PHYSICAL TECHNIQUES IN BIOLOGICAL RESEARCH

edited by

WILLIAM L. NASTUK

Columbia University College of Physicians
and Surgeons, New York

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CONTRIBUTORS TO VOLUME VI

Numbers in parentheses refer to the page on which the contributor's article begins.

KENNETH S. COLE, Laboratory of Biophysics, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland (263)

HERBERT DERN, Electronics Research Laboratories, Columbia University, New York, New York (99)

KENNETH KING, Columbia University, New York, New York (1)

JOHN W. MOORE, Laboratory of Biophysics, National Institutes of Health, Bethesda, Maryland (77, 263)

HERMAN P. SCHWAN, Electromedical Division, Moore School of Electrical Engineering, University of Pennsylvania, Philadelphia, Pennsylvania (323)

WILLIAM SILER, Department of Physics, Memorial Hospital for Cancer and Allied Diseases, New York, New York (1)

ROBERT E. TAYLOR, Laboratory of Biophysics, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland (219)

JOHN B. WALSH, Electronics Research Laboratories, Columbia University, New York, New York (99)

PREFACE

This volume covers some of the more sophisticated analytical methods and experimental techniques used in electrophysiological research. The first chapter deals with the processing and analysis of information by computer methods. In the following chapter the operational amplifier is given expanded treatment. This simple, inexpensive device can be used as an analog computer but it has various other important applications, and placing emphasis on it seems justifiable.

Often in electrophysiological research the investigator is concerned with the analysis of complex waveforms. For example, they appear in testing the response of recording equipment, or in bioelectric recordings made from complex biological systems. Familiar examples of the latter are the electroencephalogram and the evoked potentials recorded from selected regions of the brain. The chapter on complex waveforms serves to introduce the reader to methods of analysis of such waveforms and to signal characterization and detection.

The chapter on cable theory provides a compact presentation of this classical approach to the electrophysiological behavior of axons. A helpful list of references has been included. Chapter 5 contains a critical discussion of the voltage clamp technique which has been applied so effectively to squid axons. This powerful approach is now being used in the study of other excitable cells. The final chapter provides a discussion of impedance measurements, a technique which has yielded much critical data bearing on membrane behavior.

As planned originally, this volume included a chapter designed to acquaint the reader with control theory and servomechanisms. Unfortunately, a number of problems arose during the preparation of the chapter and its publication was prevented. This is a field of growing importance in biological research, and, in the future, publication of an introductory treatment of it would be desirable.

The graduate student or senior experimenter will, I hope, find this volume informative and useful. The material is difficult and sometimes the reader will need to enlarge his background. To help him, the authors have included references to much valuable literature.

In the preparation and editing of this volume I have been assisted by several men to whom I wish to express my sincere appreciation and gratitude. They are R. H. Cole, K. S. Cole, F. S. Grodins, A. L. Hodgkin, H. Karp, W. A. Rosenblith, A. F. Sciorra, R. W. Stacy, and Y. Takahashi.

I have also been assisted by many others who gave advice and criticism

directly to the contributors. This valuable aid has been acknowledged at the close of individual chapters but I would like to add my appreciation and thanks for it.

March 1963 WILLIAM L. NASTUK

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* Edited by Gerald Oster and Arthur W. Pollister.

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VOLUME V

LIST OF ABBREVIATIONS

atm—atmospheres
cm—centimeter
cos—cosine
coul—coulomb
cps—cycles per second
°C—degrees Centigrade
d—dyne
deg—degree
log—logarithm_{10}
ln—logarithm_e
gm—gram
in.—inch
kc—kilocycle per second
kg—kilogram
mc—megacycle per second
m—meter
msec—millisecond
mw—milliwatt
pps—pulses per second
sec—second
v—volt
w—watt
μ—micron
μsec—microsecond
μv—microvolt
μw—microwatt
Ω—ohm

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6. Determination of Biological Impedances

HERMAN P. SCHWAN

CHAPTER 1

FUNDAMENTALS OF DIGITAL AND ANALOG COMPUTERS

William Siler and Kenneth King

I. Introduction

1. Place of Computers in the Bio-Sciences

In the last few years the applications of computers in the biomedical sciences have increased phenomenally (Ledley, 1959; Lusted, 1962). Computers have been installed or are on order at several medical centers; special sections devoted to data-processing techniques in the life sciences have been set up at several major universities; at least two computer manufacturers have activated groups for investigating the biomedical possibilities of their equipment; and many individual researchers have acquired some competence in the computer field and, working with mathematicians and computer experts, have solved or at least attacked biological or medical problems with data-processing techniques. As an example of the rapid growth of the field, we note that in October 1961 what is believed to be the first full time research computer to be installed in an American hospital was delivered; in March 1962, there were three research computers installed in hospitals in the New York City area alone. Typical research computers are shown in Figs. 1, 2, and 3.

The reason for this highly accelerated growth is that computers and data-processing techniques frequently enable the researcher to do work and employ methods otherwise completely impossible. Further, the development of sophisticated languages for communication with computers, the rapid advances in mathematical techniques appropriate for computer use, the striking improvements in the computers themselves and the associated

FIG. 1 Example of a minimum digital computer facility (courtesy Bendix Corporation).

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equipment, and the dissemination into the bio-scientific fraternity of computer competence have made it increasingly easy for the bio-researcher to employ these tools fruitfully. It is confidently expected by most workers actively concerned with the biological uses of computers that this growth will continue for many years to come.

Some of the diverse biomedical applications are:

biostatistics,
simulation of biological systems,
storage, retrieval, and analysis of medical data,
collection and analysis of masses of biological data,
clinical applications to diagnosis and therapy.

Because the field is expanding so rapidly, and in so many different directions, an exhaustive treatment cannot be given in this chapter. Instead, we will be primarily concerned with the fundamentals of computers, with references to some typical examples of advanced work in selected areas.

2. Biological Information

If computers are to be employed most fruitfully, it must be understood that they are *information* processors, and not simply *number* processors.

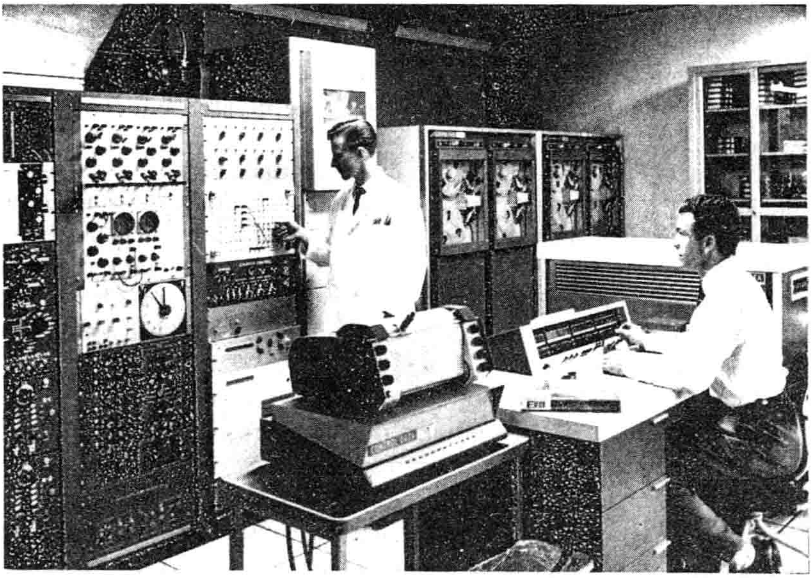

FIG. 2a Hybrid computer facility at Albert Einstein Medical College. On the right are four digital tape transports. Behind the technician is the analog tape transport. On the left are the A-D and D-A conversion equipment and specialized equipment. In front are the digital computer and x-y plotter. (Courtesy Dr. Josiah Macy, Albert Einstein Medical College.)

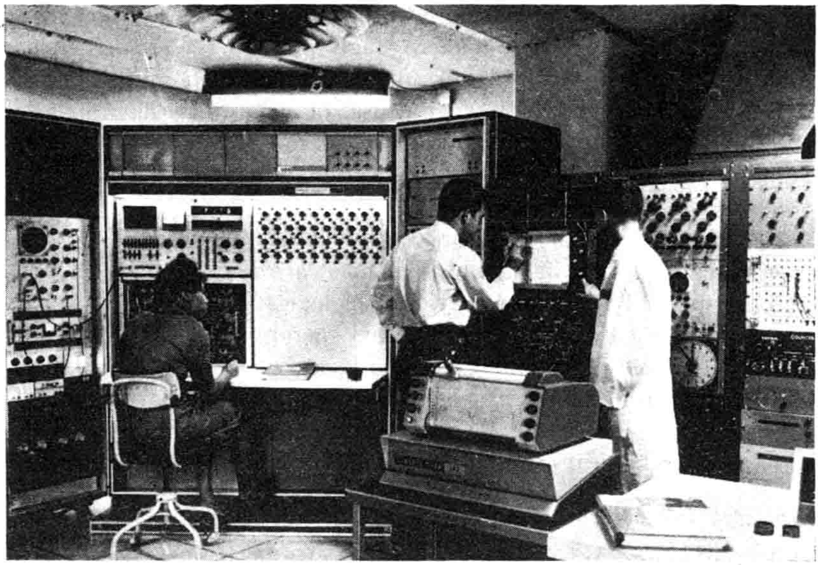

FIG. 2b The same computer facility showing the analog computer at left, and the conversion and specialized equipment at right. (Courtesy Dr. Josiah Macy, Albert Einstein Medical College.)

There are two main branches of biomedical information: quantitative and qualitative. Quantitative information may be divided into two classes: *analog* data and *digital* data.

Analog data implies representation of a magnitude by an analogous magnitude, usually in the form of voltages varying with time. The voltages may be generated by the computer itself, or may be measurements of a biological phenomenon. In the latter case, a transducer is usually employed to convert the quantity being measured to a voltage, and a preamplifier and amplifier usually bring the voltage output of the transducer to a convenient level for computer input.

Digital data implies representation of a magnitude by a "number," usually in the form of a series of numerical measurements. Analog data are usually continuous; digital data are discrete. However, both systems can handle continuous or discrete information.

Qualititative information, or "soft" data, includes all information which is neither analog nor digital as defined above. Such data are common in medical work; if a patient has a hacking cough, this is information, but clearly not numerical information. Such data cannot at present be handled directly by computers. They are usually put into digital form by use of a *coding scheme*.

FIG. 3 Large-scale computer facility (courtesy International Business Machines)

3. Automatic Computation Equipment

Analog computers process information in analog form, as voltages varying continuously with time. Such computers are quite useful for solving differential equations, and for simpler operations such as addition, multiplication, integration, and differentiation. Since elementary functions such as exponentials, sines and cosines are generated by solving simple differential equations, such functions may be easily generated by analog computers. The main element of the analog computer is the *operational amplifier*, which can be used to add, subtract, invert sign, integrate, or differentiate. By addition of *nonlinear elements*, multiplication of variables may be performed and special nonlinear functions generated.

Digital computers process information in digital form. If analog information is to be processed in a digital machine, it must first be converted to digital form by use of an analog-digital converter. The digital computer is a most flexible and powerful piece of equipment, whose capabilities are far from fully known. Any operation which may be performed on an analog computer may also be performed on a digital computer (although often less conveniently), but digital computers can solve many problems which an analog computer cannot handle. For example, digital computers have the capability of performing symbolic logic on a mass scale. Both the information on which the computer operates, and the instructions for processing the information, are stored within the computer. In addition to the computer itself, devices for reading information in and out of the computer are necessary; typewriters, punched-card equipment, punched-paper-tape devices, and magnetic-tape drives are common items of equipment.

For processing analog information on a digital computer, special equipment is necessary. The analog-digital, or A-D converter is essential, and its counterpart, the D-A converter, may also be used. If the data are processed at the same speed at which they are generated, the computation is said to proceed in *real time*. If the computer is hooked directly to the device which generates the information, so that the data are fed into the computer as they are generated, we have *on-line* computation; if the data are not to be processed on-line, the information must be stored temporarily for later processing *off-line*. Usual storage devices are magnetic tape for storing the information in analog or digital form, and punched paper tape or punched cards for storing digital information. Transducers, amplifiers, and possibly analog computers for preconversion processing of the data may also be desirable. When both analog and digital computers are linked for processing the same information, we have *hybrid* computation. When the information is processed on-line, and the results of the computation used to control, in some way, the process which generates the data, we have *closed-loop* computation; when the answers produced by the computer do not control the process which generates the information, we have *open-loop* computation. Several precautions must be taken in online closed-loop work, such as validity checks, processing-time checks, possible time-sharing of computer programs, and so forth.

Up to this point, the discussion has been concerned with the *general-purpose* computer. Very frequently, *special-purpose* computers or computing devices to be used in conjunction with other equipment may be assembled from standard components, both analog and digital. If the information is analog in nature, often special-purpose analog computers assembled from commercially available components may greatly assist the investigator in extracting relevant information from a mass of data. This is particularly true in biomedical work, when such operations as auto- and cross-correlations, power-spectrum analysis, data smoothing, and integration may be conveniently performed by a special-purpose analog computer. If the information is digital in nature, such as (for example) the output of a scaler attached to a scintillation crystal for radioisotope tracer detection, a special-purpose digital computer may be assembled using digital modules now available commercially from a number of manufacturers. In some cases, a small analog-digital converter, in combination with a limited number of digital modules, may greatly assist the investigator. An example of fruitful application of this work is the elimination of noise from evoked potentials by means of continuous-averaging techniques.

Electric accounting machinery, or EAM equipment, represents an important class of automatic calculating equipment, although it does not lie in the realm of the true computers. This equipment, found in almost every accounting office, processes digital information, almost invariably recorded on punched cards. Simple correlations and statistical work may be conveniently performed, and (with a rather sophisticated approach) second-order differential equations have actually been solved on this equipment. The primary items of equipment are the *key punch*, which produces punched cards from data entered on a keyboard; the *sorter*, which picks out of a deck of punched cards those which have a particular column punched with a particular hole; and the *accounting machine* or *tabulator*, which can add multiple columns of numbers at one time, print out individual cards and totals as instructed, and make very simple decisions as to alternative courses of action.

4. Problem Preparation

No matter what form of automatic computing equipment is used, the problem must be stated exactly if it is to be solved. The question of what constitutes an exact problem statement is one which can only be answered completely by a person versed in computer methods. Usually more information is required than is realized by the scientist who wants his problem to be solved. For example, the problem of evaluating a definite integral between certain known limits where the function to be integrated is specified completely would seem to constitute an exact statement of a problem. However, since computers perform integration numerically rather than analytically, additional specifications are required; for example, the method of numerical integration (trapezoidal rule, Simpson's rule, or other) must also be given. While most problems are specified mathematically, many problems may be solved where the statement of the problem is logical rather than mathematical. This class of problems is of increasing interest and importance, particularly to workers in the biomedical field. An example of this type of application is the search of stored medical records to give the physician the chart numbers of all patients who exhibit a particular group of characteristics. Other such applications include learning and teaching machines, simulation of neuro-networks, and pattern recognition.

After the problem is stated properly, it must eventually be translated into a language which the computer can directly understand and obey. We are now ready to enter the programming stage.

5. Computer Programming

The program is a series of instructions which enables the computer to perform its desired function. It must be understood clearly that computers have no brains or judgment whatever, and must be instructed precisely, in enormous detail, exactly what to do. Instructions for digital computers are entered into the computer's internal storage, or *memory*, and are obeyed as read from memory. Analog computers are programmed by wiring, as is electric accounting machinery. In any case, the programmer "solves" the problem. The attitude commonly met, "let's give the problem to the computer and let it solve it," is unfortunately quite inaccurate.

Basic programming for an analog computer consists of specifying the interconnections between operational amplifiers and possibly nonlinear elements. These interconnections usually involve precision resistors and capacitors. While differentiation may be performed by an analog computer, integration is much more easily done, and differential equations are usually programmed by integration. After the necessary connections are specified, intitial conditions must be set up by applying specified voltages to the proper places. Constants are entered by setting coefficient potentiometers. After the initial conditions are set up, the computer is usually allowed to run free, unless it is used as a data-processing device. In biomedical data processing using analog computer elements, special circuitry is frequently necessary to accomplish the desired function. The programming of an analog computation may, therefore, frequently require the attention of an expert in electronics. The transactions of the IRE Professional Group on Bio-Medical Electronics are a rich source of applications of analog equipment to biomedical problems.

Programming for digital computers is usually more complex than for analog computers. However, the problems which may be handled on a digital computer may be much more complex than those which can be solved on analog equipment. The basic instructions which the digital computer can directly obey are very simple, such as add, subtract, and do *this* or *that* depending on the sign of a number. It is common for the total number of instructions in a digital computer program to run into the thousands. To ease the programming effort, special *programming systems* have been developed which enable the programmer to communicate with the computer in a simple language. The most important of these are the *symbolic assembly* programs, and the *algebraic compilers*. The latter enables one to program using a semi-English semi-algebraic language which is easily understood by a person with some mathematical training. Programming is also eased because many problems (such as matrix inversion) appear again and again, and a host of pre-prepared programs for commonly encountered problems is available for most computers. These are commonly known as "canned" programs.

6. Availability of Equipment

The high cost of time on computers and programming assistance has deterred many researchers from making use of data-processing techniques.

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