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Biological Modeling: A Program to Calculate the Input from Observations on the Output

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Synopsis: In the usual situation, a model is constructed, and coefficients are adjusted until the predicted response to a known stimulus agrees with the observed response to the same stimulus in the real situation. Then the model can be used to predict the response to other stimuli.
  The reverse situation, while it is of practical importance, has not received much attention. This is the problem of finding the stimulus which would produce an observed response. A published attempt to solve this problem contains a fundamental error. The LaPlace transform method is shown to be applicable, but it is difficult to implement. The recommended solution is a digital computer program which compares the response predicted by a model with the observed response, and corrects the input until there is agreement between the two. This program is described, with examples of its use.

In recent years many scientists have published the results of their experiences with models. A favorite model is that of the metabolism or transport of various substances in the human body. Such a model is constructed from mass balances and kinetic measurements. The response, or output, of the system to a disturbance or input is measured. Adjusting the coefficients gives a model which responds like the system being modeled.

URANIUM EXCRETION MODEL

In the usual situation the model is used to predict blood levels or excretion of a substance of which a known dosage is given. Fish (1958) made a model of the movement of uranium in the body. In this instance, uranium was picked up by the body from the surroundings and appeared in the urine. The output could be measured, but the history of the input was unknown. The object of the simulation was then to be able to predict the input function from measured output data.

Our interest here is not so much in the model itself as in the "inverse model" described by the author of the paper described above. Figure (1) is the complete diagram (Figure 6 in the original paper), which the author states is "rather simple in principle." As described in the article "the set of excretion data is expressed as a function generator in which voltage is made to correspond to uranium excretion rate. If the output of the model is not equal in magnitude and opposite in sign to the excretion data voltage at any particular time, a very large error signal is obtained from the high gain amplifier. This will increase the model excretion rate to more nearly approximate the excretion data."

Even without trying it, anyone familiar with computers or control theory would be suspicious of this inverse model. The principle is used for analog computer generation of square root or logarithm; it falls down in this case because of the time lags. The first non-zero values of excretion data drive the recorder off-scale before the input signal gets through the time lags of the various parts of the circuit.

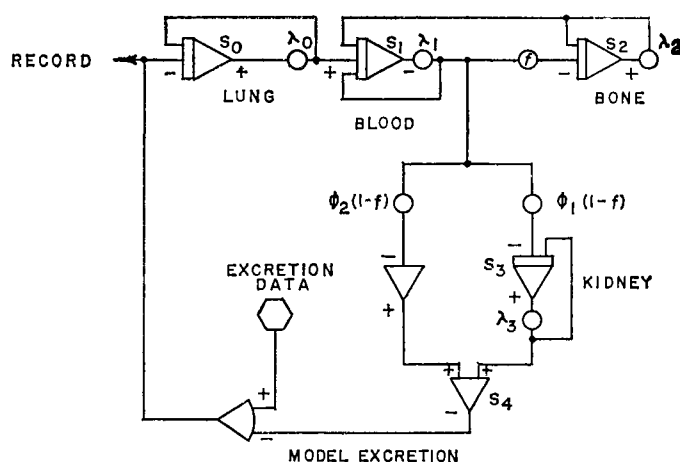1 The University of Iowa, Iowa City, Iowa 52242.

Figure 1. Computer circuit for Model of Uranium Transfer in Man (Fish, 1958).

So, the problem remains, and it is likely that its solution would have applications in other areas. It's not enough to criticize this attempt to perform a very useful simulation—we should further consider how it should be done correctly.

INVERSE SIMULATION WITH AN ANALOG COMPUTER

One possible method is the inverse simulation method based on control theory (Osburn 1967). This method has been applied by us to the uranium problem posed by Fish. It involves an analysis of the model in terms of the transfer function. This is shown below for the simplified model of uranium movement in the body previously described.

The transfer function, which is the ratio of the LaPlace transforms of the output, Y, to the input, X, is

$$\frac{Y(s)}{X(s)} = \frac{(a_1\,a_3)\,s^2 + (a_1\,a_2\,a_3 + a_1\,a_3\,a_5 + a_1\,a_4\,a_5)\,s + (a_1\,a_2\,a_3\,a_5 + a_1\,a_2\,a_4\,a_5)}{s^3 + (a_1 + a_2 + a_5)\,s^2 + (a_1\,a_5 + a_2\,a_5 + (a_1\,a_2)\,(1-f))\,s + a_1\,a_2\,a_5\,(1-f)} \qquad (1)$$

This transfer function is in the form

$$d_0 = a_1\,a_2\,a_5\,(a_3 + a_4) \qquad (2)$$

$$d_1 = a_1\,(a_2\,a_3 + a_3\,a_5 + a_4\,a_5) \qquad (3)$$

$$d_2 = a_1\,a_3 \qquad (4)$$

$$c_0 = a_1\,a_2\,a_5\,(1-f) \qquad (5)$$

$$c_1 = a_5\,(a_1 + a_2) + a_1\,a_2\,(1-f) \qquad (6)$$

$$c_2 = a_1 + a_2 + a_5 \qquad (7)$$

$$c_3 = 1 \qquad (8)$$

$$\frac{Y(s)}{X(s)} = \frac{d_0 + d_1\,s + d_2\,s^2}{c_0 + c_1\,s + c_2\,s^2 + c_3\,s^3} \qquad (9)$$

A function, M, is defined thus:

$$M = \frac{Y(s)}{d_0 + d_1\,s + d_2\,s^2} = \frac{X(s)}{c_0 + c_1\,s + c_2\,s^2 + c_3\,s^3} \qquad (10)$$

The first part of Eq. 10 defines M from the function Y: $d_2M'' + d_1M + d_0 = Y(t)$. The second part uses the function M to define $X(t)$:

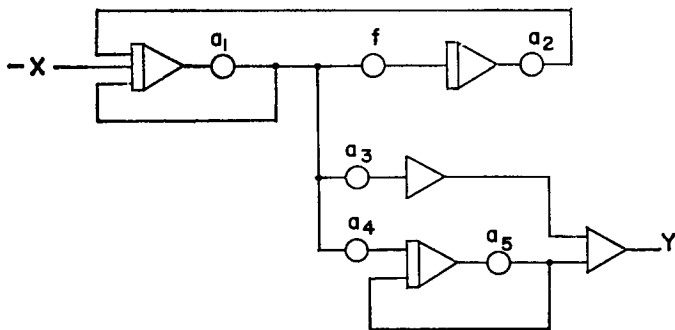$$X(t) = c_0\,M + c_1\,M' + c_2\,M'' + c_3\,M''' \qquad (11)$$

Figure 2. Simplified circuit to show labeling of parameters.

To show that this does indeed predict the input curve, the computer circuit was set up on an Electronic Associates TR-20 analog computer as shown in Figure 2, using these values: $a_1 = 2$, $f = 0.5$, $a_2 = 1$, $a_3 = 0.5$, $a_4 = 0.5$, and $a_1 = 1$. For a ramp input, X, as shown in Figure 4, the output, Y, was obtained.

The values for the inverse simulation were calculated from Equations 2-8, as follows: $d_0 = 2$, $d_1 = 3$, $d_2 = 1$, $c_0 = 1$, $c_1 = 4$, $c_2 = 4$, $c_3 = 1$. The circuit shown in Figure 3 was set up with these values, and the Y obtained from the simulation introduced as shown. As shown in Figure 4, the X predicted by the inverse simulation circuit is a ramp function, identical to the original input.
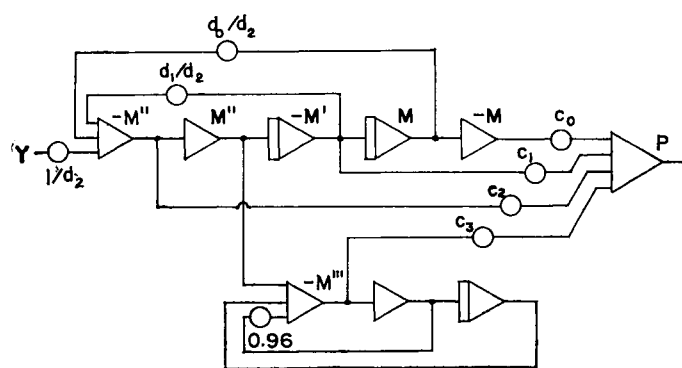
Figure 3. Circuit for Inverse Model based on LaPlace transformation, to give predicted input P from observed output Y.
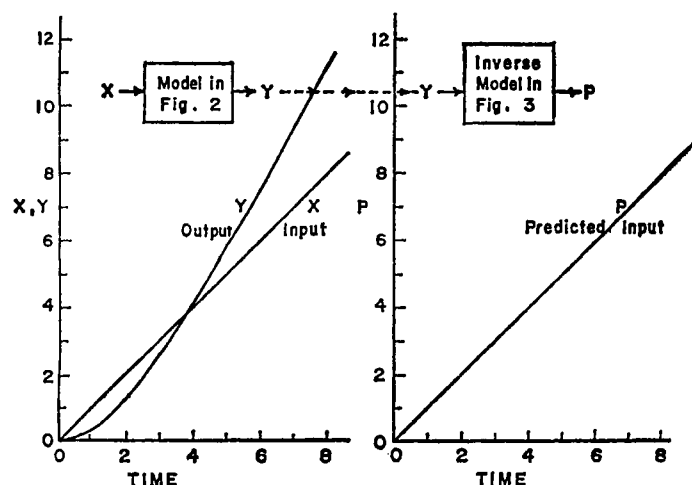

Figure 4. Results from circuit shown in Fig. 3. The predicted input matches the known input.

DIGITAL COMPUTER PROGRAM

Although this method works, it is limited to linear systems, and involves a great deal of mathematical manipulation and analysis. A further disadvantage is that usually one or more differentiations are involved, which magnifies any random errors. In the search for a better method, it was decided to use the "brute force," or direct engineering approach.

In principle, the method of Fish is used, but by using a digital computer the difficulty with time lag is circumvented. A value of input, X, is assumed, and the output, Y, at the end of a small time interval DT is calculated. A subroutine which solves the model is used for this calculation. This output is compared with the observed output. Since DT is usually smaller than the time interval between observations, an interpolation subroutine is used to give the observed out-

put. In the example to be presented, a quadratic interpolation between three points was used.

If the calculated value of Y differs from the observed, the value of X is raised or lowered as indicated, and the calculation repeated. This is continued until the difference is less than any desired value. The calculation is then repeated for the next time interval. This gives X as a series of steps, but for a small DT this is essentially a smooth curve.

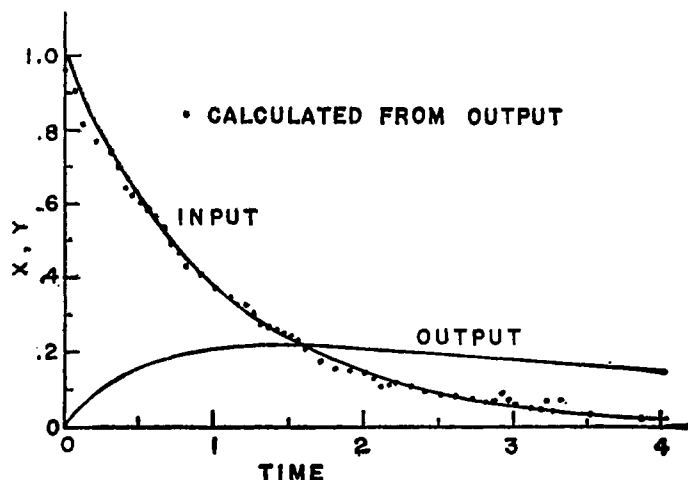Figures 5, 6, and 7 demonstrate the results obtained by the computer program.

Figure 5. Result of Digital Computer simulation for an assumed input. The output was computed from the Model, and the points on the input curve were predicted with the aid of the program.
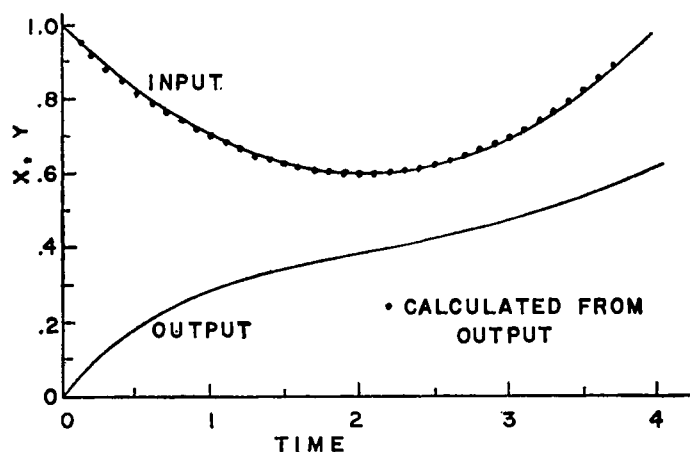

Figure 6. Same for an exponential input.

In each case, the form of the input to the model was assumed and the output found by solving the model on a computer.
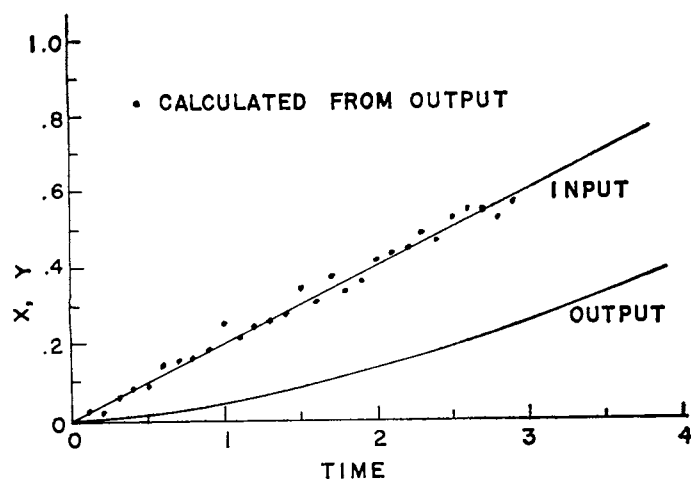
Figure 7. Same for a linear input, with less accurate output data.

The assumed inputs and calculated outputs are shown as solid lines. Points from an output curve were fed as data to the inverse modeling program, which calculated the input as described. Points obtained from this calculation are plotted on the graphs for comparison with the original curves. Figures 5 and 6 are based on a digital solution of the model. The agreement between actual and predicted values is seen to be very good. For Figure 7, the model was solved on an analog computer, and values of output read from a plot. This produced some cycling as shown, since something equivalent to a differentiation is taking place to magnify any irregularities in the output curve.

It is seen that the method gives usable results. It is easy to use, requiring only a routine to solve the model. The technique should find uses in other areas of simulation and modeling. A copy of this computer program, in FORTRAN IV, is available from the author on request.

Literature Cited

Fish, B. R. 1958. "Applications of an Analog Computer to Analysis of Distribution and Excretion Data," *Health Physics* 1:276-281.

Osburn, J. O. 1967. "The Inverse Model," *Instr. and Control Systems* 40:131-133.