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Digital Electronic Computers in Biomedical Science

Computers make solutions to complex biomedical problems feasible, but obstacles curb widespread use.

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One of the most remarkable aspects of modern technology is the rapidity with which the field of high-speed digital electronic computers has developed. Although the first few computers were successfully operated barely 10 years ago, several thousands are in use today. Within that single decade this entirely new field has penetrated almost all phases of modern civilization, from nuclear energy production and missile design to the processing of bank checks and business inventory control. And in the research stages are already components that might make feasible computers many-fold more complex than present-day computers. It has been suggested that perhaps we are on the threshold of a new era in the history of mankind, arising from the utilization of electronic computing machines—likened to the industrial revolution, which was derived from the utilization of machines that automatically make commodities, thereby vastly increasing man's productive capabilities. Now we have available machines that vastly increase man's "thinking" capabilities, using "thinking" in the sense of planning, analyzing, computing, and controlling. We know the effects of this new era will be great, but we can now only speculate on the forms they will take. Not only will its influence be directly marked on the economic, political, and social aspects of our civilization, but it will have a tremendous effect in the physical and biomedical sciences as well.

Already there has been extensive use of computers in technology and the physical sciences. But in the biomedical sciences their use has barely begun. It is to be noted, however, that perhaps the greatest utilization of computers will be in biomedical applications. The problems that arise here characteristically involve large masses of data and many complicated interrelating factors, and it is just these types of problems for which computers are primarily suited. Also of great significance are the recent, dynamic changes taking place in the biomedical fields themselves: For example, biological processes are now being examined in terms of atomic structures, energy levels, binding forces, molecular configurations, and the kinetic and thermodynamic details of biochemical reactions. Increasing quantization, with concurrent emphasis on the biophysical and physiochemical bases of biological systems, is rapidly bringing a large portion of biomedical science to a point where complicated mathematical manipulations and mass data reduction and analysis are absolute prerequisites to further progress. The advantage in the use of computers for such purposes is not derived merely from the fact that the computer can perform complex mathematical and logical operations rapidly, but rather from the observation that the electronic computer makes feasible the solutions to problems that could not otherwise be approached. In this article the extensive applicability of computers in biomedical science is illustrated by means of specific examples, and then some of the important problems and obstacles arising in such utilization of computers are discussed (*1*).

I have in general confined my remarks to digital rather than analog computers, because it is digital computers that are capable of performing various complicated *logical* processes. This is not to imply that the analog computer does not have an important role in biomedical research; but the analog computer is usually of a more specific nature, not as capable of performing generalized computational procedures.

Analogy between hand computation and the functions performed by the parts of a digital computer. A general rule for evaluating the capabilities of a digital computer is: if the steps in the solution of a problem can be broken down into sequences of unambiguous instructions that conceptually could be performed by a very patient secretary who has no knowledge of the subject matter but who has infinite perseverance and can follow instructions precisely, never making an error, then the problem can be solved on a digital computer. This rule is an oversimplification only insofar as the necessary computation time on the computer and the cost of this time are also restrictions. It is, in fact, instructive to carry our analogy still further, describing the functions of the various parts of the computer (see Fig. 1). These are the input and output units, the memory, the control unit, and the arithmetic unit. The computer memory is analogous to the work sheet and instruction list of the hand computation: the memory stores the initial

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data to be operated on, the intermediate results and the final results, and also the instructions themselves. The control unit interprets the instructions regarding the operation to be performed, the arguments to be operated upon, and the instruction to be chosen next; this is analogous to the computing secretary's mind. The actual operations indicated by the instructions are performed in the arithmetic unit, analogous to the secretary's desk calculator. The input and output units, which for the computer can be punched-paper-tape or card readers and punchers, or magnetic tape readers and writers, or character reading machines and high-speed printers, and so forth, are analogous to the secretary's pencils and graph paper.

Besides the great speed with which arithmetical and other operations can be performed (for example, modern computers can perform close to a half million additions per second) the computer derives its unique logical powers from its instruction-handling capabilities. These are basically of four types.

First, there is the chain instruction-sequencing capability of the computer to execute a list of instructions in sequence. For example, if

$$(ab + c)/d$$

is to be computed for given values of a, b, c, and d, the computer could be made to execute a sequence of instructions that formed the product $a \cdot b$, then added c to this result, and finally divided the sum by d.

Second, there is the decision capability of the computer to choose between alternative sequences of instructions for subsequent computations, depending upon the outcome of some previous computation. For example, suppose several different statistical procedures were to be applied to each set of input data, depending upon certain characteristics. In such a case the computer would be made to evaluate these characteristics for each set of data as it is received, and thence would choose the appropriate computational procedure to perform.

Third, there is the recursive computational capability of the computer to execute iteratively a sequence of instructions. For example, if a power series is being evaluated to a particular accuracy, each time a successive term of the series is computed its value is compared with the allowed error; if the term is smaller, the computer goes on to another part of the program, but if the term is larger, the computer adds it to the partial sum, adjusting certain constants, and repeats the general sequence of instructions to evaluate the next term.

Fourth, there is the instruction modification capability of the computer to change some of the instructions in its memory and then go on to compute with these modified instructions. In this way, for example, the computer itself can be made to write a sequence of instructions. This capability, and the other three as well, has implications more important and far-reaching than the mere ability to compute at high speed.

Examples of the Utilization of Computers

At present there are some hundreds of applications of computers being made in the biomedical sciences. Most of these are being made by relatively isolated research workers who are, with only few exceptions, people with extensive cross-disciplinary backgrounds. They include professors of anatomy who are also x-ray spectroscopists, physicians who were once electrical engineers, biophysicists and physiologists who originally were physicists, psychologists with extensive mathematical background, and others. As in any new field, the research workers involved are only recently becoming aware of each other's work. Media for the exchange of ideas in this field are not yet adequately developed; most of the communications among researchers in the field have been at several conferences and symposia. In general the biomedical utilization of computers is hampered by lack of available machine time, inadequate peripheral equipment, insufficient funds, and a lack of coding and programing assistance. On the other hand, those biomedical researchers who are using computers are to be congratulated for their success in bringing many difficult and diverse disciplines to bear on their problems, for their often ingenious uses of the computer, and for their persistent, resolute pioneering spirit in the face of severe obstacles.

It is of course impracticable to review here those hundreds of applications already in progress, or the many more that are being proposed. Hence I shall only mention applications sufficient, I hope, to indicate the immense potential of this powerful new tool. The illustrations are based on unpublished as well as published material, proposed as well as completed and in-progress applications (see the "Selected Bibliography" at the end of this article). It is most convenient to consider the applications in four basic (but inevitably overlapping) categories: (i) numerical solutions to (partial) differential equations of biology and medicine; (ii) simulations of biological systems or aspects thereof as entire entities; (iii) biomedical data processing and reduction; (iv) biomedical information retrieval systems.

Numerical solutions to differential equations. One method for studying a biological phenomenon is to make some hypotheses concerning its mechanism, write the corresponding (in general, partial) differential equations, and compare the solutions of the equations with experimental data. If the solutions do not agree with the data, the hypotheses are altered, and the process is repeated. This method of course has been used for centuries in the physical sciences. In many instances it is not too difficult to write partial differential equations to describe a complex phenomenon reasonably; however, more often than not it is found that such equations cannot be solved by conventional analytic methods. Yet, with the utilization of electronic computers they may frequently be solved numerically. Indeed, the numerical solution is often the most desirable, since it can be compared directly with the experimental data.

Computers are being used to assist in the complicated and extensive computations that are frequently involved in obtaining information about the precise atom-structure or the over-all size and shape of crystallizable molecules, from x-ray diffraction patterns. Various organic molecules have been and are being analyzed by this method, including the well-known cases of vitamin B_{12}, myoglobin, hemoglobin, lysozyme, and the hydroxyapatite of teeth and bone. These methods are also being applied to the analysis of the structures of amino acids and peptides, and the over-all shape of nucleic acids and other large molecules. For noncrystallizable substances, information about their structures can be obtained from scattered light interference patterns, osmotic pressure and viscosity measurements, and sedimentation rates. Here the computer could again significantly assist in the computations involved.

Another relatively active field in the use of computers is the study of differential equations relating to the mechanisms of biological systems. The famous Hodgkins-Huxley equations, and several variations thereof, have been analyzed with respect to the properties of excitable membranes. Besides the computations, well under way, concerning the nature of nerve-fiber conduction, other studies will apply these equations to muscle-fiber excitability. Other equations, relating to semipermeable membranes and the diffusion and motility of large molecules, could be solved numerically on the computer for complicated geometries and other specifications. This capability presents a further tool in the study of the nature of the physical phenomena involved in intracellular dynamics.

Complicated sets of interrelated differential rate-equations can in many cases be solved on the computer. Such computations have been applied to multiple-reaction-rate problems involved in the exploration of certain metabolic processes. Computations involving such sets of equations have been used to predict intermediate reactions from a knowledge of experimentally determined final reaction rates. Another important problem using rate-equations to which computers have been applied is that of tracing through the various organs and systems of the body the time course of injected radioactive substances, for diagnosis of metabolic disturbances. For example, if radioactive iodine is used for a test of hyperthyroidism, the amount of radioactive substance would be measured as a function of the time in such "compartments" as the blood iodide, the protein-bound iodine, the thyroid gland, the feces, and the excreted urine. From these data the appropriate fractional-turnover rate-equations are solved for the turnover-rate constants between compartments, these constants being the desired indices of disease. Facets of this problem are still being worked out, such as uniqueness of results, consistency of redundant information, statistical variation, and so forth. Radioactive-carbon-tagged chemicals can be used in this manner for pinpointing specific dysfunctions of the metabolic pathway, opening up new fields of research in computer-aided specific diagnostic analysis. Finally,

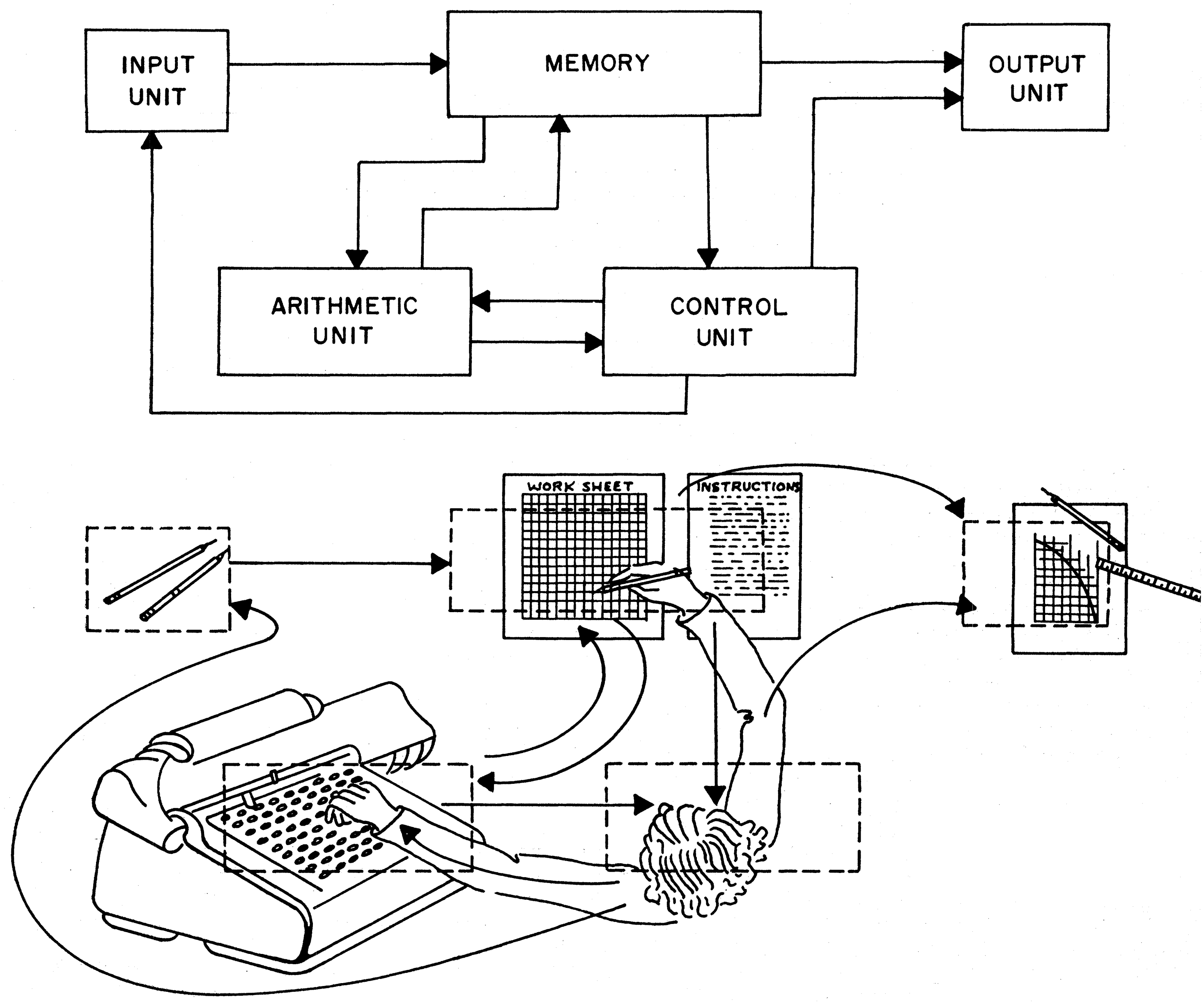

Fig. 1. Analogy between manual computing and an electronic digital computer. The arrows indicate the flow of information.

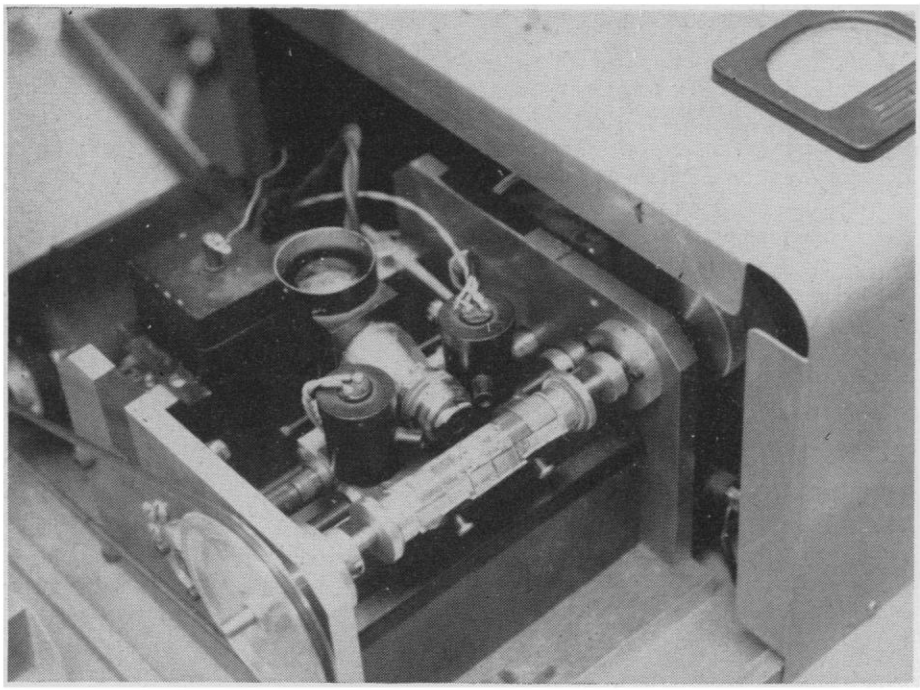

Fig. 2. Picture-reading machine for input to digital computer (developed at the National Bureau of Standards) showing detail of scanning phototube flanked by light sources that illuminate the picture bound around the rotating drum. [Courtesy National Bureau of Standards]

complicated rate-equations occur in many homeostatic mechanisms, such as in the regulation of the formation, maturation, and elimination of erythrocytes, lymphocytes, and granulocytes.

Other computer applications are associated with the solution of partial differential equations that attempt to describe the flow of blood in large arteries, such as the aorta. Numerical solutions to these equations can be compared with experimental results for verification of the hypotheses embodied in the equations. A study of mortality is being made with the use of stochastic differential equations, that is, differential equations with stochastic coefficients chosen from specified distributions. The solutions to such equations in general present severe analytical difficulties and can be approached only by means of direct computations with an electronic computer. One of the earliest biomedical computer applications was the evaluation of the forces applied to the teeth during mastication. The results of this study have an important application to the proper construction of full dentures and other prosthetic appliances, as well as to orthodontics. Many other examples, too numerous for description here, exist in such widespread fields as determination of radiation dosage, quantum mechanics applied to molecular metabolic reactions, analysis of circadian cycles, and so forth.

Simulation of biological systems. Complicated and highly involved phenomena, such as entire biological systems, can be analyzed by means of computer simulations. Usually a great deal is known about the local-component aspects of such a system; but a study of how these many complicated parts combine to make the whole has not heretofore been generally feasible because of the immense amount of calculation required. However, these calculations can frequently be accomplished if the functional equations of the component parts and their interaction rules are assembled on a digital computer. The purposes and uses of a computer simulation are to enable (i) the study of a complicated system as an integrated result of many individual, interacting component parts, (ii) the evaluation of the relative influence of each small component in relation to the whole system, (iii) the testing of hypotheses about a part of a system for consistency with known data about the whole system, and (iv) the designing and planning of future, more critical experiments concerning still unknown components of the system. Unfortunately, although many large-scale system simulations have been carried out on digital computers in the military and business fields, few if any have been accomplished in the biomedical field.

Many physical and chemical characteristics of biological phenomena evidently can be studied only by considering individual molecular reactions. Here, mathematical analysis based on large numbers of statistical aggregates of molecules does not suffice. An important method for studying such complicated phenomena is the so-called Monte Carlo simulation, which in most instances can be carried out only on an electronic computer. With Monte Carlo methods, the effect of individual molecular motion, collisons, chemical reactions, and interacting forces can be simulated according to some assumed model, and the over-all statistical responses of the system can be predicted, to be compared with experimental results. The initial state of the model is first described, including estimates of the sizes, shapes, initial positions, velocities, and orientations of each of the molecules of the system. Then a stepwise process for following the individual particles through increments of time is established that includes the molecular kinetics and possible chemical reactions. The "Monte Carlo" aspect of such a simulation enters as random numbers are successively chosen from appropriate distributions, for the determination of the initial conditions of each molecule and for other random processes that may enter into the dynamics of the system during the stepwise incremental time computations. The origin of the physical characteristics of colloids, jells, and other suspensions is being investigated in this manner. Certain enzyme systems, too, are being studied by this process. The method could also be applied to many aspects of cellular dynamics for a better understanding of the roles of various cytological structures.

In addition, Monte Carlo simulations have been applied to cell division problems in which the computed resting time between individual cell divisions depends on the selection of a random number from a given distribution function. The effect that varying this function has on the total number of cells obtained after a given period of time has been studied in connection with the growth of malignant tumors. Similarly the motion of sperm cells in electric fields was studied to determine whether a nonrandom drift actually occurs. The simulation of genetic changes can also be useful for evaluating rates involved in genetic dynamics. Analogously, much can be learned from Monte Carlo simulations of epidemics, where the spread of a disease from individual to individual is determined by laws with random components. Some work has already been accomplished on computer simulations of self-organizing neural nets, in the investigation of learning, pattern recognition, and other phenomena of the brain. Here the organization of "connections" between *individual* neurons is simulated: The connections are made or broken according to certain general rules associated with simulated stimuli input to the neural net, and with certain random processes. The way in which the simulated neurons then *collectively* organize themselves is studied as the simulation progresses.

Biomedical data processing and reduction. There are a great many applications of computers in the straightforward statistical analysis of medical records, experimental results, and other data. Notable is the large variety and amount of psychological research being accomplished: the psychologists always seem to be among the first to take advantage of the computer in a newly established computing center. Computers are aiding the statistical evaluation of new drugs, correlation of disease with various possible etiologies, studies of the effectiveness of new cures and preventives, and so forth.

A different kind of data reduction problem is involved in connection with various continuous recordings obtained from living animals, such as electrocardiograms, electroencephalograms, gastroenterograms, and electromyograms. Projects concerned with the first of these are usually directed toward attempts to correlate the recordings with abnormalities and diseases. However, before a digital computer can be applied to the analysis of such recordings, the recordings must first be put into digital or numerical form. Only recently has an integrated program been established for the mass collection of electrocardiograms in such form. On the other hand, much work has been accomplished in applying the computer to the problems of electroencephalograms. Here the purposes of the analyses are to learn more about the brain mechanism as well as to correlate with diseases. The problems here, however, are more severe, since the recordings appear to have large random components. Auto- and cross-correlation techniques, averaging, and pattern-recognition methods have been applied, particularly with regard to auditory and other sensory studies. Digital computer application to the analysis of electroencephalographic recordings, from animal experiments on the mechanisms of the brain, are currently being initiated. Further modes of analysis, such as the use of stochastic differential equations, are being anticipated. Thorough evaluation of these data without the use of a computer would generally be infeasible.

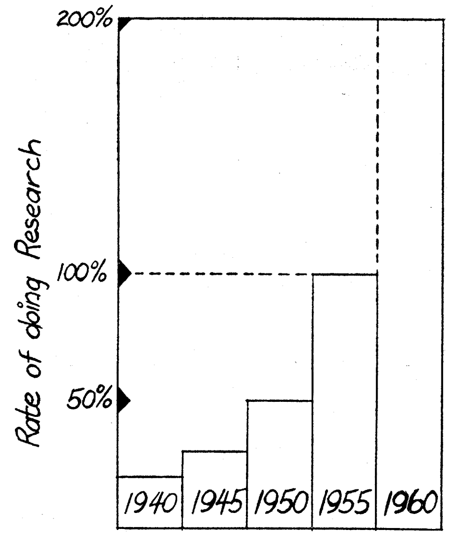

Fig. 3. Estimated rate of doing research. Indices used to measure this rate were estimates of research manpower employed, funds expended, and pages of published results. The data were extracted from J. A. Shannon and C. V. Kidd [*Science* **124**, 1185 (1956)], annual appropriations to NIH, *American Men of Science*, *Chemical Abstracts*, and from other sources.

An interesting possible application of computers is sequential microphotographic analysis. The purpose is to take full advantage of a relatively recent development in the collection of biological data, namely, the production of remarkable motion-picture photomicrograms of important biological processes such as capillary blood flow, motion of mitochondria in a cell, and so forth. A unique use of the digital computer for the analysis of these pictures arises in connection with the recent development of a picture-reading machine that can record in the memory of a computer a black and white version of an entire picture, as seen by a scanning photomultiplier tube (see Fig. 2). As an example, consider a motion picture taken of differentially stained nervous tissue through a microscope as the plane of focus is moved through the tissue section. By comparing successive frames of the movie, it may be possible to have the computer automatically trace thousands of neuron-array axon connections, a procedure that could not be feasibly accomplished manually. The process is similar to the automatic tracking of aircraft by computers, on successive sweeps of radar antennas. The same process can be applied for the detailed mapping of capillary beds, to obtain quantitative information on the physical relationships between the capillaries and the glomerulae of the kidney or the alveolae of the lung. Successive frames of films showing dynamic cellular processes can be analyzed by this method to obtain quantitative kinematic relationships, which can then be used to analyze the forces involved.

Information retrieval. The difficulties in sifting the past research results of others, and in keeping abreast of current research results, are rapidly increasing. The growing acuteness of this problem in the biomedical fields is due to the rapidly increasing research rate, which has more than doubled since 1950. In fact, the total of all medical research expenditures in the United States will probably have doubled again in the period from 1955 to 1960 (see Fig. 3). Recognition of these problems in other fields as well has stimulated much current work in various basic and applied aspects of information retrieval. Some of the basic work is concerned with the application of computer methods to automatic language translation, to automatic abstracting, to semantic problems as applied to retrieval, and so forth. Several commercial firms are presently working on specialized automatic information retrieval machines designed to retrieve information on a multidimensional or coordinate basis. Various ideas have been proposed for the utilization of such machines by research workers. One of these recommends that instead of being published in journals, research results might be transmitted to a central information center. Then when a researcher desires information on a particular subject, pertinent research results would be retrieved and reports sent to him. Since in this system research results now published in hundreds of different journals would all be filed together, and since the information center's retrieval computers would retrieve on a multidimensional or coordinate basis, the reference value of such a center would be far superior to that of present-day publication methods.

Another idea utilizes a method for obtaining multidimensional or coordinate retrieval in a bound-book form of bibliography. Such bibliographies of current periodical literature in specialized fields can be prepared rapidly, and printed out in the proper page formats, by electronic computers. Offset copies of the bibliography can then be distrib-

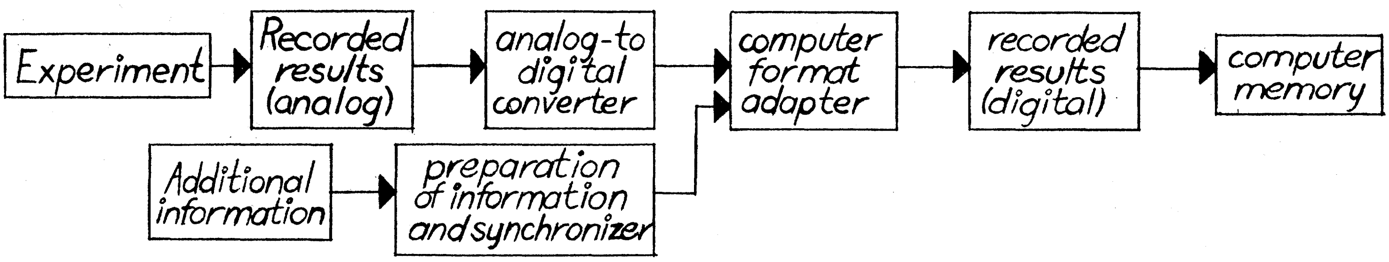

Fig. 4. Steps in data input to computer's memory.

uted to research workers in their laboratories for easy, rapid, and convenient reference. Since by this method the bibliographies would be relatively cheap to compile and print, new bibliographies including all current material could be made frequently; research workers would then throw away old bibliographies on receipt of new ones.

The great advances in medical knowledge of the past few years have not been matched with a parallel advance in making this knowledge available to the practicing physician. The information must be available in a retrievable form, for certainly a physician cannot be expected to read and remember the details of all current articles and reports with which he is confronted, on every specific disease and subject.

Thus there is also an urgent need for an information transfer system which would make *easily* accessible to the individual practicing physician the most current information or development on a disease or subject, at the *time* he needs it, at the *place* he needs it, and in a form he can use. Such a current information-transfer system could give the physician *instant reference*, in his office, to research results taken from articles published in hundreds of journals, or perhaps direct from research laboratories. Current advances in computer technology make such a plan entirely feasible. One suggestion, for example, is to use the telephone dial as the communications link between a retrieval computer and the physician. The physician could dial into the computer codes referring to diseases, drug actions, or other information desired, and would receive information by means of computer-operated talking machines, telephone-television, or other more advanced communication techniques presently available or being developed.

A national health computer network has been suggested as a means for accumulating and recalling desired aspects of individual total medical records, for assisting certain aspects of medical diagnosis, and for collecting and evaluating exceedingly important medical statistics as well as for greater public health control and for the medical information retrieval processes discussed above. For example, just the availability of the biochemical and physiological indices of an *individual's* normal state of health, which in general deviate from the *population* norms now used, may serve as an invaluable tool in instituting preventive measures *before* diseases occur, as well as in diagnosing disease states. The feasibility of such a system from a computer technology point of view is unquestioned, since there are already computers that carry out such closely related processes as making nationwide airline and hotel reservations, recording, updating, and tallying bank accounts and other financial records, controlling large-scale defense installations, and so forth. However, such a health computer network is probably still a concept of the far-distant future, for much research and planning is evidently still necessary on almost every phase of the problem.

Problems and Obstacles

Cross-disciplinary training. Although the potentialities of computers in the biomedical sciences are very great, there are several formidable problems that occur at present in connection with their more widespread use in this field. First is the gap that frequently exists between the knowledge and training of the biomedical research worker and the knowledge necessary to use the computer. There is great need for cross-disciplinary training in this area to give biologists a more thorough knowledge of those subjects required for the utilization of a computer and also to give those skilled in computer engineering and use a knowledge of the basic biological problems to which computers may be applied. In general the most fruitful applications of computers to biological problems will probably arise from the biologist who has gained the knowledge prerequisite to using the computer—for it is, of course, still primarily knowledge of the biomedical problems that must be used to evalute and judge which problems can benefit most from application of computers. However, the engineer or mathematician who can understand the significance of the various biological research developments and who knows the language of biology and medicine can be of invaluable assistance. I strongly believe that "team" approaches, where the biologist has no computer-oriented training and the engineer or programer has no biological training, are foredoomed to failure. For the full significance of the extensively detailed and often subtle aspects of the use of computers in biomedical science can be understood only by those well grounded in both fields.

From the point of view of the biomedical scientist, the main subjects in this cross-disciplinary gap lie first in the specific techniques of the actual utilization of the computer, that is, coding and programing, and second, in the mathematical methods and techniques that form the analytical basis for the statement of the problem and its preparation in a form appropriate for the use of a computer. For example, studies in the following subjects could help to bridge the gap: (i) basic coding and programing of digital computers, including the use of the automatic programing aids currently being extensively developed; (ii) sampling methods and techniques for appropriately preparing (that is, digitalizing and interpreting) experimentally generated data for use on the digital computer; (iii) minimum basic electronics and knowledge of the problems involved in analog-to-digital and digital-to-analog conversion; (iv) the origins of numbers, the meaning of significant figures and their relation to relative errors, and the effect on significance of arithmetic operations; (v) the meaning of the function concept, the classification of functions by analytic properties, the approximation of functions by series and otherwise, and numerical techniques for function evaluation; (vi) the meaning and utilization of differential equations, and techniques for their numerical evaluation; (vii) the elements of modern algebra, including Boolean algebra and related subjects; (viii) basic probability and statistics; (ix) critical analysis of the techniques of the scientific method, such as model building, testing of hypotheses, the problems of overdetermined and underdetermined systems, and so forth. This may appear as a severe and formidable course of study, but the technical problems that frequently arise in these uses of computers can be crucial. The very nature of digital computers makes stringent demands on those who wish to utilize them, almost independently of the particular application.

Necessary peripheral equipment. The second important problem associated with the use of computers in the biomedical sciences is the frequent necessity for understanding and handling rather elaborate electronic peripheral equipment. The biomedical researcher must in general work closely with experimental data and results, which he frequently generates in large amounts (in contradistinction to the physicist, who can often approach his field from an almost purely theoretical standpoint). Before these data can be utilized by the computer, they must first be converted into a form appropriate for input to the computer's memory. The electronic equipment that performs this conversion, known as peripheral equipment, besides being costly is frequently not available commercially. And even if it is commercially available, more likely than not modifications are necessary to make it compatible with the experimental setup. Thus specialized electronic equipment, often uniquely designed for the particular experimental setup involved, must frequently be constructed.

The most common problem associated with peripheral equipment is concerned with data that are generated in analog form. The digital computer requires that the analog data be periodically sampled, and converted into numerical form, by means of an analog-to-digital converter. Here problems of the data-sampling rate and also of the number of significant figures in the converted result must be dealt with. The analog data often are recorded first, to be later digitalized and read into the computer (see Fig. 4). The analog re-

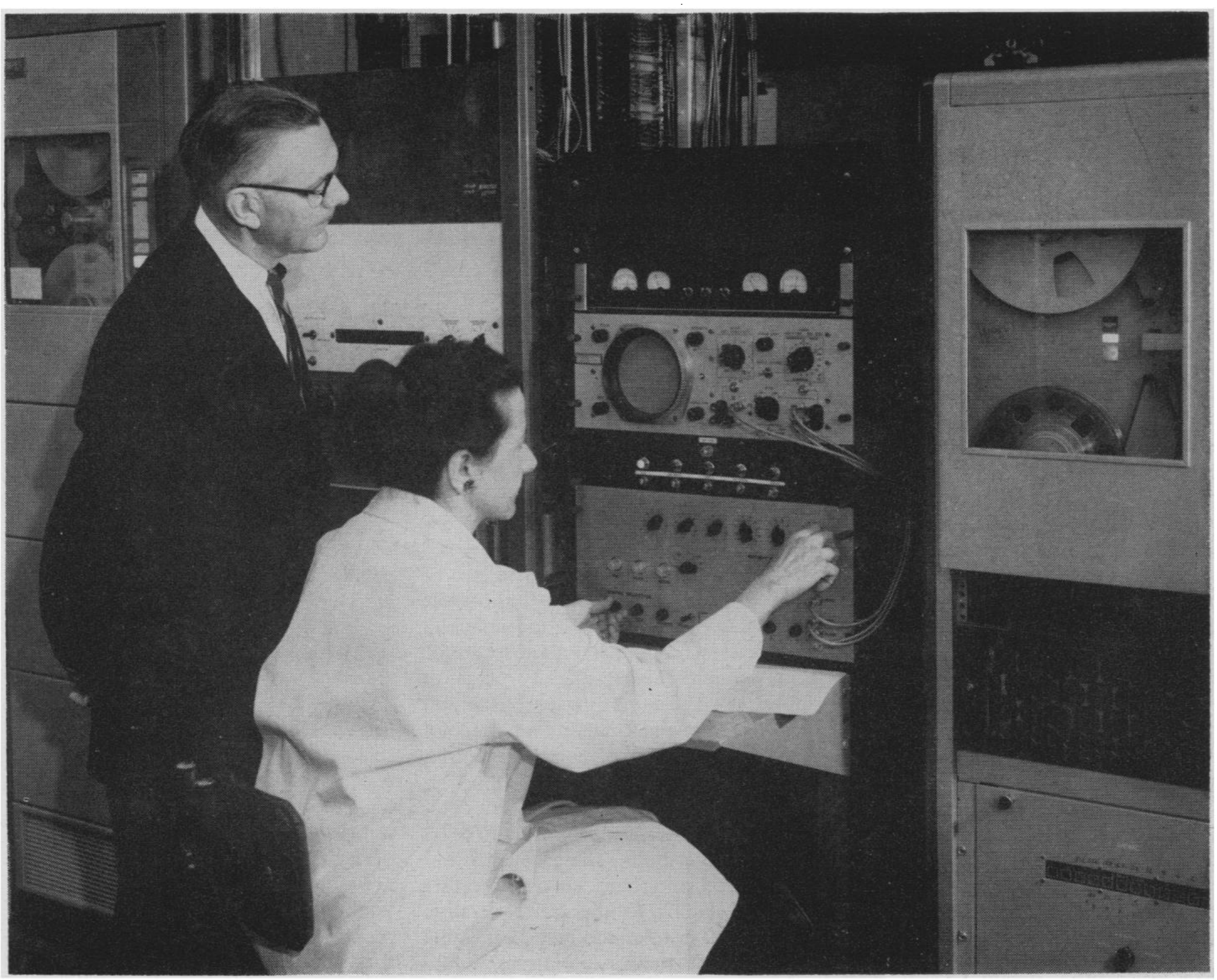

Fig. 5. Equipment for preparing electrocardiograph records for input to a digital computer, developed for the Veterans Administration at the National Bureau of Standards, showing the magnetic tape recorder containing the analog electrocardiograph records, the analog-to-digital converter, the format adapter and synchronizer for the insertion of additional information, and the magnetic tape recorder containing the digital data. [Courtesy National Bureau of Standards]

cordings can be made on magnetic tapes, by oscillographic recording, or by other means. However, the converted or digitalized data are still not ready to be read into the computer. First the numerical data must be organized into a format appropriately adapted to the particular computer used. This requires another piece of electronic equipment. Frequently additional information describing the data (for example, date, run number, specifications of the experiment) is incorporated at this time into the already converted data. Again it is sometimes convenient to record the processed information, usually on magnetic tape; this time, however, the magnetic tape can be used as direct input to the computer (see Fig. 5). Of course, not all these steps are always necessary: for example, when the computer is used in a real-time experiment—that is, when the output of the computer is to help control the experiment—it is usually desirable to transmit the generated experimental data directly through the analog-to-digital converter and format adapter into the computer, with no intermediate recording. Different kinds of analog-to-digital converters are required, depending on the forms of the analog information. For example, the most commonly used converters accept analog input as a voltage magnitude; a picture-reading machine converts black and white areas into digital form; various converters are available for mechanical analog-to-digital conversion, and so forth.

Other types of peripheral equipment frequently required are those concerned with the output of the computer, for example, special printers, pictorial displays, or digital-to-analog-output voltage converters. Still other functions performed by peripheral equipment are concerned with the transmission of digital data between computers, or between the computer and some distant location such as a hospital or a research center.

Technical communication and the exchange of ideas. Research has two aspects which seem opposed: on one hand it is very personal and private in the sense of individual creativity, while on the other hand it is gregarious, its life blood and very existence based on the extensive exchange of ideas. So it is with computer programing. In fact, it is reasonable to say that a good portion of the ingenuity and creativity of the biomedical researcher will be embodied in his coding. The accuracy, flexibility, and intrinsic structure of the computer program are of central importance in the utilization of computers. A major portion of the time and energy of a biomedical researcher using computers, and of the money he spends, is consumed in the process of setting up and evaluating his program. Therefore, he will have a strong desire to exchange ideas, and to communicate to the scientific world some of the technical advances he has made in the programing itself. However, at the present time this is indeed difficult to accomplish, for existing biological journals generally have not yet recognized the importance of the contribution of such technical communications. There are many reasons for this, one of which is the unique technical language that necessarily appears in discussions of computer programs. There are two major journals that might provide outlets for this information—the *IRE Transactions on Medical Electronics* and the *Journal of the Association for Computing Machinery*—although at present several problems are involved. The *IRE Transactions* covers the much broader field of medical electronics, and it may be questionable whether the majority of its readers are interested in coding and programing details, while the ACM journal has not itself been completely successful as an outlet for computer programs, even in fields other than biomedical science. Hence there is a need for a suitable medium to enable the exchange of ideas on the use of computers in biomedical science.

Costs and availability of computers. Another important problem to be faced in the utilization of computers in biomedical science is the high costs, incurred directly in computer usage and in the procurement and maintenance of peripheral equipment. At the present time this is coupled with the difficulty of obtaining computer time, because of the generally higher priority given to physical and engineering problems and the frequent unavailability to the biomedical researcher of necessary peripheral equipment. The cost of time on a large-scale, high-speed digital computer generally runs from $200 to $300 and more per hour. The problem is not one of reducing this cost, but rather one of coming to the full realization that this is part of the cost of utilizing computers. Again, the usually substantial costs incurred in procuring or constructing, and maintaining, peripheral equipment is characteristic of the utilization of electronic equipment, no matter what the field of application. The major problem facing many biomedical researchers in this regard is that until recently expenditures of such large amounts were not customary. The average biomedical research grant is still in the neighborhood of $15,000 per year. Thus the biomedical researcher who finds that just a part of the peripheral equipment necessary to use computers can start with costs of $15,000 or more, may understandably be reluctant to plan for the utilization of computers.

Another closely related factor is that much biomedical research is now oriented about the individual researcher: he carries through almost all phases of the research himself, frequently with little or no assistance. The number of man-hours required to construct a complicated computer program is often much too large for any single individual to accomplish alone, in any reasonable time. Thus in many instances biological scientists may find orientation toward individual research incompatible with the use of computers. I do not intend to give the impression that all computer utilization will have this characteristic, for this is far from true. But there will arise a large number of cases where the staff approach, involving the partitioning of the problem into smaller parts among the members of an integrated group, becomes an absolute necessity. This again increases the magnitude of the costs that will be incurred in research projects. From this point of view projects utilizing computers in biomedical science will frequently become more costly than heretofore. But we cannot neglect the vastly increased capabilities such computer usage presents for the exploration of the complicated and intricate biophysical and physicochemical basis of biological systems.

Conclusions

The use of computers in biomedical science vastly increases the researcher's capabilities in approaching the exceedingly complicated and extensive computations so frequently required for investigation of the more modern quantitative and mathematical biochemical and biophysical concepts. The computer makes feasible approaches to problems that could not otherwise be solved; it opens up entirely new methods of biomedical investigation; it holds promise for assisting in the more efficient utilization of research results. Significant applications of computers are found in almost every aspect of biomedical research endeavors. Although there presently exists great interest in the use of computers among biomedical research workers, we are only on the threshold of understanding their full potential capabilities. However, many severe obstacles and problems must be overcome before their full utilization can be realized. Among these are the urgent needs for personnel trained in cross-discipline fields, for more extensive exchange and communication of technical scientific information in the field, and for a thorough appreciation of the generally larger resources and efforts that must frequently be associated with such use of computers.

Biomedical research workers should be encouraged to explore the extensive research opportunities offered by the utilization of computers. Toward this end the National Academy of Sciences –National Research Council is sponsoring the preparation of a survey and monograph on the use of computers in biomedical research. This project is supported by the U.S. Air Force Air Research and Development Command, and the National Institutes of Health. The survey will include past, present, and proposed applications of computers to biology and medicine, and is designed to stimulate ideas and methods for tackling various problems. The monograph, planned to appear in the summer of 1960, is designed to function as a semi-handbook, an attempt to assist in bridging the technical gap that frequently exists between the biological researcher's training and experience and the knowledge he needs in order to use computers. It is hoped that this effort will play at least a small role in encouraging the more complete understanding and fuller realization of the tremendous potentials of computers in biomedical science.

Note

1. I wish to express appreciation to the many people throughout the country who generously discussed with me many research ideas and projects concerning the use of computers in the biomedical sciences. Special thanks are due to Louis S. Rotolo, James Bruce Wilson, and Catherine Deininger for assisting me in this study.

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Further Evidence of Vegetation on Mars

The presence of large organic molecules is indicated by recent infrared-spectroscopic tests.

William M. Sinton

There has long been evidence pointing to the presence of vegetation on Mars. Photographs taken by E. C. Slipher at Lowell Observatory for decades have shown a seasonal variation in the intensity of the dark regions. Every spring and summer, coinciding with the melting of the ice caps, a wave of darkening spreads from the polar regions toward the equator (*1*). In addition to the seasonal variation there have been nonsystematic changes: areas that were never dark have become dark, and a few dark areas have become light and have blended into the desert regions. A striking case of the appearance of a dark region occurred in 1954, when an area of 580,000 square miles at longitude 240° and latitude 20° was newly dark (*2*). The region in which it is situated has, however, been undergoing development for many years.

Some visual observers have often reported the dark regions as green or bluish, while others have found them neutral in color. Spectroscopic tests have also failed to find them green. The green color that is often seen may be only a complementary hue produced by the bright orange colors of the deserts.

Until recently there has not been a successful direct test for the presence of plants. Tests for the presence of chlorophyll have all been negative (*3; 4*, p. 362). These tests, which sought to find the high reflectivity characteristic of terrestrial plants in the near infrared, do not necessarily exclude chlorophyll. They can be explained if supposed Martian plants possess a pigment that absorbs the near infrared.

Using the 61-inch telescope of the Harvard College Observatory during the 1956 opposition, I made a new test for the presence of organic molecules on Mars (*5*). Organic molecules possess strong absorption bands at 3.5 μ as a result of the resonance of their carbon-hydrogen bonds. It was found that in the plants tested this band was double, most likely as a result of interaction between a pair of hydrogen atoms attached to the same carbon atom, as occurs in paraffin molecules.

The results of the 1956 observations indicated the presence of the band in the light reflected from Mars, but they left some doubt about the reality of the absorption. Furthermore, the regions of Mars which produced the absorption were not ascertained in this work. At the 1958 opposition the test was made again with improved equipment, and the reality and distribution of the band were established.

Instrumentation

As in 1956 the infrared from Mars was analyzed spectrally with a monochromator. A great improvement in sensitivity was obtained with a new liquid-nitrogen-cooled lead sulfide detector that was custom made by Infrared Industries, Inc. A further improvement was obtained by alternating the dispersed radiation from Mars between two separate detecting areas incorpo-

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