. 6). Crystal-controlled clock pulses are counted in a binary counter at the same time that a linear sweep is generated. The coincidence of the rising sweep voltage and the stretched pulse is detected by a comparator, and the count in the counter, proportional to the amplitude, is registered. The amplitude resolution of this system has high differential linearity over the whole range of pulse heights because it is determined by the high attainable stability of the clock frequency and the linearity of the sweep generator. However, the system requires 43 microseconds to achieve an amplitude resolution of seven bits if a 3-megacycle clock oscillator is used. The comparator must change state in less than one clock interval for a signal 1/128 full scale.

This system is not adequate for resolving nerve action potentials, which may have a duration of 1 millisecond and a rise time of 100 microseconds. According to the sampling-error formula given earlier, for a 10-percent sampling error the sampling time must be 20 microseconds.

On the other hand, generator potentials in visual receptor cells may have rise times of 10 to 20 milliseconds, and they can be encoded in such a way that a sampling error of 10 percent is obtained with sampling times of 0.5 to 1 millisecond. However, when brain waves with comparable rates of rise are evoked in relation to a stimulus, 100 trials may be required for averaging. The required aperture time may then have to be 50 to 100 microseconds within the longer sampling period. If ten different signals are to be represented, by sampling the various sources sequentially, the equipment must make the conversion 10 times faster, even though the sampling requirements with respect to each source are unchanged.

A sample-and-hold circuit is needed for sampling the signal during a short aperture time and for allowing the converter to make a conversion during the relatively longer hold time. To achieve higher speeds of conversion, methods of successive approximation or simultaneous parallel quantization are used (*15*). With these methods sampling times can be very short, permitting reproduction of waveforms with rapid rates of change, and simpler and more effective sample-and-hold circuits can be used, because the required hold time is relatively short.

In these methods the signal voltage is compared with an analog voltage produced bit by bit from the binary number stored in the conversion register. In Fig. 7, in which a six-bit binary number is assumed, the signal is first compared with a voltage proportional to the most significant bit, or 2^5. Since the signal voltage is less than that derived from the register, the entire signal is compared with that of the next most significant bit, or 2^4. The signal exceeds this voltage, so this bit in the register is set, and the difference voltage d_1 (see Fig. 7) is applied to the voltage of the next bit, 2^3. Since the voltage d_1 exceeds the 2^3 voltage, the third bit is set, and the difference voltage d_2 is produced. As the process continues the second bit is set, but the difference d_3 is too small to set either of the two least-significant bits. The number proportional to the peak amplitude is thus 011100, the fractional error in this number being d_3 divided by 64.

The successive-approximation method is carried out sequentially, synchronously with clock pulses. The most significant bit register is first set. A voltage is produced which is half the maximum voltage. This voltage, which corresponds to that of 2^5 in Fig. 7, is compared with the input. The register is reset if the input voltage is less than half the maximum voltage. The original voltage or the difference between the original voltage and the voltage of the register corresponding to the 2^5 amplitude is applied to the next stage, and the process is repeated. Each step is initiated by a clock pulse. In the parallel-quantization method the entire system of successive comparisons is allowed to take place at once, and the system comes to equilibrium as rapidly as the circuits can react. The parallel system can perform a conversion more rapidly, but it requires more complex circuitry.

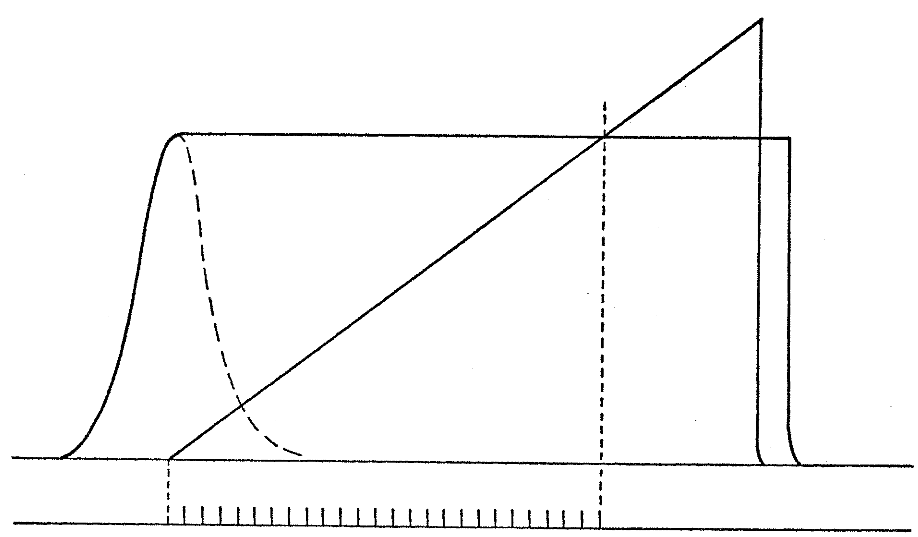

Fig. 6. The linear-sweep method of analog-to-digital conversion. (Top section) The sweep (diagonal line) is started coincident with the time of occurrence of the pulse peak. The maximum height is maintained until after the sweep terminates. (Bottom section) Clock pulses are allowed to enter a counter during the sweep voltage until the counter reaches a number proportional to the stretched pulse height.

Analog-to-digital converters which use the methods discussed above are available at prices ranging upward from \$3000. The time required for the complete conversion may be as little as 3 microseconds or as much as 100; resolution is 8 to 12 bits, and aperture times are 0.1 to 1 microsecond. The circuits of commercial equipment embody a number of variants of the basic techniques discussed.

Technique and Equipment

A special-purpose computer was developed for pulse-height analysis in nuclear physics as early as 1951 (*16*). This instrument combines a computer memory with the analog-to-digital converter discussed in the preceding section. The same basic instrument has recently been adapted for averaging evoked biological potentials (*17*) and for signal enhancement relative to the noise in nuclear magnetic resonance measurements (*14*). In another mode of operation the system can be used to obtain pulse-interval histograms (*17*). The equipment is comparable in size and complexity to a large cathode-ray oscilloscope and costs about \$10,000. An oscilloscope display and either a printed or a punched-paper-tape record are usually provided with the instrument. The device is an extremely clever and relatively inexpensive digital computer. However, it is not a general-purpose computer. It has no capability for storing a program and, as a result, has the relatively fixed range of possible applications mentioned above.

Figure 8 is a schematic diagram of this computer system; the three applications are indicated by switches *C1*, *C2*, and *C3*. With the ganged switch in position 1, the computer is used for averaging responses. Data are taken for an ensemble of signals such as are shown in Fig. 4 (top), each with the same time course. The run is started by a stimulus *g*, which initiates a train of sampling pulses, each of which advances the address scaler by one count. Thus, the address identifies the sampling time with respect to the stimulus. During a particular sampling interval, the word in the memory, addressed by the scaler, is placed in the arithmetic unit. The amplitude of the input signal is sampled, and a number is added to the datum word by accumulating clock pulses proportional to the signal amplitude. The augmented datum word is returned to the original memory address. This process is carried out for every sampling pulse, and the run is repeated as many times as necessary to obtain the ensemble average. A display of the averaged signal amplitudes *Y*, versus the time of sampling *X*, is seen on the screen of the cathode-ray oscilloscope while data are being accumulated. The display may be repeated after the runs are finished.

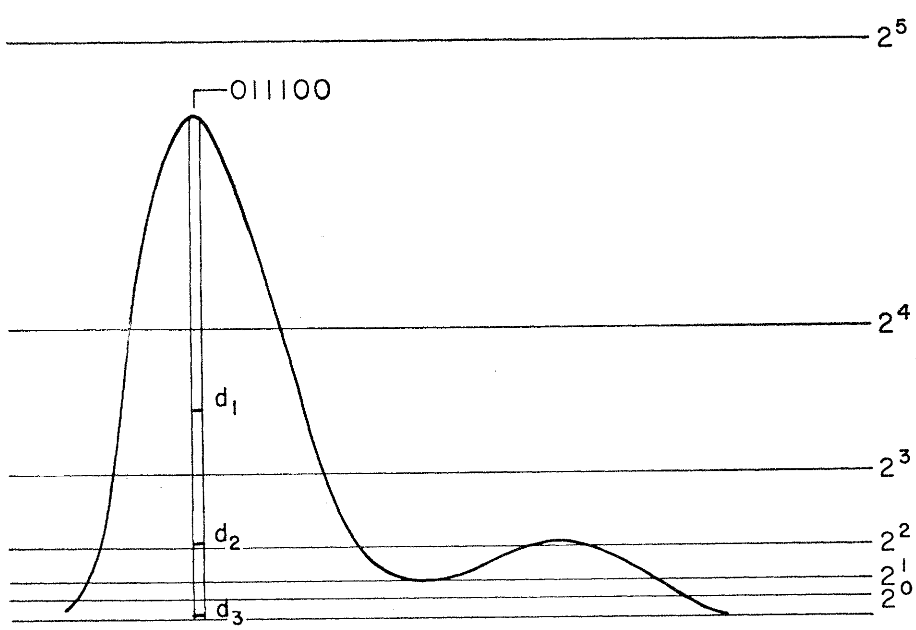

Fig. 7. Comparison of the pulse peak amplitude with voltage derived from a binary register. Maximum voltage for the most significant bit is shown by the horizontal line 2^5. Half maximum voltage is shown by line 2^4. Each horizontal line represents a voltage half that for the line above it. The peak is less than 2^5 but greater than 2^4. The difference d_1 between the peak and the 2^4 voltage is greater than 2^3, producing the difference d_2 which exceeds 2^2 by the difference d_3 (d_1, d_2, and d_3 are all measured from the bottom line). The resulting binary value 011100 is indicated at the peak.

Switch position 2 (Fig. 8) indicates the setup for measuring pulse-interval histograms. The occurrence of the first nerve impulse is sensed by a comparator, which is an analog-to-digital converter with resolution of one bit. The address scaler is reset to zero, and a train of accurately timed clock pulses is allowed to enter the scaler. When a second nerve impulse occurs, the clock pulses stop. The count in the scaler is proportional to the time interval between nerve impulses. The memory word addressed by this count is read into the arithmetic unit, is increased by one bit, and is then placed back in the same memory location. The address scaler is reset to zero, and the operation is repeated. In this application the histogram of the number of pulses *Y*, versus the pulse interval *X*, is displayed on the cathode-ray oscilloscope. A separately clocked run, after accumulation of the data, is required for the display.

In the third mode of operation the system measures the frequency distribution of the height of an ensemble of pulses. The pulse-height analysis is made by means of the method of Fig. 6. The run is started with the detection of the pulse. The address scaler is reset to zero, and a train of clock pulses is allowed to accumulate in it until the linear-sweep voltage reaches the height of the stretched pulse. The amplitude of the pulse is now represented by the count. The memory word addressed by the scaler is read into the arithmetic unit, one bit is added to it, and the word is stored back in the same memory location. After the statistics for the ensemble have been measured, a separately clocked run is made to display the data on the cathode-ray oscilloscope. The number of pulses in each amplitude increment *Y* is plotted against the pulse-height amplitude *X*.

This system has different requirements and limitations for different applications. For nuclear spectroscopy, the differential linearity of the analog-to-digital conversion is most important. Speed is a decisive factor for resolving bursts of impulses from a nuclear particle accelerator. Previous equipment required about 50 microseconds per pulse (*16*). The newest equipment, in which thin magnetic-film memories with a memory cycle of 0.01 microsecond are used, can record the pulse height within 0.1 to 1 microsecond (*18*). On the other hand, the average response computer requires about 50 microseconds to obtain each amplitude sample, so that 20 milliseconds are required to store data in 400 addresses. Only relatively low-frequency signals can be processed because of the inherently large τ_a error of this system, unless a sample-and-hold circuit is used.

A number of small general-purpose computers, ranging in price from $30,000 to several hundred thousand dollars, may be adapted for use in the biological laboratory. Provision must be made for the input and output of digital data at speeds comparable to the fundamental cycle of operations of the computer. A number of small computers also have buffered input-output channels. The Digital Equipment Corporation markets a computer (PDP-5) which is available with a built-in analog-to-digital and digital-to-analog converter, together with an oscilloscope display, for $41,000. In most other cases the user must buy or adapt special conversion equipment and logic circuits in order to use a commercial computer for work in the biology laboratory. Typically, such an "interface" costs between $10,000 and $50,000, depending on the equipment included.

The Linc computer (*19*), a general-purpose machine for biological research, has been developed at the Massachusetts Institute of Technology under National Institutes of Health sponsorship. It can be manufactured and assembled for about $30,000. The Linc is a stored-program machine and, in contrast to the special-purpose, average-response computer discussed above, requires knowledge of programming and coding techniques for its operation. The Linc includes a built-in analog-to-digital converter as well as oscilloscope display and output signals in both digital and analog form. Up to 16 different analog sources may be sampled on instruction from the computer. The same number of channels is available for sensing external events and for synchronizing the machine with them. The necessary instrumentation is incorporated directly into the program structure of the machine. Dual digital magnetic tape units of unique design permit simultaneous storage of a large program library and large amounts of data, but access time is relatively long.

The Linc has the versatility and speed of a much more expensive machine. The major limitations are the small word length (12 bits) and the small memory capacity (1024 addressable locations). The length of data runs that can be made in the course of an experiment is restricted by the memory capacity. The small word length increases the difficulty of programming large-scale, complex mathematical calculations and greatly increases the time needed for such calculations. However, the Linc is not intended for such applications; it is intended, rather, for ease of "on-line" data acquisition, for simple computation from the data, for immediate display of the results of calculations, and for analog simulation of models and control of laboratory processes.

It is possible to use a computer-center installation for "on-line" laboratory experimentation. The system set up at Albert Einstein School of Medicine in New York by Josiah Macy, Jr. (*8*), was designed for this purpose. It includes a Control Data Corporation 160-A digital computer, a Dystac analog computer made by Computer Systems, Inc., and interface equipment made by the Packard-Bell Company and Adcom Corporation. Coaxial cables run to a number of different experimental locations, so analog data may be routed to the computer and signals for oscilloscope display may be sent back to the laboratory. The experimenter communicates by telephone with the computer operator. However, the acquisition of experimental data and the display are started and synchronized by high-speed electronic signals. A similar system in which IBM and Burroughs computers are used has been developed by G. D. McCann at California Institute of Technology (*20*).

Large-computer service installations now provide data channels for "on-line" customers using phone lines or radio communication. The large machines made by the International Business Machines Company (IBM) have direct data channels for optional use (*21*). The "interface" equipment discussed, including analog-to-digital converters, multiplexers, and digital-to-analog devices, is also needed. A large computer provides great computational power and speed. However, the use of a large computer facility for "on-line" laboratory work is very expensive.

The biological experiments require high-speed input-output operations and generally cannot share computer time with other experiments. Considerable amounts of computer time are needed. Rates for use of large computers at the service installations range from $250 to $750 an hour.

An alternative approach, widely used, is to store the experimental data in analog form on magnetic tape. Special analog-to-digital conversion equipment is available to convert the analog data to a digital form in which they can be handled by the digital magnetic tape unit of a standard machine (*20*). When the data are in the proper form, all the power and capability of a large computer can be utilized in processing them.

One disadvantage is that the analysis is not available during the course of the experiment. Another is that the

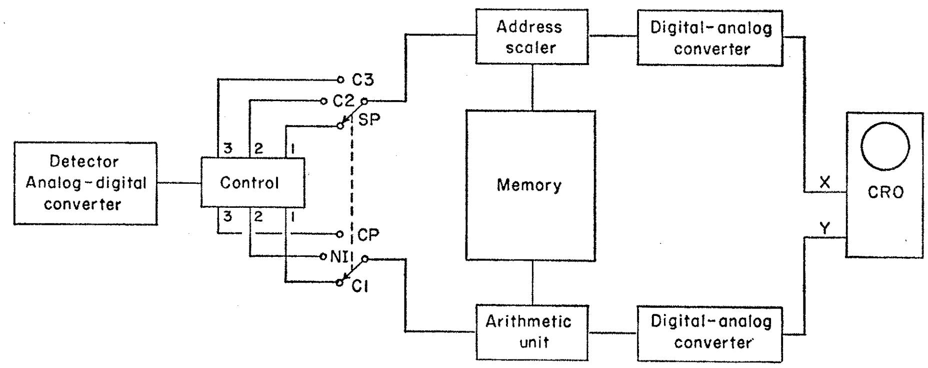

Fig. 8. Schematic representation of a special-purpose computer. The control switch shows three functions. (1) Signal averager. Pulses *SP* initiate sampling of waveform amplitude (see Fig. 4*a*) and increment address scaler. Clock pulses *C1*, proportional in number to the sampled amplitude, are added to the datum addressed. (2) Recorder of pulse-interval statistics. Clock pulses *C2* record time pulse intervals, and the count is stored in the address scaler. Nerve impulse *N1* adds 1 bit to the datum word addressed. (3) Recorder of pulse-height statistics. Clock pulses *C3* give scaler count proportional to peak height. The pulse *CP* adds one bit to the datum word representing the amplitude at that height. *S*, Input signal; *CRO*, cathode ray oscilloscope; *X*, horizontal deflection; *Y*, vertical deflection.

cost of the analog-to-digital magnetic-tape converter is comparable to the cost of a small computer. However, a number of commercial installations can provide the conversion service at rates considerably lower than those for computer time.

Summary and Forecast

The use of digital techniques in the biological laboratory is relatively recent (*22*). At present, computer equipment is extremely expensive by contrast with conventional electronic equipment. However, the costs are decreasing, and these techniques are rapidly becoming more accessible as well as more powerful. Improvement in the fabrication, size, and compactness of solid-state devices promises rapid progress in computer technology of interest to the biologist. Through the use of integrated circuits it will be possible to make general-purpose computers no larger than a laboratory oscilloscope, as compared with the present desk-size console with auxiliary cabinets. Within a decade the speed of computation will increase by an order of magnitude, and the costs will decrease significantly. Moreover, it seems likely that the parts of a computer and the laboratory "interface" will become available as modular units. An experimenter will then be able to assemble the components necessary for a particular application and change them as required. At present, one has to modify commercial equipment for the nonstandard, biological uses. However, with modular building blocks of relatively small size and more reasonable cost the digital computer may become as familiar a laboratory tool tomorrow as the cathode-ray oscilloscope or the spectrophotometer is today.

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Precision Digital Tide Gauge

Vibrating wire pressure transducers provide sea level measurements to the nearest one-tenth millimeter.

Frank E. Snodgrass

Tides were explained by an ancient Chinese writer who wrote, "Water is the blood of the earth and the tides are the beating of its pulse," but long before Newton's theory of gravity, men knew that "the movement of the ocean observes a regular series like a heavenly body, there being a daily, monthly, and yearly movement according to the influence of the moon" (*1*). Following Newton's theory of gravity such great men as Bernoulli, Euler, Laplace, Airy, Kelvin, and George Darwin were prominent in the study of the tides. A detailed theory based on the gravitational attraction of the moon and sun was developed not only for the ocean tides but also the solid earth tides as well. Harmonic analyses of tide data provided a rational method of ocean tide predictions.

For a half century after the work of Darwin, tide gauges were maintained and tide prediction tables were routinely produced, but little was done to further the understanding of the tides. High-speed computers and new electronic instruments have broken this lull. Solution of the tide equations from reasonable approximations of the real ocean basin shapes are being found. Measurement of tides and tide currents are now being made in the deep sea. Tidal charts for an entire ocean basin may soon be produced to tie together the measurements along the coasts. The puzzling problems of tidal dissipation may be solved with greater detail.

The tide gauge described in this paper is one of many new instruments made possible by the reliability of transistors and the precision of digital techniques. The purpose of the recorder is to obtain precise data of sea level fluctuations near shore to accurately describe the tides. Just as a prism and photo cell can determine light's energy spectrum, digital computers can compute the energy at the various frequencies present in the sea level record to determine the sea level spectrum. Sharp lines of energy are found at the various frequencies corresponding to the driving force of the moon and sun to describe the tides. We find, however, that the line spectrum of the ocean tides is superimposed on a continuum of energy due to low-frequency sea level fluctuations. These limit the

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