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COMPUTER MODELING of COMPLEX BIOLOGICAL SYSTEMS

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TABLE OF CONTENTS

Chapter 1

COMPUTERS IN SIMULATION AND MODELING OF COMPLEX BIOLOGICAL SYSTEMS

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TABLE OF CONTENTS

I. INTRODUCTION

Simulation and modeling are important investigative techniques in any research activity for they provide a methodology for the design, development, experimentation, analysis, and evaluation of an experiment under study. Simulation which in plain words mean feigning of a particular situation provides a common base of techniques for the study of a diversity of projects and is a means for investigating a large number of ill-defined but solvable problems. Simulation provides a challenging atmosphere which is conducive to problem solving although it approximates the actual structure of the system. Simulation may be carried out either with a digital or an analog computer. Analog computers are mostly used for the study of behavior of mechanical systems and as such their use is limited to problems related to mechanical and/or electrical engineering. Digital computers are electronic data processing devices with incredible speed. Consequently, they have wide applications in biology, chemistry, agriculture, sociology, and in other branches of natural sciences and humanities. Hybrid computers which are a combination of both analog and digital could be used to simulate more complex problems. Computer systems, whether analog, digital, or hybrid, because of their high degree of modularity and collective complexity are natural objects of simulation models. For example, a month of computer processing can be simulated depending upon the complexity of the model on one computer run of less than 30 min.

The heart of simulation is the precise mathematical description of the system to be simulated. There are many reasons why a mathematical expression is preferred to a verbal explanation to describe a system. One reason is that several systems involve many different processes occurring simultaneously. The natural language is limiting when used for mathematical description of the system. Many of the most important behavioral aspects of complex systems such as nonlinearity, redundancy, and hysteresis cannot be explained in verbal terms, whereas a mathematical description of these concepts is often both compact and precise; this can be illustrated with a few examples.

Suppose we are interested in building a mathematical model which can predict the population growth of a particular town or city. The town or city in this instance can be considered as a biological system and let "N" be the number of people at a given time, "t". Then the rate of growth of the population with respect to time, is dN/dt. The rate can be calculated in a different way. Let us assume that there are no exogenous variables such as war, famine, or pestilence affecting the system. Under these assumptions, the rates of increase by birth and decrease by mortality are constant. Obviously the number of births is proportional to the number of people alive, similarly the number of deaths. If the birth rate is "b" and the death rate is "d", the total number of births is b.N and deaths is d.N. Therefore, in a time δt, we have $(bN.\delta t)$ and $(dN.\delta t)$ births and deaths respectively.

The change in population $= \delta N = (bN\delta t - dN.\delta t)$

$$\frac{\delta N}{\delta t} = (bN - dN) = (b - d)N = \alpha N$$

$dN/dt = \alpha N$, where α is the excess of the birth rate over death rate.

A mathematical model similar to the one above can be constructed for any biological system where natural growth or decay occurs. Consider the production of certain antibiotics produced from bacterial cultures which are grown in controlled conditions. The growth of bacteria or microorganisms is governed by the same natural formula:

$$\begin{aligned} (dN/dt) &= \alpha N \\ dN/N &= \alpha dt \\ \log N &= \alpha t + c \\ N &= e^{\alpha t + c} = e^{c} = Ae^{\alpha t} \end{aligned}$$

To evaluate the constant A, we use some unknown initial conditions: Say N = N, when t = 0

$$N_0 = A\,e^0 = A$$
$$N = N_0 e^{\alpha t}$$

This is an exponential law (+ve index), and so the rate is ever increasing. In the real world situations, these assumptions may not hold.

A second example to demonstrate the application of mathematical modeling in biological systems is the growth of bacterial cells in a culture medium. Suppose, the number of bacteria in a culture medium grew at a rate proportional to the number present initially. If in an experiment, it was observed that in 1 hr the number grew from an initial 100 to 332, and we are required to build a mathematical model to predict the number of bacterial cells at the end of $1^1/_2$ hr, then, let at time "t", the number of bacteria be "x"; dx/dt = rate of bacterial growth; this rate is proportional to the number of bacteria present, namely "x" is positive. So, we have,

$dx/dt = kx; \qquad x = A\,e^{kt}$ (1)

Initially it was 100; $(t = 0, x = 100)$ (2)

It grew to be 332, in 1 hr; $(t = 1, x = 332)$ (3)

To find the number, when $t = 1.5$ (4)

$100 = A\,e^0; A = 100; x = 100\,e^{kt}$ (5)

$322 = A\,e^{k.t} = 100\,e^k; e^k = 3.32$ (6)

When $t = 1.5$, $x = A\,e^{(1.5)k} = 100\,e^{1.5k} = 100\,(3.32)^{3/2}$

$\log_{10} x = 10g\ 100 + (3/2)\log\,(3.32) = 2 + (3/2)(0.5211)$

$= 2 + 0.7816 = 2.7816$

$x = 60.47 = 605$

In the preceding paragraphs, we have often used the word "system". An understanding of the meaning and characteristics of a system is approriate before we talk about "system modeling".

The term system is used in various ways by various people to cover many uses under differing contexts. However, in broad terms, a system may be defined as that arbitrarily chosen portion of space which is under discussion. All else is called the surroundings. The system is separated from the surroundings by either an imaginary or a real boundary line. To avoid uncertainty regarding what is specified as the system, its boundaries must be defined precisely. This decision may depend upon the purpose of the study. Closed systems are those across whose boundaries matter does not pass; in open systems matter does pass. The state of a system is fixed by describing the properties of the system at any given time. A process is said to occur in a system when any sort of change or transformation takes place. These changes are due to certain interactions taking place among various entities within the system. An entity in a system is defined as an object of interest which has separate existence. The property of an entity is called its activity. Therefore, the state of a system at any given moment can be defined as the description of all entities, attributes, and activities of that given system. Activity in any process is that which causes change in the system. During the process, the system changes from an initial state to a final state through a series of intermediate states. These series of intermediate states are called the paths of the process. Anything that crosses the boundary line and enters into the system is called the "input" and the ones that leave the system are called the "output". When the activity that causes change within the system can be described in terms of its input, the activity is called deterministic whereas stochastic activities are those which vary randomly and the output is

not characterized by the attributes of the input. If the rate of change in a system over a period of time is constant, it is called a continuous system and if changes are discontinuous, they are called "discrete systems". Free systems are either wholly continuous or discrete. A homogeneous system is one in which the attributes of the entities are the same throughout and in a heterogeneous system the attributes of the entities vary from point to point. Endogeneous variables account for the activities of entities within the system and exogeneous activities are from entities outside of the system. Open systems have exogeneous activities and closed systems have endogeneous activities.

A. System Modeling

Modeling may be defined as the construction of a prototype, either mathematical or verbal, which approximately describes the behavior of a system under study. Behavioral models are especially needed where experimentation is physically or economically not practical, such as a situation study which has not been completely defined or a plan which is yet on a drawing board. There are two approaches to the study of behavior: one is experimental performed in a laboratory and the other is modeling. The models should be as abstract as possible and still be predictive. In other words, a model is something that mimics closely and foretells the relevant features of a system under consideration. The performance of a model is measured by the accuracy with which the model can predict the characteristics when applied to the system for which it was designed to handle. Accurate prediction by the model is affected to different degrees by numerous factors such as (1) proper design which includes proper specification of the system, surroundings, and the boundary lines and (2) identification and definition of individual and interrelationships of endogeneous and exogeneous entities some of which may be dependent variables and other independent variables. Absence of any information which is essential for construction of the model will lead to certain assumptions being made. The conclusions drawn from such a model will be greatly affected by the kind of assumptions made and also the input which enters into the system. A false or an unrealistic assumption leads to wrong or invalid conclusions. In brief, it can be stated that the main function of a model is to predict the performance criteria of a system under a set of conditions. Other benefits of modeling include: the design of meaningful laboratory experiments, evaluation of conflicting experimental results, and possibly offering an explanation for the differing results. If properly executed, a model should be much more efficient than either a theoretical or experimental process taken alone.

B. Model Types

Models are mainly classified into two groups: (1) physical and (2) descriptive. Descriptive models may be expressed in native languages or in terms of mathematical symbols to describe the status of variables in the system and the way the variables change and interact. Mathematical modeling needs a good knowledge of calculus.

Physical models are based on physical properties or comparison between mechanical, physical, or electrical systems and may be floor plans of a home or an industrial complex, pilot model plants of a distillation column, or instruments or means to measure the mechanical properties of a material. The advantage of a physical model is that it can be explained to any individual with limited technical knowledge. However, physical models are expensive to build, have limited use in that the model can be used only for the particular problem for which it was designed, and offer very narrow and unimaginative information to the decision-making process. Verbal descriptive models have limited communication and sometimes cannot be replicated. However, these models are the least expensive and so have found common uses in the decision process. Mathematical models mimic the conditions of a system in mathematical language or in precise mathematical formulas, which are concise and can be manipulated with ease. Besides, mathematical modeling can use numerous theorems which are available and can use high speed computers for quick calculations. Theorems are

useful in drawing conclusions from simple models and computers are useful in drawing specific conclusions from complicated models. Furthermore, mathematical analysis of a system facilitates the construction of a tentative hierarchy, whereby each of the dependent and independent variables are rated according to the degree of their activity on the system.

Here, we are exclusively concerned with only mathematical models based on digital computers of certain complex biological systems.

C. General Methods in Building a Model

Model building is as much an art as it is a science. It involves intuition, imagination, and skill. It is impossible to state a set of rules to build a mathematical model as much as it is not possible to draw a picture or paint a landscape following a list of regulations. It depends upon the viewpoint and judgment of the modeler to decide which information should be included or emphasized and to what extent in the model. However, it is possible to offer a set of guidelines or a framework around which the modeler can develop and improve his skill and imagination to build a model. Besides, experience and common sense are the other ingredients of a good model process. The guidelines or framework are very general and applicable to most systems. The specific characteristics of each system determines its own framework which should be explored by the modeler himself. The following are some of the considerations to be remembered prior to any modeling process:

1. Understand the system and its components of which the model is to be built. These include the system structure, the system entities and their activities on the system undergoing a change or transformation, interrelationships among various entities, dependent and independent variables, system boundary and its surroundings, exogenous and endogenous parameters, etc.
2. Define in clearly understandable language the objectives of the model, what it is supposed to accomplish, what data are given, and what additional data or information is needed.
3. Review your model building methodology more than once and obtain an answer as to the method under consideration will accomplish the objectives for which the model is to be designed.
4. Make a thorough literature review on system models to determine whether any modeling or approaches suggested by other investigators for systems which are closely similar to having analogous characteristics of the system under consideration. A good literature review process should not only benefit the modeler in having a better grasp and understanding of the system under his consideration, but also will forewarn him of some of the obstacles, bottlenecks or surprises which he may encounter.
5. Classify and formulate the given data. Wherever possible, reduce the verbal data into mathematical or statistical symbols or formulas. Sort out the relevant data, facts, information, or logical parts of the problem from the superfluous.
6. Examine what mathematical or statistical theory or law is applicable to process the given data and to arrive at a solution.
7. Identify what additional data are needed and how and where to go about getting these data to complete the model.
8. If the modeling process involves a large complex system, try to individualize parts of the problems which may finally lead to one comprehensive answer. In order to do this, divide the large system into smaller blocks and represent the interrelationships of the sub-blocks by arrows. Such a pictorial block-arrow diagram of a complex and large system will facilitate easy understanding of the complexity of the system.
9. Check each sub-block or part of the system for its characteristics, its significance in the overall problem, its logical position in relation to other sub-blocks, its individual contribution in the final solution, and to what extent the individual sub-blocks affect the quality of the final model designed.

10. Synthesize results of each part of the model to verify whether the final model corroborates the individual solution.
11. Pay particular attention to the fact that the model proposed is sufficiently flexible to accommodate varying input/output data.
12. Establish the accuracy of the model needed. It should be useful, feasible, and fit the situation.
13. Test the model and obtain some predicted values. Validate the model by comparing the predicted with true or experimental values. If the difference is too large or statistically significant, work backward to modify or refine the model. If there are no mathematical or logical errors and if the model is less accurate than anticipated, check your assumptions to make certain that they are valid.
14. Always indicate the limits of the model so that the person who uses the model is aware of the restrictions of the model.

This preceding information is presented for the benefit of biologists who may not be familiar with certain simulation and modeling terminologies. The rest of this chapter is an overview of areas in biology in which computers can be used to manipulate and analyze enormous amounts of complex data.

II. OVERVIEW

A. Computers in Ecology

There are two principal ways in which computers can be utilized to study ecology. First, computers may be used for data storing, correlation, and statistics. Because ecology deals with such exceedingly complex systems of organisms, it yields data in bewildering richness. Under the best of circumstances, the analysis of this data can be so time consuming as to be practically impossible if one has to analyze it using nothing more sophisticated than, say, a desk calculator. Modern computers have changed this. Now, more and more ecological data are being obtained in a form that can be fed directly into a computer for analysis. The availability of machines that are capable of handling large amounts of data has removed much of the barrier to considering highly complex systems but, needless to say, it has not eliminated the necessity for the researcher to know precisely what he is attempting to learn from his ecological data. On the contrary, the computer has placed more of a burden than before on the ecologist to formulate his questions in a very precise way. One suspects, perhaps, that this secondary effect is at least as important to the study of ecology as the more obvious one of allowing the ecologist to analyze heretofore unassailable quantities of data.

The analysis of models is the second and, perhaps, more interesting way in which a large computer can be of assistance to the ecologist. Much work has recently been done on the problem of reducing ecological problems to problems in mathematics, that is to say, to the construction of mathematical models. Because problems in ecology are themselves so complex, the models based on the ecological system are also exceedingly complicated. Hence, the analysis of these models has depended in great part on modern computers.

For example, one might be interested in the fluctuation of a certain population of organisms as a function of the food supply and the predation. At first glance, this might seem quite simple. As the food supply increases, it is certainly reasonable to expect that the population will increase. On the other hand, an increase in the number of predators will tend to decrease the population. Hence, one might obtain a set of mathematical expressions that serve to describe how the population under study varies with the food supply and the number of predators. But even such a simple-sounding model might, in fact, turn out to be quite complicated if one requires, as one should, that the model be capable of predicting results

that can actually be observed in the field. For example, an increase in the population of a certain species often heralds an increase in the populations of the species that prey upon the given organisms. It has been documented, for instance, that the populations of snowy owls in the arctic increase during times when lemmings are in abundant supply. And, another consideration: not only is the population dependent upon the food supply, but the food supply per individual is usually dependent upon the population. For example allowing too many sheep to graze on a certain tract of land may kill the grass. And finally, even if the food were in unbounded supply, the territory available to the population is usually not. For instance, it has been observed in some rats that over-crowding can cause a decrease in the population. Hence, constructing a model, which at first glance seemed childishly simple, turns out to be in reality very complex. In the actual construction of any model that is to represent a complicated system, it is safe to say that a considerable period of trial and error ensues before the model begins to predict what can actually be observed. In other words, it is usually necessary to make a number of adjustments in the model before it becomes a reasonable one. Therefore, it is very helpful if one can quickly obtain the effect that varying one of the parameters in a model will have on the model. For this reason, a computer that can, for example, plot the predicted population of a certain species is very useful.

Let us illustrate with an example how modeling can be helpful in predicting the population of a country with some given data. Suppose, it is known from a census data that the population of a particular country has doubled itself in 40 years and we are required to build a mathematical model which can predict a number of years at the end of which time the population will triple. Assume the law of natural growth applies. At time "t", if the population is "N", then:

$$(dN/dt) = k.T; \qquad N = N_0\, e^{kt} \tag{1}$$

$$\text{Here, } t = 40,\ N = 2N_0,\ 2N_0 = N_0.e.40.k;\ e^{40k} = 2 \tag{2}$$

When $N = 3N_0$, required to find "t"

$3N_0 = N_0\, e^{kt}$; $e^{kt} = 3$; $kt = \log_e^3$

Also, $e^{40k} = 2$; $\qquad 40\,k = \log_e^2$

$$\text{Hence, } kt/k.40 = \log 3/\log 2;\ t = \frac{(1.0986)}{(0.6931)} = \underline{63.2} \text{ years}$$

If you want to change the assumptions regarding, say, the change in the population of the predator as a function of the change in the population of the organism under study, then you can quickly see the change that the model predicts in the population under study.

B. Computers in Physiology

As in the case of ecology, computers are used in the physiological sciences to analyze experimental data and to evaluate models.

For example, one can extract from data the kinetic constant that relates the rate of reaction to the reactant concentration. Here, the trick is to fit the constant to the experimental data in such a way as to minimize differences between the experimental curve and the appropriate enzyme rate equation. In addition, computers have proved useful in the analysis of results that deal with very complicated metabolic and physiological problems. One such example is the flow of material through branching pathways and across cellular membranes. In many cases, these processes are fairly well understood only on the cellular level. Computers appear to be of great service in extending our understanding to the indescribably more complex case of a multicellular organism. Finally, computers are of great importance in the construction and evaluation of physiological models.

While it is true that any model that can be analyzed on a computer can also, in principle, be analyzed via manual means, the time required for the latter may make it a practical impossibility. And even if it is possible, the time required may be so great as to severely limit the number of alternative models that it is practical to evaluate.

One can quickly appreciate the utility of a computer-borne model by a considerably very simple case of a hypothetical metabolic pathway consisting of several reactions as shown diagrammatically by

$$A \rightleftharpoons B \overset{2}{\rightleftharpoons} C \overset{3}{\rightleftharpoons} \ldots$$

Imagine, furthermore, that each of these individual reactions is well understood, that is, the values for maximum velocity and Michaelis constant, k_m, are known. We simply want to know if the pathway is as drawn, that is, is it a nonbranching series in the order shown? This may be accomplished by comparing the rate of flow through the sequence (which is measurable in the laboratory) with the predicted rate under a variety of conditions. We obtain the predicted rate by solving a set of enzyme rate equations that take into consideration the fact that the product of one reaction is the substrate for the next. We might begin by making the steady-state assumption; i.e., we assume that the concentrations of the intermediates remain constant with time. This would require that the rate of formation and breakdown of each intermediate be the same and would therefore greatly simplify things. Under these conditions, we could, perhaps, make our calculation with or without the use of a computer. We would then want to abandon the steady state assumption and introduce, instead, possible branches in the chain or alter the properties of some of the enzymes. One would probably want to alter more than one variable at a time. This would make the use of computer more essential.

Consider the formation of lactic acid according to the following reaction:

$$\underset{\text{milk sugar}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow[\text{lactase}]{\text{enzyme}} 4\,CH_3CHOHCOOH$$

$$(A) + (B) \longrightarrow (C)$$

For industrial purposes lactic acid is either isolated from sour milk or made by bacterial fermentation. From the point of view of a biologist, lactic acid is very important. It has been called "the keystone of muscular activity". The energy necessary for rapid muscular action appears to be supplied by the decomposition of glycogen to lactic acid. Suppose, we are required to build a model of a bimolecular reaction such as the one shown above, we can begin as follows:

Let us assume, to begin with, there are "a" molecules of "A" and "b" molecules of "B" present in the system. A and B combine to form C. At a time "t" let "N" molecules of C be formed. This is formed by using up N of A and N of B. So, there are $(a - N)$ of A and $(b - N)$ of B left over.

The rate of formation of "C" molecules is proportional to the product of the number of molecules of each substance present.

$$(dN/dt) = k\,(a - N)(b - N)$$

$$\frac{dN}{(a - N)(b - N)} = dt; \int \frac{dN}{(a - N)(b - N)} = t + \text{constant}$$

$$t + (E) = 1/(a - b) \int [(1/(b - N) - 1/(a - N)]\, dN$$

$$= \frac{1}{(a - b)} \log \frac{(a - N)}{(b - N)}$$

where T = 0, we have N = 0; (E) = 1/(a − b) log (a/b) substituting for the constant E, we have

$$t + \frac{1}{(a - b)} \log (a/b) = \frac{1}{(a - b)} \log \frac{(a - N)}{(b - N)}$$

$$t = \frac{1}{(a - b)} \log \frac{b(a - N)}{a(b - N)}$$

Likewise, if we try to be so specialized, we could speak on the subject of drug-receptor interaction, and the role of the computer in such a process.

C. Computers in Drug-Receptor Interaction

It was well known that animal cells are bounded by membranes which, apart from anything else, prevent the inner contents from spilling out. The membrane is, however, far more than a passive constraining skin: it is a dynamic structure which controls the passage of chemicals into and out of the cell. Furthermore, it is also responsible for detecting the presence of certain signals such as hormones and for passing on the appropriate message to metabolic machinery of the cell.

Hormones are in the business of communication at the cellular level: they have often been called chemical messengers. They are secreted into the blood stream by specialized glands and exert their effects on particular "target" tissues. Hormone molecules, such as the catecholamines and the protein and glycoprotein hormones have very definite molecular shapes, and their target cells are those which have on the surface of their outer membrane specific receptors for these hormones. Each type of receptor is absolutely specific for binding only one type of hormone. And each cell type in the body has its characteristic hormone receptors. Many hormones, neurotransmitters, drugs, and cellular toxins initiate their action via specific interactions with plasma membrane receptors.

At the present time, the study of hormone receptor mechanisms is entering an exciting phase. Classical receptor theory gives a mathematical description of drug-receptor interaction in terms of a dose-response relationship derived by applying the mass action law to the reversible reaction between the drug molecule and a vacant receptor. This satisfactorily explains most of the experimental findings; however, there are still experimental results which show systematic deviations from the predicted results.

A computer simulation able to check different manners of interaction was tried in order to get similar shapes to the experimental dose-response curves. A dose was taken as a set of random numbers/drug molecules/spread over the elements/cells/ of a matrix/tissue. The criterion for computing the response suggested by the classical receptor theory implicitly supposes that each cell yields a response proportional to its fraction of occupied receptors. However, this might not be the case for some tissues and that is why several alternative criteria for computing a response were classified and used in the computer program which generates dose-response curves. A special attention was paid to the hypothesis of all-or-none functioning cells, having a threshold number of receptors to be occupied in order to onset the release of a "quantum" response. The curves obtained in this case showed a similar shape to the experimental curves for which the classical approach leads to systematic deviations.

When a normal distribution of the threshold of minimal number of occupied receptors was considered, the curves became less steep/the slope for the dose equaling the dissociation constant decreased and the general shape became nearer to the shape predicted by the classical receptor theory. All the generated curves were analyzed by both linear transformations and direct least-squares method. The program is also useful for studying the distribution of drug molecules on the receptors of a tissue under other different criteria: metabolic pathways of

the drug, the presence of a competitive or noncompetitive antagonism, the time course of the steady states of a cell, the presence of an endogeneous competition giving a basal response.

D. Computers in Modeling, Structure, and Function of Biomedical Effectors

The investigation of animal limb movements needs the introduction of special models. In high accuracy measurements the acquired data are heavily linked to the model used and the same results obtained in different models may not always be comparable. Numerical calculations in the investigation of biomechanical effectors are very complicated whereas simple topological properties of these systems are very promising in applications. Construction of abstract models for observational purposes in which sets of bones, B, joints, J, and muscles, M, are considered enables the development of comprehensive biomechanical system theory in relational approach. The relational modeling used is a general method for transforming given empirical system in an abstract model. The introduction of R-extremitators as abstract open chains of BJ, BM, or BJM type gives interesting results in the investigation of many biological systems of movement. The description of R-extremitators in generalized fuzzy set notation is useful also in other applications. The determination of suitable functionals on extremitators gives the possibility of comparison of different biomechanical structures, measurement of their similarity, estimation of a coefficient of anthropomorphism for medical modeling, and other biological applications. Topological modeling enables very general and deep insight in the structure and function of biocybernetic systems of movement.

E. Computer-Aided Mathematical Models for the Biological Age of the Rat

The study of influences on the aging process requires mathematical models of the biological age as a standard against which deviations from the so-called "normal age" can be measured. A long-term cohort study with initially 1100 male Sprague-Dawley rats served to establish multiple regression models of biological age and to test influences on aging. Twenty-three parameters from a total number of 42 were selected for a general model.

By means of a factor analysis, the general model was subdivided in 6 factor models of biological age to distinguish between primary and various types of secondary aging changes. Factor 1 can be interpreted as an expression of primary aging. Factors 2 to 5 obviously represent system-specific secondary aging, including compensatory changes. Factor 6 was attributed to general changes in lipid metabolism not directly connected with aging.

F. Computers in Neurophysiological Systems

The mathematical analog-model of the nervous cell is employed to reflect axiomatically the real neuron features. The computer is engaged to investigate the functional activities of the systems composed of such elements. The computer models of random neural nets have been developed with probabilistic-statistical organization in agreement with the available neurophysiological data concerning the central nervous system structures and functions. The initial functional activity of such nets is investigated followed by the subsequent "training" of nets for certain "behavior" types; for that special computer programs are employed. The original training algorithm allows evaluation of the system structural-functioning parameters and to change them according to the instruction goal. Methods of visualizing the above-mentioned computer experiments on the drafting machine BENSON-200 have been developed, including formation of random neuron structures and their dynamics in the training process.

G. Computers in the Determination of the Effect of Body Temperature on Thermal Regulation

There are some trials to deliver breathing gas mixtures at 100% relative humidity at body temperature. To accomplish this requirement and not withstanding the large variability of

inspiratory flow patterns of patients requiring mechanical ventilatory support, these devices must incorporate heaters with high power ratings. Heater failures have resulted in fires and thermal injuries to patients.

Four simultaneously obtained temperature measurements on patients receiving mechanical ventilation over an 8-hr period reveal that as the temperature of inspired air is warmed with a humidifier to body temperature, the body heat loss through respiration is reduced. This mechanism requires a redistribution of cardiac output to the skin. Analysis revealed that skin temperature reflects peripheral perfusion. Subsequently, when the inspired gas temperature was decreased the cardiac output and oxygen uptake returned to control values.

H. Computers for Cell Analysis in Hematology

The microscopic inspection process occupies a central role in the hematology laboratory. A major portion of the work in these laboratories is involved with manually locating, classifying, and examining or counting, various cells under the microscope. For example, the purpose of the differential white blood cell examination is to establish the percentage of each of the cell types indicated in the blood stream. This involves manually locating hundreds of blood cells on a stained slide and classifying them into a number of different categories. The percentage of each cell type present is then reported as a result of the examination.

In addition to quantitatively reporting the percentages of different white blood cell types, subjective visual evaluations of the stained red blood cells are also reported. Determinations of typical cell types, variations in red cell shape, variations in red cell size, and estimates of all hemoglobin content are all made. Even though these evaluations are all subjective in nature, they are often critical to the diagnosis of anemia.

These manual processes in hematology are tedious, time-consuming, and sensitive to subjective error. The impact of automation on these visual inspection processes is to relieve the drudgery and improve the speed and throughput of tests performed in the laboratory, while also improving the quality of results. In this regard, the use of digital image processing techniques to analyze and classify peripheral blood cells has developed very rapidly in the last few years. This technology has now matured to the point where there are instruments working routinely in clinical laboratories automatically processing blood slides on a daily basis. An example of a state-of-the-art commercial system for white blood cell classification in routine use today is the Leukocyte Automatic Recognition Computer (LARC).

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Chapter 2

A FOUR-LEVEL SOFTWARE ENGINEERING APPROACH TO MODEL COMPLEX BIOLOGICAL SYSTEMS

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TABLE OF CONTENTS

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I. INTRODUCTION

Biological systems are very complex, which makes computer simulations and modeling of them difficult and challenging. Furthermore, the physiological complexities of biological systems makes it very difficult to formulate hypotheses to explain their behavior and to test such hypotheses. Many of the most important aspects of behavior of complex systems such as nonlinearity, redundancy, and hysterisis cannot be explained in verbal terms whereas, a mathematical description of these concepts is often both compact and precise. This mathematical description of the system can be described by a logical data structure language. This pseudo language (called an algorithm) can be transformed into any known programming language and can be implemented on any computing system and is also suitable for easy modifications of the model. Mathematical description of the system and software procedure modeling of the mathematical description of the system are playing an increasing role to in understanding the inherent complexity of the system. In this situation, modeling biological systems from a software engineering viewpoint gives the researcher a direct access to formulate a logical structure of all the variables of the system. In the following paragraphs we will attempt to identify those features of software engineering and the modeling process that are most important to biological systems. It is our contention that software engineering techniques are helping to model complex systems, although such a contention is admittedly far from perfect.

The remainder of this chapter is organized as follows: concepts of complexity and computer modeling, software concepts in modeling, an example, and some general conclusions.

II. CHARACTERISTICS OF BIOLOGICAL SYSTEMS

Complex biological systems are those wherein the number of attributes to describe or characterize the systems is too many, and so is the number of variables affecting the system. Not all the attributes are necessarily observable. Very often the characteristics of the biological system defy the definition, philosophy, and scope. In other words, the structure of configuration of the system is rarely self-evident. Over the past 10 years many researchers have been working with various approaches on the development of models of biological systems such as growth of cancer cells, pharmocological activity of a particular drug on humans and animals, understanding and working of DNA molecules, and cognitive process of human systems. Most notable are the works of Crick,[3] Davidson and Britten,[1] Leventhal and Davison,[12] Guyton and Coleman,[20] Coleman,[24] Iyengar and Quave,[21,22] and Iyengar.[23] Recent studies of modeling complex biological systems are available in the following references: 25, 26, 27, 28, 29, and 30.

A. Modeling Criteria of Biosystem

There are a number of criteria that must be considered in choosing a model for a given system. These include generality, development of an algorithm, computational effort, storage requirement, numerical stability, and implementation effort. Computational effort is tied to the storage requirement since one may choose to recompute values to save storage. We may think of the computational effort associated with the type of statistical modeling used. It is difficult to generalize about storage requirements since the storage requirements are dependent on both the problem solved and implementation. For most models which are used in practice, all of the algorithms are fairly stable. However, for some parameter values, some or all of the algorithms will experience numerical difficulties.

B. Model Behavior and Complexity

The use of models of computation allows the examination of the behavior of systems we wish to study and focuses attention on existence and complexity processes for the model.