SIMULATION IN LIFE SCIENCES

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Modeling has long been important in the life sciences, but detailed, physically based models have only begun to be used. The range of application and the variety of mathematical methods used is already great. New computer hardware advances should make life sciences modeling more practical in the near future.

I. INTRODUCTION

The great importance of modeling in all science has been well-stated by Rosenblueth and Wiener (ROS-45) who point out that

> "The intention and the result of scientific inquiry is to obtain an understanding and a control of some part of the universe",

and that

> "No substantial part of the universe is so simple that it can be grasped and controlled without abstraction. Abstraction consists in replacing the part of the universe under consideration by a model of similar but simpler structure."

The great complexity and variability of biological organisms have led to the use of models for their study (HAR-66) (BEN-72) (PER-68) (VIC-74), though not without some questions and doubts. Since modeling is essential to all scientific thinking, it would seem that these doubts must relate to the methods used in modeling. These methods, more and more, are based on the use of mathematical descriptions, which in turn are simulated on computers. The growth in the use of computer simulation in biomedical and life sciences generally indicates that there is some growth in acceptance of such methods in these "soft" sciences.

In this paper the scope of present applications of modeling in life sciences will be examined, and a long but not exhaustive classification set of such applications will be given. References will include some examples of recent work in each of the various applications, together with some older basic important papers and books. A list of mathematical and computer techniques used in modeling, also not exhaustive will be given. Finally, present trends and future possibilities will be examined.

II. APPLICATIONS OF MODELING

The three principal stages of work in most of sciences are:

(1) Measurement (2) Modeling (3) Use of models

In this paper little attention can be given to the important techniques of measurement, relating to instrumentation and data acquisition; attention will be focused on techniques and uses of modeling.

Modeling, in the life sciences, has three principal uses:

(1) In research to assist in the verification of hypotheses, and to suggest new approaches in experimental work.

(2) In teaching, to demonstrate basic principles.

(3) In clinical and applied work generally, to aid in the determination of procedures, such as patient treatment.

Applications in the literature refer almost exclusively to the first of these three uses. In the list of eighteen modeling application areas that follows, most of the references are given as recent examples. Reference will be made to two quite different modeling schemes — physically-based or deductive modeling related to structure and internal functioning of a system, and black box or inductive modeling in which the model is derived from input and output signals with no particular relation to the structure of the system being modeled (SHA-69).

(1) *Neural Models*

Excellent reviews of neural modeling have been given by Ashby (ASH-66) and by Harmon and Lewis (HAR-66). In the latter reference it is shown that models may be devised to work at various levels, from the study of membrane excitation, pioneered by Hodgkin and Huxley (HOD-52), through pulse processing in single neurons, relationships in networks of neurons (DEU-67) and large system (e.g., eye tracking) studies.

A recent example of physically-based neural modeling is given by Plonsey (PLO-74), while Marmerelis and Naka (MAR-74) given an example of inductive or input-output modeling. Rotterdam, et al (ROT-74) and Greco and Clark (GRE-76) described neural modeling in which physically based methods are used wherever possible, with input-output schemes used elsewhere. Such a scheme seems to be the best possible in most modeling problems including more than a small portion of the nervous system.

Neural systems represent at once the greatest need and the greatest challenge for modelers, because of their great importance in physiological function, and because of their complexity. Microelectronics may be of great help here in the future, both in measurement instrumentation and for use in simulation computers.

(2) *Sensory Systems*

Sensory systems such as those of vision and hearing involve sensory acquisition of data from the environment, neural system processing of this data and in some cases feedback control mechanisms (for eye tracking, for example). Developments in these fields have been marked by the discovery of important non-linearities in pupplary response (CLY-61) and the study of complex hydrodynamics in the cochlea (VON-70) (PET-50) (GEI-76).

(3) *Physiological Regulatory Systems*

Typical systems involving feedback control but in which most sensors are internal include heart rate control (RUS-61) (GUY-63) (CHE-74), lung ventilation control (GRA-49) (SMI-74), and the regulation of body water and electrolytes (ELK-60). Models of these systems are usually based on a combination of physical and input-output modeling, the latter being used for portions of the control system involving the central nervous system. Combination of interacting control systems in one model may lead to rather large simulations.

(4) *Muscle Models*

Models of a muscle based on the work of Huxley (HUX-57) and others usually have a 3-element form (BRA-67) (STE-74) (GLA-74). The modeling of a skeletal muscle system (INB-76) requires the simulation of at least a pair of opposing muscles, together with a complex neural control. Muscle mechanics have also been applied to studies of the heart (DON-71), where they must be combined with fluid flow models.

(5) *Body Motion Models*

A number of studies have been made (FRA-70) (GUB-74) (TOW-73) on the kinematics of walking or other gaits of bipeds. These studies may be related to study of the human, design of prosthetics, or, in the case of quadruped studies, to walking machines. Rather different studies relate to body motions caused by heart action (ballistocardiography) (STA-67). Modeling studies have been made that inter-relate heart motion to fluid flow and heart movements (TOM-74). Many models, important in vehicle safety study, have been developed for study of the mechanics of the human spine (SCH-73) (CRA-76) and of the human head (TAL-75) under stress or impact.

(6) *Prosthetic and Life Assist Device Modeling*

The modeling of prosthetic devices such as artificial limbs, heart valves or life assist devices is much like any engineering device or system modeling. Such models (LAU-71) may also need to include a physiological model of some related sub-system.

(7) *Pressure-Flow or Momentum Transport Modeling*

The modeling of pressure-flow dynamics of blood flow in the circulatory system (BEN-72) or of air flow in the lungs and associated airways (GOL-73) both require the use of some form of the wave equation. In most dynamic simulations the partial differential equations for wave motion are converted to difference form for digital computer simulation, or to difference form except in the time dimension, for analog simulation (RID-67). In some cases, physical models may be used in connection with studies of such devices as heart valves or balloon pumps (JON-72).

(8) *Mass Transport Modeling*

Mass transport may occur by diffusion, or because a substance is carried by fluid flow. Diffusion, as described by the partial differential equation for diffusion, is usually modeled in a difference or difference-differential form known as compartmental analysis (ATK-69). In the fluid flow case the pressure-flow equations (above) may be used to "drive" the mass transport model, resulting in a multiple model (RID-75-11). Usually, however, this flow transport can be handled by compartment analysis, like that used in diffusion studies.

Some recent papers from the vast literature on applications of compartmental analysis have been included among the references (FIN-75) (BRO-75) (HOW-75) (SMIT-74) (SUD-75) (YAO-73).

(9) *Chemical Reaction Models*

Biochemical reactions are of the greatest importance in physiology, and may need to be modeled in connection with, for example, muscle studies (CHA-65). Typically these reaction equations are imbedded in the compartment equations used with mass transport.

(10) *Thermoregulatory System Modeling*

The transport of heat by fluid flow and diffusion is usually handled by compartment analysis methods like those used in mass transport studies. However, the details of the model and the involvement with the central nervous system are quite different. A review of this field by Bligh is rather complete and useful (BLI-66) while a recent paper by Seagrace is illustrative of present work in thermoregulation (SEA-74). Stolwijk and others at the Pierce Foundation are known for their detailed model studies of thermoregulation in the human (HARD-70).

(11) *Population Dynamics Modeling*

Population modeling (SCH-71) is usually of more concern to demographers than to physiologists, but some aspects (WAR-75) may be classified as bioscience. Perhaps more importantly, the mathematics of population dynamics is used in cell dynamics and epidemic modeling (see below). Reference will be made later in this paper to the stochastic nature of population models.

(12) *Cell Dynamics Modeling*

The growth of cells may be described with the aid of mathematics developed to describe population dynamics (DON-75) (LUM-75). Discrete modeling programs have been specially written for the study of cell dynamics (EVE-75) (MAU-73). Closely related to cell dynamics is embryonic development. Here graphical methods have also been used (BEZ-75).

(13) *Epidemic Modeling and Simulation*

Epidemic models may also be based on the mathematics of population dynamics. Both deterministic and stochastic models have been used to study epidemics in large populations, and spatial factors may have to be included (BAI-67). Chain-binomial models are used in small-scale epidemic studies. A recent example of epidemic modeling concerns rubella (HOR-74).

(14) *Genetics and Chromosome Mapping*

The mathematical modeling used in genetics is again related to that used in population dynamics studies (IOS-73). Graphics may also be used in connection with chromosome mapping aspects of genetics (BAI-67).

(15) *Ecological Modeling*

Modeling of ecology relates to population modeling, but must include effects of the environment and of inter-species competition (GIL-74).

(16) *Medical Diagnosis*

Continuing efforts are being made to apply computers to medical diagnosis, which usually involves some modeling of the diseases being considered. Also the diagnostic process itself has been modeled (WIE-75). Some of the diagnostic techniques used involved cluster techniques (HAN-74) and learning techniques (LIV-73).

(17) *Hospital Organization and Management and Health Services Modeling*

A variety of modeling schemes have been used in the study of hospital organization and operation ranging from the empirical recursive models of Vaananen, et al. (BAI-74) to the dynamics state variable models of Gudaitis and Brown (GUD-75). Discrete modeling is used, in general, and statistical methods may employed (KAO-74). Auxiliary functions, such as blood-bank organization have also been modeled (RAB-73).

Health Services studies differ from hospital models discussed above in that they may deal with screening procedures (HART-73), health indices, (CHI-73) or mental health centers (ROB-72).

(18) *Medical Education System Modeling*

A number of efforts have been made to model various aspects of systems of medical (FOR-74) and nursing (QUI-73) education. The importance of physiological teaching models (BROD-73) (ENG-75) (RID-72) was referred to earlier in this paper.

III. MATHEMATICAL AND COMPUTER TECHNIQUES USED IN MODELING

The proper description of many biological systems requires the use of partial differential equations, which must be time-dependent unless only static solutions are of interest. In order to obtain solutions these equations must be converted to ordinary differential equations by the use of finite difference approximations (PORE-60) or by the use of finite element methods (HUE-75).

The proper description of many biological systems requires the use of partial differential equations, which must be time-dependent unless only static solutions are of interest. In order to obtain solutions these equations must be converted to ordinary differential equations by the use of finite difference approximations (FORE-60) or by the use of finite element methods (HUE-75).

Some of the areas of science which provide the basic descriptive equations which in turn may be expressed as ordinary differential equation approximations include biochemistry, hydrodynamics, thermodynamics and chemical kinetics.

Milsum (MIL-66) has discussed the application of control system theory to biological systems, and Beneken has given examples of such applications in the cardiovascular field. More general papers on system theory applied to biology have recently appeared (LAZ-74) (MCL-74) as well as description of discrete system simulation (GUD-75).

Probability and Statistics are of great importance in neural modeling as well as population dynamics and related fields (BAI-67) (CHI-73) (IOS-73). More indirectly, they are useful in most of the modeling mathematics listed below.

Information Theory has been used in connection with identification in compartmental analysis Reich and Zinke in (BAI-74), in neural studies (BAR-74), and cardiovascular system parameter estimation (RID-75-2).

Identification and parameter estimation (EYK-74) techniques have been applied both for input-output model building (MAR-74) and finding parameter values of physically-based models (RID-75-2).

Both game theory and decision theory have been discussed by Quastler (WAI-65) as bases for modeling, and dynamic programming has been used by Christ (CHR-73) in studies of computer-aided diagnosis. These methods are generally referred to as operations research.

Graphical methods (as discussed by Waterman in (WAT-65) and Bailey in (BAI-61)) are important in genetics and have been used in such diverse fields as the study of embryonic development (BEZ-75) and of aging (KAN-75). Pattern recognition has been used in diagnosis (PAT-74).

Although analog computers have long been used in the study of dynamic systems described by ordinary differential equations, hybrid computers (BENN-74) have been more successfully used for large system simulations. Digital languages such as CSSL (Continuous System Simulation Language) have been developed for all-digital simulation (BEN-74). Other digital languages such as GPSS have been written for discrete system simulation, and augmented or improved versions of these have been developed for biological studies (REI-74) (EVE-75). Language for combined continuous and discrete system simulation have also appeared (COL-74) (SIG-74).

IV. PRESENT TRENDS AND FUTURE POSSIBILITIES FOR SIMULATION IN LIFE SCIENCES

The advent of the computer age has changed the nature of applied amthematics in the "hard" sciences and engineering by making it possible to seek numerical solutions which are more direct and have less approximations than the closed-form solutions of the past era. However, new mathematical methods, particularly in numerical analysis, have had to be developed along with computer hardware.

In the "soft" sciences, the use of mathematics was never as highly developed, and the problems encountered in simultaneously beginning to use both computers and the new computer-oriented applied mathematics have been great. New instrumentation devices have provided large amounts of new and important data on which models can be based. All these complexities may help to explain some of the lack of acceptance of modeling techniques in the biosciences as well as in environmental-economic-social models such as those of Forrester (VIC-74). The rather general acceptance of computers and computing, and the steady improvement in computers and computer programs together with the efforts being made to apply simulation in the biosciences should help to overcome reluctance to use the more involved models for which the new methods are most useful.

Of the three principal uses of life sciences modeling (research, teaching, applied), only the first two are in general use today. But computers are now beginning to be used in closed loop care of patients (SHE-74), and it may be expected that as these methods are further perfected and as computers are improved, clinical applications of large scale modeling will appear.

Research modeling has been hampered by the difficulties of programming hybrid computers, or the poor man-machine communication and inadequate speed of serial digital computers. The recent development of the micro-processor and integral circuit memory devices, now often combined as a complete computer on a tiny silicon chip.

This may soon make possible an all-digital hybrid computer of reasonable cost. Such a machine should provide much greater speed of solution of large simulations than the serial digital machine of today (WIN-75) and yet possess its usual advantages of precision, floating-point operation, logical capability and memory, which are lacking in analog machines.

COMPUTER SIMULATION STUDY OF THE CARDIOVASCULAR AND RELATED PHYSIOLOGICAL SYSTEMS

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Summary

This paper gives a brief overview of some of the present problems and achievements in cardiovascular modeling. Typical of most of the simulations described is a level of complexity such that all-analog simulation often requires too slow. Thus, with today's technology, a hybrid computer is an essential simulation tool. Fortunately, in both the case of multiple model simulation, and that of parameter estimation, the describing equations may be logically divided into groups suitable for solution on the two parts of a hybrid computer, with the overall result that real time operation, or faster, is possible.

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ANALOG COMPUTER SIMULATION OF ABNORMAL PERIODIC BREATHING

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Abstract

The human respiratory system is compared to a technological feedback control system. Oscillation of the technological system is discussed and related to abnormal oscillation of human respiration (Cheyne-Stokes breathing). A mathematical model of the human respiratory control system, utilizing CO_2 control of respiration only, is derived and programmed on an analog computer. The resulting computer study has shown that, as in the technological system, an increase of open-loop gain and/or delay time around the open loop can cause the respiratory system to become unstable and oscillate in an abnormal manner.

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COMPUTER SIMULATION STUDIES OF THE VENOUS CIRCULATION

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Abstract

An analog computer model of the human cardiovascular system has been set up in which detailed attention was given to the representation of pressure and flow events in the veins, including effects of gravity, collapse, breathing, and the action of venous valves. This model, which includes a control loop for heart rate, was checked against human venous pressure waveforms and against response of the human to tilt-table experiments. These comparisons indicate that the model is valid for the study of postulated venous tone control characteristics; it should be useful in the study of the mechanisms of venous return and circulatory system response during unusual acceleration conditions.

V. *REFERENCES*

(ASH-66) Ashby, W.R., "Mathematical Models and Computer Analysis of the Function of the Central Nervous System", *Am. Rev. Physiol. 28*, p. 89, (1966).

(ATK-69) Atkins, G.L., *"Multicompartment Models for Biological Systems"* Methuen & Co. Ltd., London, (1969).

(BAI-61) Bailey, N.T.J., "The Mathematical Theory of Genetic Linkage", Clarendon, Oxford, (1961).

(BAI-67) Bailey, N.T.J., *"The Mathematical Approach ot Biology and Medicine"*, John Wiley & Sons, London, (1967).

(BAI-74) Bailey, N.T.J., Sandor, B.I. and Tsanev, R., Eds., *"Mathematical Models in Biology and Medicine"*, North-Holland Pub. Co., Amsterdam, (1974)

(BAR-74) Barrett, T.W., "Analog to Digital Conversion of Information: A Structural Model of the Basic Functional Unit of the Central Nervous System", *T. I. T. Jl. of life Sci.*, 4, pp. 59-66, (1974).

(BEA-60) Beament, J.L. (Ed.), *"Models and Analogues in Biology"*, (Symp. of Soc. for Exptl. Biol., No. 14), Academic Press, N.Y., (1960).

(BENN-74) Bennett, A.W., *"Introduction to Computer Simulation"*, West, St. Paul, (1974).

(BEN-74) Beneken, J.E.W., "Some Computer Models in Cardiovascular Research" in *Cardiovascular Fluid Dynamics*, D.H. Bergel, Ed., Academic Press, London, (1972).

(BEZ-75) Bezem, J.J. and Raven, C.P., "Computer Simulation of Early Embryonic Development", *Jl. Theor. Biol., 54*, pp. 47-61, (Oct. 1975).

(BLI-66) Bligh, J., "The Thermosensitivity of the Hypothalamus and Thermoregulation in Mammals", *Biol. Rev. 41*, pp. 317-367, (1966).

(BRA-67) Brady, A.J., "The Three-Element Model of Muscle Mechanics, Its Applicability to Cardiac Muscle", *The Physiologist, 2*, p. 75, (1967).

(BRO-75) Brodan, V., Hajek, M. and Kucian, J., "Analog Model of Kinetics of Calcium in Healthy Subjects during Alimentary Ca Absorption", *Comput. Biol. Med., 4*, pp. 257-267, (1975).

(BROD-73) Brody, H.A., Lucaccini, L.F., Kamp, M. and Rozen, R., "Computer-Based Simulated Patient for Teaching History-taking", *Jl. Dent. Educ. 37* (8), pp. 27-31, (August 1973).

(CHA-65) Chance, Britton, "Transients in Metabolism: An Approach to the Chemical Mechanisms of Metabolic Control", in *Theoretical and Mathematical Biology*, T.H. Waterman and H.J. Morowitz, Eds., Blaisdell, New York, (1965).

(CHE-74) Chess, G.F. and Calaresu, F.R., "A Mathematical Model of the Vagus-Heart Period System in the Cat", *IEEE Trans. BME-21*, pp. 21-27, (Jan. 1974).

(CHI-73) Chiang, C.L. and Cohen, R.D., "How to Measure Health: A Stocchas--tic Model for an Index of Health", *Int. Jl. Epidemiol.* 2(1), pp. 7-13, (Spring 1973).

(CHR-73) Christl, H.L., "The Use of Dynamic Programming in Sequen-Diagnostic Methods", *Method Inf Med. Suppl. 7,* pp. 209-214, (1973).

(CLY-61) Clynes, M., "Unidirectional Rate Sensitivity: A Biocybernetic Law of Reflex and Humoral Systems as Physiologic Channels of Control and Communication", *Annales N.Y. Academy of Sciences 92,* pp. 946-969, (1961).

(COL-74) Colella, A.M., O'Sullivan, M.J. and Carlino, D.J., *"Systems Simulation",* D.C. Health & Co., Lexington, Mass., (1974).

(CRA-76) Cramer, H.J., Liu, Y.K. and von Rosenberg, D.U., "A distributed parameter model of the inertially loaded human spine", *Jl. Biomech. 9*(3), pp. 115-130, (1976).

(DEU-67) Deutsch, S., *"Models of the Nervous System",* Wiley, N.Y., (1967).

(DON-75) Donaghev, C.E., "A Computer Simulation Program for the Study of Cellular Growth Kinetics", *Comp. and Biol. Res., 8,* p. 118, (1975).

(DOND-71) Donders, J.J.H. and Beneken, J.F.W., "Computer Model of Cardia Muscle Mechanics", *Cardiovasc. Res Suppl. 1,* pp. 34-50, (1971).

(ELK-60) Elkinton, J.R., "Regulation of water and Electrolytes", *Circulation 21,* pp. 1184-92, (1960).

(ENG-75) Englert, R., "Demonstration of an Electronic Analog Computer for Simulation of Pharacokinetic Models used in Teaching", *Naunyn Schmiederbergs Arch. Pharmacol. 287,* Suppl. R68, (1975).

(EVE-75) Evert, C.F., Jr., "CELLDYN, — A Digital Program for Modeling the Dynamics of Cells", *Simulation,* pp. 55-62, (Feb. 1975).

(EYK-74) Eykhoff, P., "System Identification-Parameter and State Estimation" John Wiley, (1974).

(FIN-74) Finkelstein, S.M. *et al.,* "In Vivo Modeling for Glucose Homeostasis", *IEEE Trans. BME-22,* pp. 47-52, (Jan. 1975).

(FOR-74) Forsyth, B.R., *et al.* "Computer Modeling in Planning Graduate Medical Education", *Jl. Med. Educ. 49*(3), pp. 200-283, (March 1973).

(FORE-60) Forsythe, G.E. and Wasow, "Finite Difference Methods for Partial Differential Equations", Wiley, New York, (1960).

(FRA-74) Frank, A.A., "An Approach to the Dynamic Analysis and Synthesis of Biped Locomotion Machines", *Med. Biol. Engg., 8,* pp. 465-476, 1970).

(GAB-75) Gabrovec, I., Kordas, M. and Popovic, B., "An Attempt at Simulation of the End-plate Current, *Jl. Theor. Biol., 55,* pp. 29-45, (Nov. 1975).

(GEI-76) Geisler, C.D., "Mathematical Models of the Mechanics of the Inner Ear" in *"Handbook of Physiology: The Auditory System"* 5(2), W.D. Keidel and W.D. Neff (Eds.), Springer-Verlag, Munich, (1976).

(GIL-74) Gilpin, M.E., "A Model of the Predator-Prey Relationship", *Theor. Popul. Biol.* 5(3), pp. 333-344, (June 1974).

(GLA-74) Glantz, S.A., "A Constitine Equation for the Passive Properties of Muscle", *Jl. Biomech.,* I, pp. 137-145, (1974).

(GOL-73) Golden, J.F., Clark, J.W., Jr. and Stevens, P.M., "Mathematical Modeling of Pulmonary Airway Dynamic, *IEEE Trans. Biomed. Engg., BME-20,* pp. 397-404, (Nov. 1973).

(GRA-49) Gray, J.F., *"Pulmonary Ventilation and its Physiological Regulation"* Thomas, Springfield, III., (1949).

(GRE-76) Greco, E.C., Jr. and Clark, J.W., Jr., "A Mathematical Model of the Vagally Driven SA Nodal Pacemaker", *IEEE-TBME BME-23(3),* pp. 192-199, (May 1976).

(GUB-74) Gubina, F., H mami, H. and McGhee, R.B., "On the Dynamic Stability of Biped Locomotion", *IEEE Trans. Biomed. Engg. BME-21,* pp. 102-108, (March 1974).

(GUD-75) Gudaitis, W.V. and Brown, R.A., "Modeling a Hospital Organization", *IEEE Trans. SMC-5,* pp. 441-446, (July 1975).

(GUY-72) Guyton, A.C., *et al.*, "Circulation: Overall Regulation", *Ann. Rev. Physio. 34,* pp. 13-46, 1972.

(GUY-63) Guyton, A.C., *"Circulatory Physiology: Cardia Output and its Regulation",* Saunders, Philadelphia, (1963).

(HAN-73) Hansert, E., "A Model for Analysis of Symptom Clusters in Alternative Symptoms", *Methods Inf. Med. Suppl. 7,* pp. 187-196, (1973).

(HAR-66) Harmon, L.D. and Lewis, E.R., "Neural Modeling", *Physiological Reviews, 46,* pp. 513-591, (July 1966).

(HARD-70) Hardy, J.D., Gagge, A.P. and Stolwijk, J.A.J., (Eds.) *"Physiological and Behavioral Temperature Regulation",* Thomas, Springfield, III., (1970).

(HART-73) Hartz, S.C., "A Statistical Model for Assessing the Need for Medical Care in a Health Screening Program", *Clin. Chem. 19*AVQ, pp. 113-116, (Jan. 1973).

(HOD-52) Hodgkin, A.K. and Huxley, A.F., "A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve", *Jl. Physiol. 117,* p. 500, (1952).

(HOR-74) Horwitz, J.S. and Montgomery, D.C., "A Computer Simulation Model of a Rubella Epidemic", *Comp. Biol. Med., 4,* pp. 189-198, (1974).

(HOW-75) Howell, J.R. and Huf., E.g., "Metabolic Compartmentation in Amphibian Skin Epidermis: A computer Simulation Study", *Computers and Biomed. Res. 8,* pp. 72-87, (1975).

(HUE-75) Huebner, K.H., *"The Finite Element Method for Engineers,"* Wiley, New York (1975).

(HUX-57) Huxley, A.F., "Muscle Structures and Theories of Contraction", *Progr. Biophys. Chem. 7,* pp. 255-318, (1957).

(INB-76) Inbar, G.F. and Joseph, P.J., "Analysis of a Model of the Triceps Surae Muscle Reflex Control System", *IEEE Trans. SMC-6,* pp. 25-32, (Jan. 1976).

(IOS-73) Iosifescu and Tautu, P., *"Stochastic Processes and Applications in Biology and Medicine II-Models",* Springer-Verlag, Berlin, (1973).

(JON-72) Jones, R.T., "Fluid Dynamics of Heart Assist Devices" in *"Biomechanics"* Y.C. Fung, N. Percone and M. Auliker, Eds., Prentice Hall, (1972).

(KAN-75) Kanungo, M.S., *"A Model for Aging", Jl. Thebr. Biol. 53,* pp. 253-261, (Sept. 1975).

(KAO-74) Kao, E.P.C., "Study of Patient Admission Policies for Specialized Care Facilities", *IEEE Trans., SMC-4,* pp. 505-512, (Nov. 1974).

(KAR-75) Karfunkel, H.R., "A Computer Program for the Simulation of the Temporal and Spatial Behavior of Multi-Component Chemical Reaction-Diffusion Systems in the Plane", *Comp. Biol. Med., 5,* pp. 29-38, (1975).

(LAU-71) Lautier, A., Grossin, R. and Laurent, D., "The Use of Mathematical and Physical Models for Optimization of Oxygenators", Trans. *Am. Soc. Artif. Intern. Organs 17,* pp. 303-308, (1971).

(LAZ-73) Lazlo, C.A., Levine, M.D. and Milsum, J.H., "A General Systems Framework for Social Systems", *Behavioral Scie., 19*(2), pp. 79-92, (Mar. 1974).

(LIV-73) Lively, W.M., Szygenda, S.A. and Mize, C.E., "Modeling Techniques for Medical Diagnosis. I. Heuristics and Learning Problems in Selected Neonatal Hepatic Disease", *Comput. Biomed. Res. 6*(4), pp. 393-410, (Aug. 1973).

(LUM-75) Lumb, J.R., "A Regenerating Computer Model of the Thymus", *Comp. Biol. Med., 5,* pp. 379-392, (1975).

(MAU-73) Mauer, A. M., Evert, C. F., Jr., Lampkin, B. C. and McWilliams, N. B., "Cell Kinetics in Human Acute Lymphoblastic Leukemia: Computer Simulation with Discrete Modeling Techniques", *Blood, 41,* pp. 141-154, (Jan. 1973).

(MAR-74) Marmarelis, P.Z. and Naka, K.-I., "Identification of Multi-Input Biological Systems", *Trans. IEEE Biomed. Eng'g., BME-21,* pp. 88-101, (March 1974).

(MCL-74) McLead, J., "Behavioral Science, System Theory and Simulation", *Behavioral Science, 19*(1), pp. 57-69, (Jan. 1974).

(MES-68) Mesarovic, M.D. (Ed.), *Systems Theory and Biology,* Springer, (1968).

(MIL-66) Milsum, J.H., *"Biological Control Systems Analysis",* McGraw-Hill, New York, (1966).

(PAT-74) Patrick, E.A., Stelmack, F.P. and Shen, L.Y.L., "Review of Pattern Recognition in Medical Diagnosis and Consulting Relative to a New System Model", *IEEE Trans. SMC-4,* pp. 1-16, (Jan. 1974).

(PER-68) Perkins, W.J. and Hammond, B.J., "The Mathematical Study of Biological Systems", *Biomedical Engineering,* pp. 113-118, (March 1968).

(PET-50) Peterson, L.C. and Bogert, B.D., "A Dynamical Theory of the Cochlea", *Jl. Acoust. Soc. of Amer., 22,* pp. 369-381, (1950).

(PLO-74) Plonsey, R., "The Active Fibre in a Volume Conductor", *IEEE Trans. BME-21,* pp. 371-381, (Sept. 1974).

(QUI-73) Quiring, J., "A Model for Curriculum Development in Nursing", *Nurs. Outlook 21*(11), pp. 714-716, (Nov. 1973).

(RAB-73) Rabinowitz, M., "Blood Bank Inventory Policies: A Computer Simulation", *Health Services Res. 8*(4), pp. 271-282, (Winter 1973).

(REI-74) Reitman, J., "The Engineering Role of Simulation", *IEEE Trans. SMC-4*, pp. 208-213, (March 1974).

(RID-67) Rideout, V.C. and Dick, D.E., "Difference-Differential Equations for Fluid Flow in Distensible Tubes", *IEEE Trans. BME-14*, pp. 171-177, (1967).

(RID-72) Rideout, V.C., "Cardiovascular System Simulation in Biomedical Engineering Education", *IEEE Trans. BME-19*, pp. 101-107, (Mar. 1972).

(RID-75-1) Rideout, V.C., "Mass Transport Simulation using Compartments and Multiple Modeling", *ISA Trans. 14*, pp. 109-114, (1975).

(RID-75-2) Rideout, V.C. and Beneken, J.E.W., "Parameter Estimation Applied to Physiological Systems", *Proc. AICA, 17*, pp. 23-36, (Jan. 1975).

(ROB-72) Robins, A.J., "Administrative Process Model for Community Mental Health Centers", *Community Ment. Health Jl., 8*(3), pp. 208-219, (Aug. 1972).

(ROS-45) Rosenblueth, A. and Wiener, N., "The Role o Models in Science", *Phil. Sci. 12*, pp. 316-321, 1945.

(ROT-74) Rotterdam, A. Van, Habets, A. and Wouters, W., "Field Potentials in the Dentate Area of the Cat — Experimental Findings and Biophysical Models", *Prog. Rpt. 4*, Inst. Med. Phys., Utrecht, pp. 104-113, (1974).

(RUS-61) Rishmer, R.F., "Cardiovascular Dynamics," Suanders, Philadelphia, (1961).

(SAF-76) Saffer, S.I. *et al.*, "Use of Non-Linear Programming and Stochastic Modeling in the Medical Evaluation of Normal-Abnormal Liver Function", *IEEE-TBME, BME-23*(3), pp. 200-206, (May 1976).

(SCH-73) Schultz, A., *et al.*, "Analog Studies of Forces in the Human Spine: Mechanical Properties and Motion Segment Behavior *Jl. Biomechanics, 6*, pp. 373-383, (1973).

(SCHW-71) Schweitzer, D.G. and Dienes, G.J., "A Kinetic Model of Population Dynamics", *Demography 8*(3), pp. 389-400, (Aug. 1971).

(SEA-74) Seagrave, R.C., "A Model of Human Thermoregulation During Water Immersion", *Comp. Bio. Med. 4*, p. 165, (1974).

(SHA-69) Shapiro, H.M., "Input-Output Models of Biological Systems: Formulation and Applicability", *Computers and Miomed. Res. 2*, pp. 430-445, (1969).

(SHE-74) Sheppard, L.C. and Kirklin, J.W., "Cardiac Surgical Care Computer System", *Fed. Proc. 33*(12), pp. 2326-28, (Dec. 1974).

(SHI-74) Shinners, S.M., "Modeling of Human Operator Performance Utilizing Time Series Analysis," *IEEE Trans. SMC-4*, pp. 446-458, (Jan. 1974).

(SIG-74) Sigal, C.E. and Pritsker, A.A.B., "SMOOTH: A Continuous-Discrete Network Eimulation Language", *Simulation 22*, pp. 65-73, (March 1974).

(SMI-74) Smith, E.J. and Dutton, R.E., "Dynamic Model of Ventillatory Response to Changes in PO_2 at the Carotid Body Chemoreceptors", *IEEE Trans. BME-21*, pp. 227-231, (May 1974).

(SMIT-74) Smith, G.A. and Llaurado, J.G., "Computer Modeling of Nonsteady State Sodium Kinetics in Liver". *IEEE Trans. BME-21*, pp. 433-443, (Nov. 1974).

(STA-67) Stair, I. and Noordergraaf, A., *"Balistocardiography in Cardiovascular Research"*, Lippincott, Philadelphia, (1967).

(STE-74) Stern, J.T., Jr., "Computer Modeling of Gross Muscle Dynamics", *Jl. Biomech.*, *7*(5), pp. 411-428, (1974).

(SUD-75) Sudova, K. and Langer, P., "Iodine Kinetics and Hypothalmo-Pituitary Regulation of Thyroid Function Following its Short-Term Inhibition", *Computers and Biomed. Res. 8*, pp. 88-96, (1975).

(TAL-75) Talhouni, O. and DiMaggio, F., "Dynamic Response of a Fluid-Filled Spherical Shell — An improved model for Studying Head Injury", *Jl. Biomech. 8*(3/4), (1975).

(TOM-74) Tomek, I., "Simulation of the Motion of the Heart", *Simulation, 22*, pp. 76-80, (March 1974).

(TOW-73) Townsend, M.A. and Seireg, A.A., "Effect of Model Complexity and Gait Criteria on the Sythesis of Biped Locomotion, *IEEE Trans. Biomed. Engg., BME-20*, pp. 433-444, (Nov. 1973).

(VIC-74) Vichnevetsky, R., "Modeling, Simulation and Interdisciplinary Research", *Tech. Rpt.* 32, Dept. of Computer Sci., Rutgers Univ., N.J., (1974).

(VON-70) VonBekesy, G., "Enlarged mechanical model of the cochlea with nerve supply" in *"Foundations of Modern Auditory Theory"*, J.V. Tobias (Ed.), Academic Press, N.Y., (1970).

(WAR-75) Warner, R.D., Robertson, D.R. and Leigh, E.G., Jr., "Sex Change and Sexual Selection", *Science*, 190, pp. 633-638, (Nov. 14, 1975).

(WAT-65) Waterman, T.H. and Morowitz, H.J., (Eds.) *"Theoretical and Mathematical Biology"*, Blaisdell, New York, (1965).

(WIE-75) Winer, F., "Computer Simulation of the Diagnostic Process in Medicine", *Computers and Biomed. Res., 8*, pp. 129-142, (1975).

(WIN-75) Winograd, S., "On the Speed Gained in Parallel Methods", in *New Concepts and Technologies in Parallel Information Processing*, E.R. Caianiello, NATO Advanced Studies Institute Series, Series E, Applied Sciences No. 9, Noordhoff Intl., (1975).

(WOO-73) Woo, J. and Rootenberg, J., "Digital Simulation of an Adaptive System for Long-Term Ventilation of the Lungs", *IEEE Trans. Biomed. Eng'g., BME-20*, pp. 475-476, (Nov. 1973).

(YAO-73) Yao, H. and Diana, J.N., "Computer Simulation Model for Transient Transcapillary Fluid Exchange", *IEEE Trans. Biomed. Eng'g., BME-20*, pp. 427-433, (Nov. 1973).