The same technology which has made the pocket calculator an individual possession now has the potential for providing personal computers which can be used for a variety of functions, including self-instruction. Microprocessors, semiconductor memories, economical mass storage devices, and conventional video monitors are being combined into sophisticated computer systems which can be purchased at reasonable prices, even at neighborhood shopping centers. Although these small computers do not have the capacity and speed of large time-shared macrocomputers, their large numbers and convenient accessibility could have considerable impact on the educational system once instructional programs are available. Furthermore, their portability and ability for rapid interaction between the student and machine can provide compensating advantages over those remote terminals which are tethered by telephone lines and which often have limited communication speeds.

This paper describes how a small digital computer can be used to simulate the classic peripheral nerve demonstration in which the action potential responses to pairs of stimuli are used to illustrate the properties of excitable membranes: local response, summation, threshold, refractory period, accommodation, and anode-break excitation. The simulation involves digital solutions of the Hodgkin and Huxley equations (1) which constitute the explanation universally used in textbooks, so the exercise is no more realistic than this model. Graphic and tabular displays do provide the students with information about how the individual conductances change with time as a result of stimuli, how the ionic currents vary, and that these currents add to change the membrane voltage. A major benefit of this simulation over the frog nerve experiment itself is that the student can gain insight regarding the mechanism commonly proposed to explain the action potential. The hardware is sufficiently flexible that models of other physiological processes can be demonstrated as the software programs are developed.

The Computer System

Personal computers have the general size and appearance of an electric typewriter plus television set, or the remote computer terminals seen in many businesses; however, the microcomputers are complete systems and require only an external source of power. A wide variety of small computers are now available but unfortunately the configuration with optimal features for simulation now requires incorporating components from different manufacturers. This is aided by the popularity of the S-100 bus standard, a scheme where different modules use the same connectors and pin assignments. The appendix describes the configuration the author has assembled for graphic simulation of the spike within ten seconds and also an economical version which is adequate for slower tabular presentations. The balance of the present section discusses some of the equipment considerations involved in implementing the action potential example which is described in the following section.

The central part of the computer contains the microprocessor, power supply, and interfacing circuitry for peripheral devices such as a mass storage unit, video monitor, and printer. Integral components should include a sturdy keyboard and circuitry capable of starting up the programs without special technical skills. Within the computer should be memory storage space for between 16K and 32K characters for programs. Additional special circuits may be advantageous as will be discussed below. The printer is not required for the student to use the computer. Unless program listings are required for software development the printer cost, bulk, noise, and mechanical vulnerability weigh heavily against the small advantage of a permanent copy of the exercises.

Video monitors are quite adequate for both graphic and alphanumeric displays. The computer provides modulated voltages to a television raster according to information stored in the memory. This raster sets the limits of vertical resolution while the monitor responsiveness sets the horizontal resolution. Although many computer hobbyists modify television sets for inexpensive displays, slightly better quality video monitors are recommended for their eye-pleasing contrast and legibility of characters. The lecture room used by the author happened to have several large monitors originally used for video cameras. During lecture the simulation was demonstrated to the whole class, then the computer was moved to the library where the students used it with two small 9 inch monitors.

Many personal computers come with an alphanumeric display capacity of 16 lines of 64 characters which is quite adequate for instructions and tabular simulations. To use this for graphic display of an action potential gives the appearance of plotting by typewriter in that the verticle resolution is limited to 10 mv over the range -120 to +20 mv and time resolution is limited to 0.4 msec over the range 0 to 12. Some computers have graphic capabilities or these may be added; typically, for a resolution of 256 by 256 points, an available feature will be described in the section on graphic simulation of the action potential.

The most economical mass storage medium is the common audio tape cassette upon which program information is coded by an audio frequency signal. Tape recorders are very reliable in the hands of students but the method takes up to 4 minutes to load a program from tape into memory. This is not a serious limitation if one exercise is to be used for an extended period, but it is impractical when many programs are to be run at one sitting. Recent advances in another storage medium, called flexible, or "floppy" disks, now permit loading programs within 10 seconds from a reusable disk costing a very few dollars. The electronic interface and drive motor unit costs less than $1,000 and is a very wise investment if the computer is to be used extensively.

Unfortunately, neither different audio tapes nor different disks are fully interchangeable between units from different manufacturers. The so-called "CP/M" disk operating system seems to be the emerging standard and it is available on 8" IBM format disks and on the popular 5" North Star and Micropolis disks. There are other special system considerations that can be best appreciated after the following description of the simulation program itself.
Action Potential Simulation

Since the Hodgkin-Huxley "space-clamped" model for excitation is one of the most popular quantitative models used in teaching physiology, its simulation can illustrate the features and limitations of personal computers. The reader is referred to the chapter by Dr. Peter Stewart (2), who has used simulation extensively in his teaching at Brown University, for FORTRAN statements which are direct adaptations of the original non-linear differential equations. The Appendix to the present paper lists a version written for BASIC by the author.

In practice the student turns on the computer and loads the program into memory from the mass storage device. Following instructions on the screen specific values can be assigned to stimulus parameters, such as the amplitude and duration of each of two stimuli as well as the time interval separating them. Once these are entered the computer goes through iterative solutions of digital forms of the Hodgkin and Huxley equations, first using the membrane voltage to evaluate the first-order rate constants which determine the rates at which the ionic "on" and "off" factors change from one state to the other. These rates of change operating for a finite time increment establish new values of the membrane conductances and currents; the currents are added, including any stimulating current, and then used to calculate the incremental voltage change. Once the voltage is updated, the process is repeated. Depending upon the objectives of the exercise any combination of the computed variables can be displayed in numerical tables or by graphics for selected iterations.

Figure 1 is a photograph of the video screen showing the questions and responses which might be involved in illustrating the larger stimulus which is needed to evoke a regenerative response during the relative refractory period. By pressing the RETURN key in response to the first question the student has left the initial steady state values of the rate constants and dimensionless variables at those for a resting potential of 90 mv, the value used in this program. To mimic anode-break excitation the initial membrane voltage could have been set to some hyperpolarized value which would have determined the initial Na+ and K+ conductances and time constants. The second line on the screen allows the operator to suddenly displace the membrane voltage to some value, and has a "default" value equal to the resting membrane potential.

The stimulus intensities are in μA/cm² and the durations in milliseconds. The choice of these parameters depend upon the instructor-designed protocol for the exercise. Students like to make a game out of finding the exact threshold stimulus magnitude at which Na+ and K+ currents will balance for several milliseconds before one exceeds the other. For measuring the stimulus strength-duration curve the duration can be consistently set to specific values while the amplitude is varied until threshold is found. The time course of the refractory period can be mapped out by varying the duration of the time delay to the second, or test, stimulus looking for its threshold at each time delay. The process of accommodation can be demonstrated nicely by having the conditioning stimulus at a very low amplitude, e.g., 2 units, and long duration, e.g., 8 msec; then at 8 msec the stimulus is increased to a standard threshold value. During the conditioning stimulus it is possible to follow the Na+ inactivation and increased K+ conductance so that K+ current out is able to keep up with stimulating current in. At the time of the test stimulus it takes a very large magnitude to get a regenerative spike.

Figure 2 is a tabular presentation of the membrane conductances, currents, and voltage for the first 2.2 msec after the application of the stimulus amplitude of 50 units for 0.2 msec. The instructive information is contained in the temporal changes in membrane Na+ and K+ conductances, the initially greater Na+ in than K+ current out so that there is a net accumulation of positive charge inside of the cell. This depolarization enhances the Na+ conductance change until the driving force upon that ion is reduced, Na+ inactivation begins, and K+ current begins to increase. At the time of 1.6 msec the net current becomes outward (the squid axon data was obtained at temperatures lower than those found in mammalian axons) and thereafter K+ current out exceeds Na+ current in unless an unusually large stimulus is applied. The simulation can be stopped at any time by pressing a specific key and continued by pressing another; a third key can be programmed to restart the exercise from the beginning.

![Fig. 1 Establishing the conditions to be simulated. The program requires the user to enter the experimental conditions. This is done by answering queries and sending the information to the computer by pressing the 'Return' key. Default values have been stored, e.g. (RTN = -90) to simplify the entry process. Here the membrane is left at the resting potential (-90 mv), no displacement voltage is requested. The first stimulus is given an intensity to 50 units (micromamps/cm²), for a duration of 0.2 millisecond. An 8 millisecond delay is requested. The second stimulus is assigned an intensity of 200 units and applied to a period of 0.5 millisecond.](image1)

![Fig. 2 Tabular presentation of the results of the simulation for the conditions selected in Fig. 1. Computed values of membrane conductances, individual currents, total membrane current; and membrane electric potential. The values were computed for each 0.04 msec but displayed every 0.2 msec. The screen can display only 16 lines at a time so the columns labels must be repeated periodically. The computation can be stopped for study, continued, or reinitialized by pressing specific keys.](image2)
Whereas the axon operates in infinitesimal calculus the computer seeks solutions at specific time increments. The choice of iteration and displayed time increments are a compromise between the accuracy of the solution and the total time required to achieve the solution. For Figure Two the computation interval was 0.04 msec, every fifth value of which was displayed. Larger computation intervals lead to spurious oscillations whereas the information rate of 3 sec per displayed line is about right for assimilation of the many variables changing during the peak of the spike. In displaying graphic solutions the time for each iteration becomes very significant and involves both the hardware and software considerations outlined in the next section.

**Graphic Display Of The Simulation**

Most personal computers do not come with sufficient graphic resolution to present a realistic action potential; furthermore, they handle scientific computations so slowly that the total time for simulating the spike and recovery period is excessive. Figure 3 is a photograph of a simulation for the stimulus parameters indicated in Figure One, where the graphic resolution is 256 by 256 points, obtained by adding a special interface card. This gives a vertical resolution of 1 mv which is quite adequate and still leaves enough space for a display proportional to the stimulating current. The computation increment was used 1/30 millisecond with two sweep display options. A fast sweep, showing 0 to 7.5 msec, displayed every computed point and is useful for observing threshold phenomenon. In order to study the refractory period a slow sweep of 0 to 15 msec displayed every-other computed value for a total of 225 points at displayed increments of 1/15 msec. In principle any of the computed variables can be displayed provided the screen does not become too cluttered: in practice the combination of voltage and stimulus seems to be very effective.

![Graphic presentation of the results of the simulation for the conditions selected in Fig. 1. The plot contains, in the upper curve, computed membrane potential in mv versus time in milliseconds; the second curve indicates the time, duration and intensity of the stimulus, vertical resolution for the membrane potential is 1 mv: for the stimulus intensity is 5 units. Horizontal resolution for the time axis is 1/15 millisecond. The simulation when programmed in BASIC requires 2 - 5 minutes compared with 14 seconds if programmed in machine language using a numerical processor chip such as the AM-9511 (see text).](image)

The time to simulate and display the 7.5 msec sweep can range from 8 sec using machine language and special hardware to as much as 3 min using some versions of BASIC. The time to do one iteration starting from a given membrane voltage, computing conductances and currents and then the new voltage involves such variables as: the microprocessor machine cycle time, the kind of programming language used, the algorithms which evaluate the exponential functions in the H-H equations, and the method of numerical integration of the non-linear equations. Full discussion of each of these is beyond the scope of this paper but it is possible to indicate the most practical places to improve the speed of numerical computations, an important consideration in any simulation.

The most popular 8-bit microprocessors run at either 2MHZ or 4MHz for executing individual references to memory, a factor of two, however, the 4MHz versions require more expensive memory and more critical electronics. Machine language programming can run as much as 100 to 1,000 times as fast as does the high-level languages, but, there are several versions of BASIC, the programming language most often supplied with personal computers. The slower versions have the great accuracy required in business accounting by use of binary-coded-decimal (BCD) arithmetic but the total time to display a graphic spike is prohibitive. Versions of BASIC copyrighted by Microsoft, Inc. use a floating point format (analogous to scientific notation); it has sufficient accuracy and executes most functions significantly faster than do the BCD versions. In addition, this format is compatible with a new arithmetic processor chip, the AM-9511, which can perform arithmetic and evaluate transcendental functions with a single machine instruction in a fraction of the time required for the successive additions and subtractions required of machine language subroutines. It is anticipated that numerical processors will be considered in future versions of both BASIC and FORTRAN so that one can program in the high-level languages and have rapid execution of compiled programs which approach machine language speed and compactness.

**Summary**

The ability of microcomputers to present graphic displays of dynamic responses of physiological systems coupled with their economy and accessibility may help realize the largely unfilled potential of computer-assisted-instruction, but the real limiting factor will be the extent of the commitment of the participating faculty. Realistic instructional models which require the statement of hypotheses in concise logical terms should advance physiology as a scientific discipline.

**Appendix**

This section describes a minimal computer system, the author’s choice of a desirable configuration using components on the market today, and a listing of the simulation in BASIC.

Much of the promotion of the under-$1,000 computers stresses their potential for games, but one should not overlook their ability to do simulation in tabular form and with limited graphic resolution. One model with a resolution of 48 vertical by 128 horizontal points can compute and display 6 milliseconds of an action potential with a resolution of 3 mv in a total time of 2 minutes. It can be purchased with Microsoft BASIC in a read-only-memory and with an additional 16K of memory for programs, all contained within the keyboard cabinet. This, plus the audio cassette mass storage and video monitor, provides a compact and economical introduction to simulation. Although these small units can be extended to include rapid floating-point processors and high-resolution graphics it seems more appropriate to start with a system larger than this.
There are several models of small computers which incorporate the popular S-100 bus hardware and which can be used with the CP/M disk operating system, two suggested steps toward standardization. The one used by the author was a SOL, manufactured by Processor Technology of Pleasanton, CA, which has a reliable keyboard; an operating system which is activated when the power is turned on; and built-in interfacing for an audio-tape cassette mass storage device, video monitor, external printer, and remote computer access as a terminal. It also has five slots for S-100 bus cards for additional memory and special hardware.

Two of the S-100 slots contained 16K memory each, available from a number of different suppliers. One slot had the interface to the floppy disk, manufactured by Microplis Corporation of Canoga Park, CA. This particular mass storage device stores 143K characters on one 5½" disk and the drive unit head is removed from the recording surface if not addressed within a fixed time delay. The fourth slot had a 256 by 256 graphics interface card (including 8K of memory) manufactured by Matrox Electronics of Montreal. The remaining bus slot contained the AM-951 arithmetic processing unit on an interface board manufactured by MemTech Co. of San Diego. Two Sanyo model VM-4209 9" video monitors were used, one for the stimulus parameters and tabular information, the other for the graphics. This total package, costing about $4,000, could be used for simulation of a wide variety of physiological processes and other more general computing applications as well. This technology is changing rapidly and it is possible that the total system may become available from a single manufacturer at lower cost.

The following listing of a program to simulate the Hodgkin and Huxley equations, written in Microsoft BASIC, requires less than 3K of memory beyond the BASIC itself. For clarity it does not include the second stimulus, error messages for unreasonable entries, nor formatting of the computed variables. It is capable of displaying the solutions illustrated in Figure Two at less than 10 seconds per line, depending upon the particular computer being used.

```
10 'HODGKIN-HUXLEY SIMULATION
20 INPUT "STIMULUS AMPLITUDE = "; SA
30 INPUT "STIMULUS DURATION = "; SD
40 MV=-90: T=0: DT=1/25
50 Gosub 200: 'SET ALPHA,BETA
60 N=AN/(AN+BN): H=AH/(AH+BN): M=AM/(AM+BM)
100 'MAIN LOOP <------------------
110 Gosub 200: 'SET ALPHA,BETA
120 Gosub 400: 'UPDATE G,I,V
130 T=T+DT 'T=END OF INCREMENT
140 PRINT T; G; I; V; H; M; A
150 Goto 100: '-------------------
210 V=-MV-90: 'V=0 AT REST
220 IF V>25=0 THEN V=25.1
230 IF V<10=0 THEN V=-10.1
240 BN = .125*EXP(V/80)
250 BM = 4*EXP(V/18)
260 BH = 1/(EXP((V+30)/10)+1)
270 AN = .61*(V+10)/(EXP((V+10)/10)-1)
280 AM = .1*(V+25)/(EXP((V+25)/10)-1)
290 AH = .87*EXP(V/20)
300 RETURN
400 'UPDATE CONDUCT, CURRENT, VOLAGE
410 DN = AN+(1-M)*BN+DH: N=N+DN+DT
420 DH = AH+(1-M)*BH+HM: M=M+DH+DT
430 D1 = AN+(1-M)*BN+DH: H=H+D1+DT
450 GN = .66*N*N*N*N: GNM=129*M*M*M*M
460 IK = G*K*(V-12): INA= GNA*(V+115)
470 IL = .3*(V+10.6): IT = IK+INA+IL
480 IF T<SD THEN IT=IT+SA 'ADD STIM
490 V=V-IT+DT: MV=-V-90
500 RETURN
```

REFERENCES


ENVIRONMENTAL PHYSIOLOGY OF FISHES

An Advance Study Institute on the Environmental Physiology of Fishes will be held under the auspices of the NATO-Scientific Affairs Division, Université de Montréal and Bishop’s University from the 12th to the 26th August 1979 in Lennoxville, Québec, Canada. About sixteen leading workers in the field will deliver lectures on the role of chemical and physical factors on the physiology of fishes as well as the responses of fishes to a combination of these factors (rhythms, behavior, etc.). About 80 participants at the postdoctoral or senior postgraduate level will be chosen to attend from among the applicants. Preference will be given to citizens of the NATO member countries, some of whom may also be awarded financial assistance towards travel and/or living costs. Interested persons may contact: Professor M.A. Ali, Dept. de Biologie, Université de Montréal, Case Postale 6128, Montréal H3C 3J7, Canada.