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THE USE OF SYMBOLIC COMPUTER GRAPHICS IN DYNAMIC MODELS OF BIOLOGICAL SYSTEMS

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DISCLAIMER

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Mark W. Horovitz*

INTRODUCTION

Computer-based graphical techniques are now available which permit a biologist or medical researcher who is not a computer specialist to construct and test mathematical models of biological systems. I believe such methods are fun and easy to use and will be valuable if they permit us to advance beyond the extremely simple models popular in the past. These techniques are useful in studies of systems consisting of a number of interconnected elements, where each element consists of a simple well-defined operation. Tracer, chemical, and cellular kinetic studies as well as electrical and fluid-flow networks have been simulated by this method.

THE CONSTRUCTION OF GRAPHICAL MODELS

Our interactive computer graphics modeling program is named PICASSO[1,2]. I will discuss it from a user's point of view. The building blocks of our graphic structures are called elements. Each element has a name, a symbol, and a definition. An element which is not composed of other elements is called a primitive element and has a text definition. The text should be a set of statements which have meaning in some programming language such as FORTRAN or MIMIC[3]. After the user has named an element, a graphic editor is used to draw a symbol for it. Examples of such symbols are shown in Figures 1 and 2. When some primitive elements have been defined, more complicated elements can be constructed by combining the symbols for these primitives into a single new symbol, the definition of which refers back to the text definition of its components. This is called a Macro definition. Macros can be defined in terms of other Macros to build a hierarchy of connected symbols.

Models are created by arranging symbols, lines, and labels to describe graphically the desired arrangement of elements. When a graphical model has been completed, it can be automatically translated into a program. Since the user generates the text definition of his elements, he can choose to define these in any programming language for which a compiler is available on our computer.

TRACER KINETICS

I will use compartmental models of tracer kinetics to illustrate our procedures. The essentials of compartmental systems can be explained by considering a system of water tanks interconnected by pipes. Each pipe contains a pump which pumps

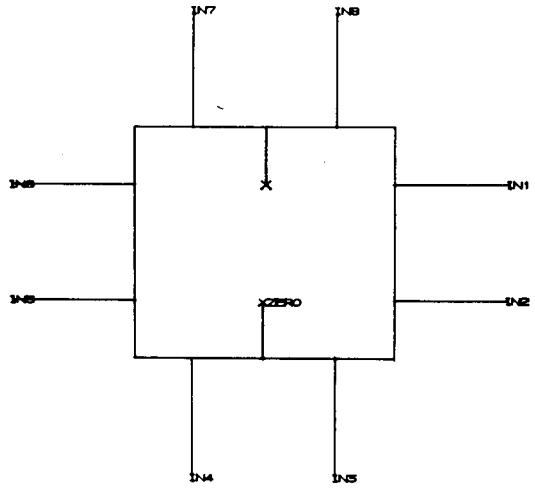

Figure 1. Symbol for compartment.

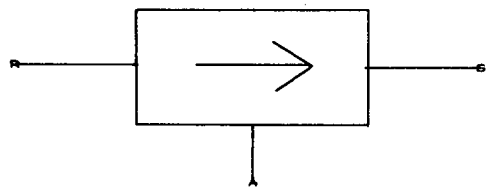

Figure 2. Symbol for flow channel.

water at a constant rate. Each tank is connected to two or more other tanks. The water flow rates are such that the system is in a steady state; the water level in each tank is constant with time. This is called a steady state compartmental system; the tanks are called compartments. We now introduce a tracer, such as a colored dye, into one of the compartments. Each tank has stirrers which keep the water and dye in the tank uniformly mixed. The dye will evenually be spread throughout the system. Our theoretical problem is to compute the distribution of tracer in each compartment as a function of time, given the compartment sizes and flow rates. In the experimental situation we have to solve the inverse problem: given measurements of the amounts of tracer in the compartments, compute the compartment sizes and flow rates.

The equations for a general steady state compartmental system and their solutions are shown in Figure 3. Figure 1 shows a graphic symbol for a compartment; the element is named COMPRT. It has eight connections and two internal variables, X and XZERO. X represents the amount of tracer in the compartment and XZERO is its initial value. In Figure 2 we see an element called CHANEL, which represents a channel of flow between compartments, it has a parameter labeled A.

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$X_i(t)$ = AMOUNT OF TRACER IN COMPARTMENT i AT TIME t

EQUATIONS

$$\frac{dX_i}{dt} = \sum_{j=1} R_{ij} X_j \qquad (i = 1, 2, \cdots, n)$$

$$R_{ii} = -\sum_{\substack{k=0 \\ k \neq i}}^{n} R_{ki}$$

SOLUTION

$$X_i(t) = \sum_{j=1}^{n} A_{ij} e^{-bjt} \qquad (i = 1, 2, \cdots n)$$

$R = A\,b\,A^{-1}$ (HERE R, A, b ARE MATRICES)

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Figure 3. Compartment analysis.

Figure 4 shows a diagram for a two-compartment model with a single flow channel. The simulation will go from zero time to time = TFIN. The symbol at the top of the diagram denotes that the program will request the user to supply parameter values for R1, XZ1, and XZ2 via the teletype. The "scope-like" symbols on the lower right side specify that CRT graphs of X_1 and X_2 versus time are to be generated. Figure 5 displays the MIMIC language program automatically generated from the simple model shown in Figure 4. An eight-compartment model, representing short-term plutonium tracer kinetics in the rat is shown in Figure 6. The compartments are labeled bone, liver, etc. Some channel flow parameters here have fixed values, others are to be varied with each simulation run. Figure 7 shows the percentage of total tracer in the BONE and PFREE compartments computed as a function of time for one particular set of parameter values. This graph is intended to illustrate the display format; the actual results and conclusions of our plutonium model have been published elsewhere [4].

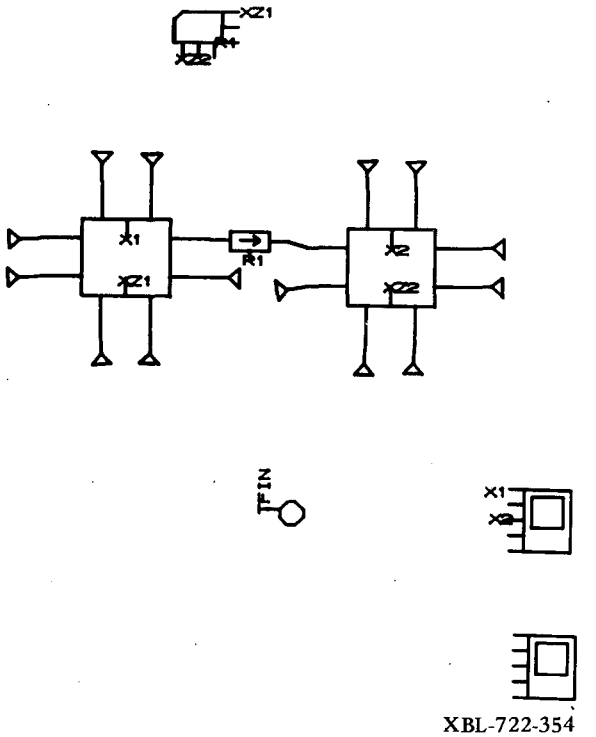

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Figure 4. Diagram for two-compartment model.

```
1  *IAM      MIMIC RUN OF COMP1 PRODUCED BY MIMVERT
2            XZ2       XZ1
3            G001      0.0
4            G002      0.0
5            G003      0.0
6            G004      0.0
7            G005      0.0
8            G006      0.0
9            FG008     X1
10           FG009     X1
11           FG006     X1
12           FG003     X1
13           FG001     X1
14           FG002     X1
15           FG004     X1
16           FG005     X1
17           X1        INT((G008+G009+G006+G003+G001+G002+G004+G005),XZ1)
18           G010      FG008*R1
19           G008      -G010
20           G009      0.0
21                     PAR(XZ2,XZ1)
22                     FIN(T,TFIN)
23           G011      0.0
24           G012      0.0
25           G013      0.0
26           G014      0.0
27           G015      0.0
28           FG016     X2
29           FG017     X2
30           FG015     X2
31           FG013     X2
32           FG011     X2
33           FG010     X2
34           FG012     X2
35           FG014     X2
36           X2        INT((G016+G017+G015+G013+G011+G010+G012+G014),XZ2)
37           G017      0.0
38           G016      0.0
39                     PLO(T)
40                     PLO(T)
41                     END
42
```

Figure 5. MIMIC program for two-compartment model.

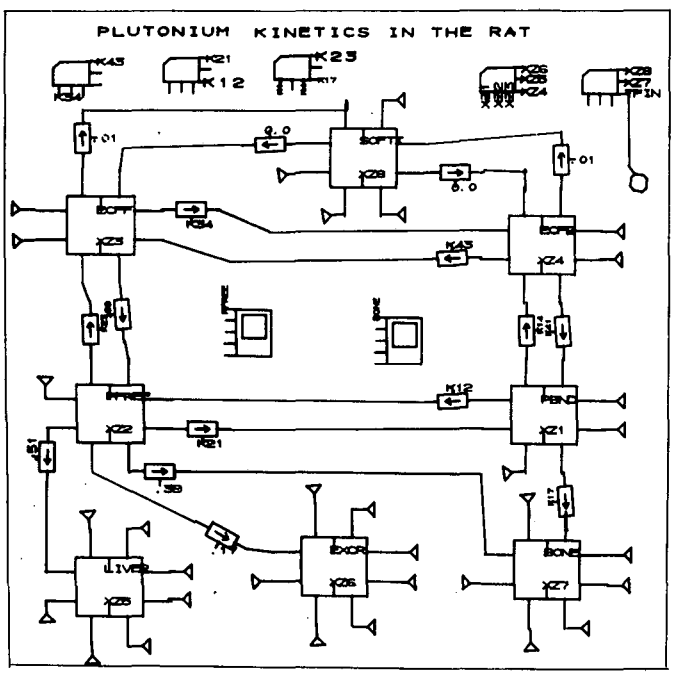

Figure 6. Plutonium kinetics in the rat.

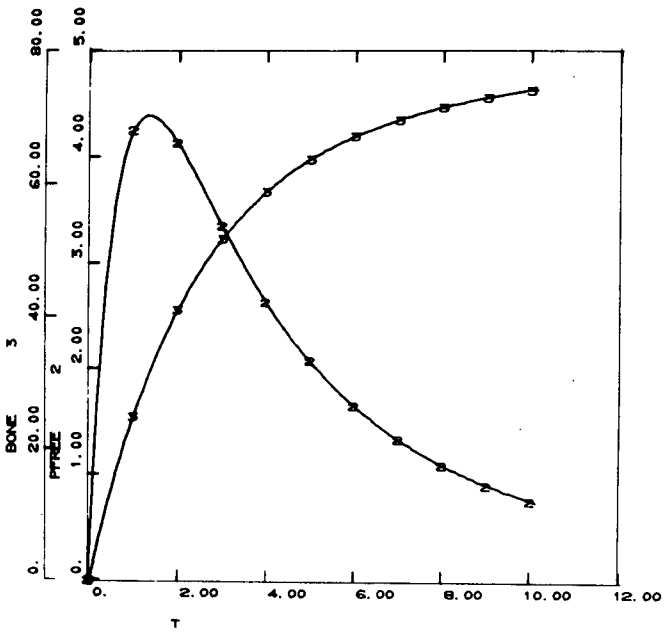

Figure 7. Simulation results for plutonium model.

THE PROCESS OF MODEL BUILDING

Let us now follow the steps that one might go through to construct and test a model such as the one shown in Figure 6. Assume that we have experimental data on the amount of tracer as a function of time after injection, in various parts of the body of the experimental animal. We start by seeking an appropriate mathematical form to fit the data, such as a power series or a sum of exponential terms. We might first try one exponential term and then successively fit two, three, and four terms, using a least-squares minimization routine. A number of interactive programs are available to carry out this task [5, 6]; we use the MINUIT program [7]. Suppose this process shows that a sum of n different exponential terms fits all the experimental data well. This would suggest that we construct and test an n-compartment model. We can use PICASSO to construct such a model, translate the model into a program, compile and execute the simulation, and display the results for comparison with experiment. If the model's performance is incorrect we can either change parameter values and then try another simulation run, or else we can return to the graphic editor and change the structure of the model. When a satisfactory model has been constructed we can use the MINUIT program to find parameter values that give a least-squares fit.

APPLICATION TECHNIQUES

Figure 8 shows a diagram for a model of iron kinetics in humans. Compartmental models have been used to interpret iron tracer data [9]. Since erythropoiesis in the bone marrow is a cellular process, its kinetics are not well approximated by a few compartments. Mathematical models which describe these processes in terms of cellular growth and cellular iron uptake rates have been devised [8]. It seems that few biologists have used such models,

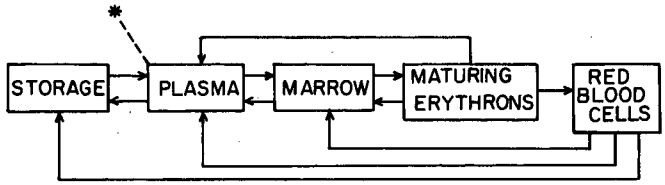

Figure 8. Iron compartmentation and kinetics.

probably because of difficulties with the mathematics. Graphical modeling techniques can be applied to this type of problem and could lead to more widespread use of models incorporating detailed realistic biological mechanisms. In the past we have often omitted many detailed features in our models in order to gain mathematical simplicity. I have again used compartmental models for illustration; however, oversimplified models can also be found in other areas of biology.

Since our graphics program can be easily interfaced with a variety of programming languages or programs, the study of one system from several points of view is aided. Let us, for example, consider a model of several types of cell populations where transformations occur between the various types of cells. We can use differential equations to describe the behavior of the mean number of cells of each type. A continuous system simulation language, in our case MIMIC, would be used in the simulation. Once a satisfactory model for the behavior of the mean cell numbers has been obtained, we may want to study statistical fluctuations in the populations. A discrete event simulator, such as GPSS, could be used at this stage.

In testing models with many elements, the ability to go back and forth between model construction, simulation, and fitting is particularly useful. One can separately construct, test, and optimize subsections of the system. These small models can then be combined while fixing some parameters at their best fitting values. The number of variable parameters is thus reduced when the complete model is studied. This can alleviate the common difficulty of finding a unique best model for a complex system.

Computer System

PICASSO is implemented on a CDC 6600 computer with a CDC VISTA 250 display system. The programs and graphical libraries can be permanently stored on an IBM 2321 data cell. Graphical documentation is provided in the form of microfilm and microfiche. The interactive programs run within our PTSS time-sharing system. PICASSO is currently used with MIMIC, CORNAP [10] and FORTRAN.

ACKNOWLEDGEMENT

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