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CERTAIN CONSIDERATIONS ON THE SELECTION OF MODELS FOR
BIOLOGICAL SYSTEMS

by

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This note is based on a talk given at the Bio-Medical Engineering Seminar with Prof. R. S. Mackay (Fall 1962). The author gratefully acknowledges the helpful discussions with Prof. E. I. Jury and Prof. G. Westheimer, which lead to some of the thoughts exposed in this note.

The reasons for constructing a mathematical model for a biological system can be classified in the following three categories.

a) A certain biological system is part of a larger control system. For the design of the latter, one needs the transfer function of the first. This is, for example, the case of a human operator included in a fire control system.

b) Better understanding of a given biological system, as for example the mechanism through which the blood pressure of an animal is regulated.

c) By studying a biological system to get ideas useful for engineering design. A classical example is the general category of adaptive control systems.

The requirements from a mathematical model are not the same for all the three cases.

A general obvious requirement is, however, a good agreement of the output of the model with the output of the real system for the same kind of input.

If it happens for a limited class of inputs, the ones that are usually expected, it is enough for the first purpose. It is not too difficult to construct such a model, especially for linear systems.¹

In the second and third case a more accurate description is needed. A satisfactory input-output relationship is not enough. But here we meet with difficulties. Given a "black box" there is no experimental way to identify its interior unless the only unknowns are a finite number of parameters.² Even in the simplest case of a linear dynamic system there are parts of it which cannot be identified from input-output relationships.³ Therefore, the model must be designed in advance!

What are the criteria for the selection of a model?

McRuer and Krendle⁴ state that the best choice is the one that gives a model in the form best suited for computations. That is as a linear rational transfer function. Under this consideration they proposed a model for a human operator in tracking systems with the following transfer function:

$$\frac{K_p e^{-\tau s} (s + a_1)}{(s + \omega_1) (s + \omega_2)}$$

Such a "rude" choice of a model was justified concerning its purpose.

Rational functions have been used also for the description of the pupil and accommodation reflexes^{5, 6} but this is not justified because it does not give any insight into the problem. Moreover because of the limited form of test signals the generality of the models is questionable. Simple steps or sinusoidal inputs are quite inadequate for nonlinear systems^{7, 8}, as is the case with all biological systems. The result is that there is a high degree of arbitrary choice of models which differ basically from each other. As an example we are going to consider models for the eye accommodation reflex proposed by Stark⁶ (Fig. 1) and the author (Fig. 2 and 3). All three models presented a behavior more or less similar to the actual system, although not in very good agreement with the detailed experimental results.

We cannot make any choice between the 3 models unless we start considering the physiological details of the system (Figures 4 and 5). Then it is seen that the model of Figure 2 must be rejected because there is no evidence of a sampling mechanism on the retina, i. e., the feed back path. On the other hand, the ciliary muscle-lens system is practically a mass-spring system without local loops so its dynamic response can be only of 2nd order. So the model of Figure 1 is not justified.

Moreover, there is an indication against all three models, i. e., the fact that the system is not sensitive to the sign of the error⁹ (Figure 6), at least in the absence of clues like chromatic aberration, etc.

So we reach the conclusion that if a model is to be used for either the second or third mentioned purpose it must be, at first, designed through pure physiological consideration, and then test signals may be used for the determination of parameters. An example of this approach can be found in the work of Adolph.¹⁰

Of course it might be found from the tests that there is no set of parameters satisfying the experimental input-output relationships.

In that case the model must be changed but only keeping in mind the physiological structure. Now one may raise the question-- What if a deadlock is reached, i. e., no possible physiological model can be in agreement with the experimental results? The answer is that such a deadlock is going to be the very desirable result of an experiment because it is going to lead to a reexamination of the physiological system, i. e., a possible positive contribution in physiology.

We will try now to formulate certain general characteristics for models for biological systems and discuss possible choices among different types. This will lead into the formulation of a general model for physiological control systems:

(i) Continuous or discrete (sampled-data) models. Recently, the use of sampled-data models for biological systems has been suggested^{11, 12}. The justification of this choice has been given by Young¹² (p. 95) as follows:

"This type of model was resorted to because it affords a straightforward description of certain experimental results which could not be explained by any continuous linear model. "

This is not, however, a satisfactory justification because a non-linear continuous model might have been even better.

The Bode plot (gain vs. frequency) of many biological systems presents a "hump"¹³ (Figure 12) like the one shown in Figure 7, and this has been considered as an indication that the system is discrete because a sampled-data system has a similar "hump" near the sampling frequency. However, a high order linear or non-linear system may have a similar behavior⁶ (p. 350). Moreover, the suggestion of a unique sampling frequency for the whole human organism does not hold because this "hump" appears at different frequencies for different systems varying from 1 to 100 cps¹³ (Figure 12).

So it is difficult to have any sound conclusion from the experimental results.

Going into physiological considerations we see that the smaller units in the human organism are really discrete, i. e., the neurons

transmit information in a pulse frequency modulation form. However, as soon as we consider a nerve trunk we see that the information flow is practically continuous due to the large number of conducting fibers¹⁴ (Vol. II, p. 3).

So before going into a sampled-data model a larger class of continuous or even discrete, but not as simple as a S. D. system, models must be tried, and then if there is still strong evidence of sampling, a physiological research on the subject may be started trying to determine which organ or system has this sampling-like performance.

(ii) Threshold. This is a general feature of all biological systems, and it plays a very important role in many cases¹⁵ (p. 38, 391, 426, etc.). An immediate result of this fact is that biological systems are never zero-error systems so it is not always necessary to include in the model a pole at the origin.

(iii) Pure delay. This is due not so much to the finite velocity of the impulses in the nerve fibers but mostly results from the synaptic transmission. The time delay at synaptic transmissions is more or less known¹⁵ (p. 134, 136) and this information together with the estimated number of synapses included in a reflex arc might be used to check the experimental results. It must be pointed out that, in systems having both dead zone and pure delay, there is the possibility of overestimation of the latter when not steep enough input is used (Figure 8).

(iv) Saturation or relay non-linearities. It is easily understood that any transfer function of a biological element must have a saturated element because the capabilities of muscles, nerves, etc., are not unlimited. Moreover, there are indications due to experimental work,^{16,17} that the behavior of some of them is of the relay (bang-bang) type. This is in agreement with the opinion that a biological system must be optimal in a certain sense due to the evolution development. Of course this is not much of a scientific argument; however, together with the experimental results it is an indication that at least a certain class of systems works in this way.

(v) Double paths. There are indications that many systems show different dynamics depending on the sign of the error or its derivative.

This results from the different neural pathways for a different sign of the error. For example, the near-to-far accommodation is carried through the sympathetic nervous system, but the far-to-near accommodation is carried through the parasympathetic nervous system¹⁵ (p. 224). The same is true for the pupillary reflex to the light intensity¹⁵ (p. 224). On the other hand, experimental work on the heart rate respiratory reflex showed a similar behavior.¹⁸ In that case the vagus inhibition V is related to the thorax circumference by either

$$\frac{-Ks^2}{(1 + \tau_1 s)(1 - \tau_2 s)} \quad \text{if } \frac{dR}{dt} > 0$$

or

$$\frac{K' s^2}{(1 + \tau_1 s)(1 + \tau_2 s)(1 + \tau_3 s)} \quad \text{if } \frac{dR}{dt} < 0.$$

This fact can be tentatively generalized for any model of a biological system unless there is definite proof of a similar response in both ways.

(vi) Even function of the error. There are cases when a system is basically sensitive only to an even function of the error (for example, absolute value). This is the case of the accommodation reflex as it has been mentioned already. In order that such a system may work satisfactorily the need of a compensator arises. Its purpose is that when the system operates in the "wrong" mode, it reverses operation. A possible but oversimplified implementation of such a scheme is a device which checks the derivative of the absolute value of the error. If this keeps on increasing, then the reversal occurs.

Theoretical study of such systems (even function of the error) has been done already for certain cases.⁹

(vii) Quickened Systems. There is evidence from experimental work⁹ that the feedback path in certain biological systems is not only unitary but also proportional to the velocity and higher time derivatives of the output (Figure 9). Such a system is said to be quickened (essentially

equivalent to tachometer feedback) and has generally better performance than a system with unitary feedback. If this is really the case with many biological systems, one sees that a very common way to get the open loop transfer function does not hold any more. According to that method an external unitary positive feedback was added to the input cancelling in this way the negative natural feedback which was supposed to be unitary.

(viii) Double adaption. A classical example of this phenomenon is the regulation of the light intensity to the eye. For small variation, this is obtained through the pupillary reflex, while for larger variation the retina sensitivity is changed which has, however, a much slower response.¹⁹ So the variations of the pupil diameter as a function of the light intensity have the form shown in Figure 10.

The same phenomenon is found in the neuron excitation [difference between conditioning and blocking stimuli¹⁵ (p. 64)].

So in any proposed model, care of this feature must be taken, although for high frequency inputs this can be overlooked.

Having in mind the points just exposed, one may propose as a rather general model the one shown in Figure 11. The diodes D_1 and D_2 are not always diodes with the common meaning except in the cases of systems which are sensitive to the sign of the error (for example, pupillary reflex to light intensity). Generally there are two exclusive channels (when one is on the other is always off) controlled by the computer shown.

There are many other general comments that can be made, for example, the phenomenon of inhibition and the fact that in most systems two paths are constantly conducting, but they are cancelling each other. An input tends to silence one and excite the other, and this results in a net output at the end.

The unilater response is another feature, i. e., many systems show the same response to inputs of opposite signs. In that case one may say that the system is only absolute value of error-rate sensitive.

However, although we did not exhaust the discussion of all general features of biological systems, we hope that enough evidence has been

given about the way that a model for a biological system must be selected.
In short, the conclusion of this study can be stated as follows:

Not the simpler model must be chosen but the one which is "more isomorphic" with the actual biological system.

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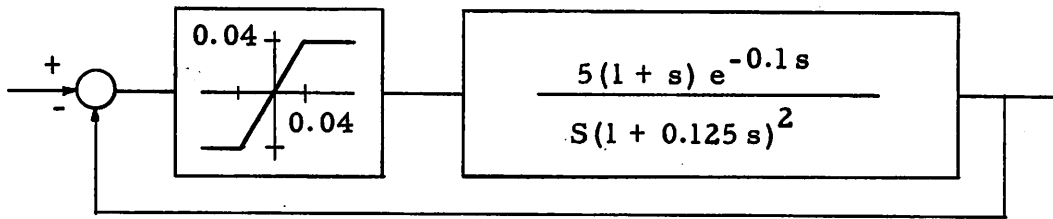


Figure 1. Model proposed by L. Stark, et al. (See Ref. 6)

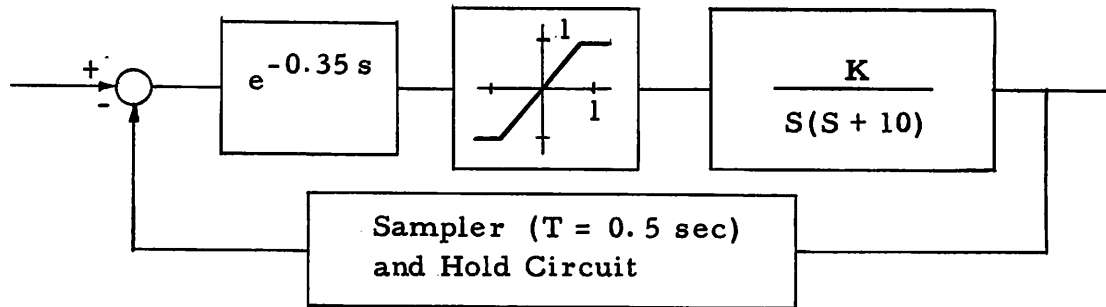


Figure 2

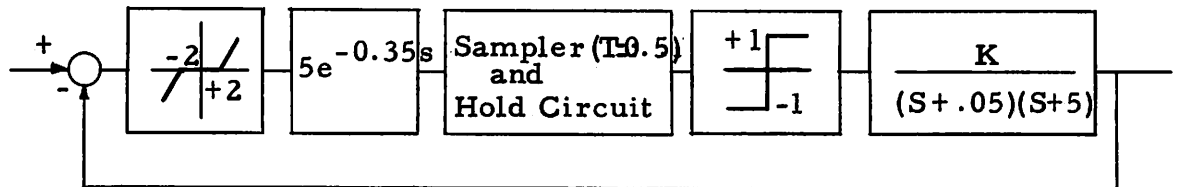


Figure 3

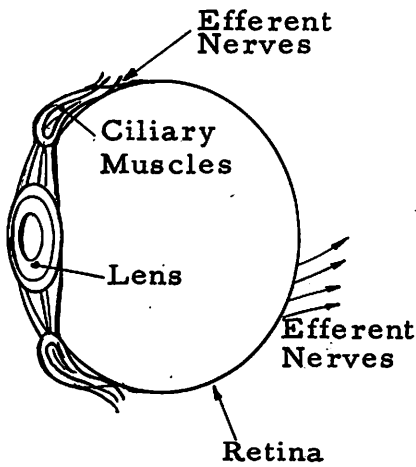


Figure 4

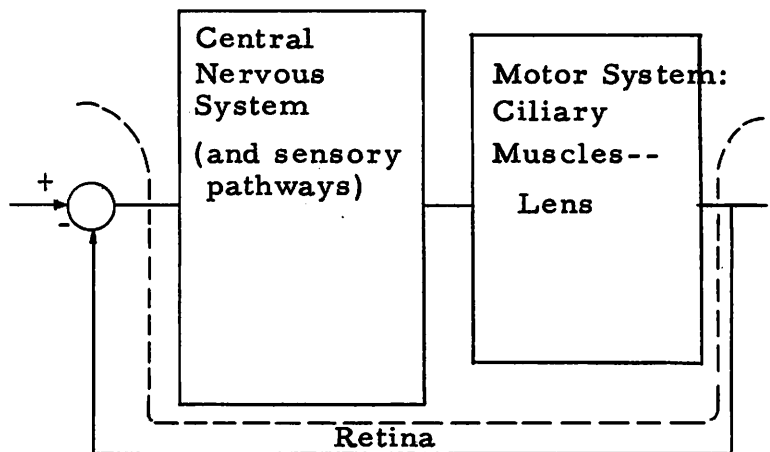


Figure 5

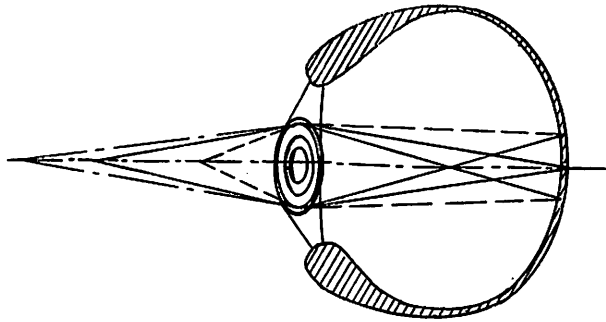


Figure 6. No Sensitivity to the Sign of the Error

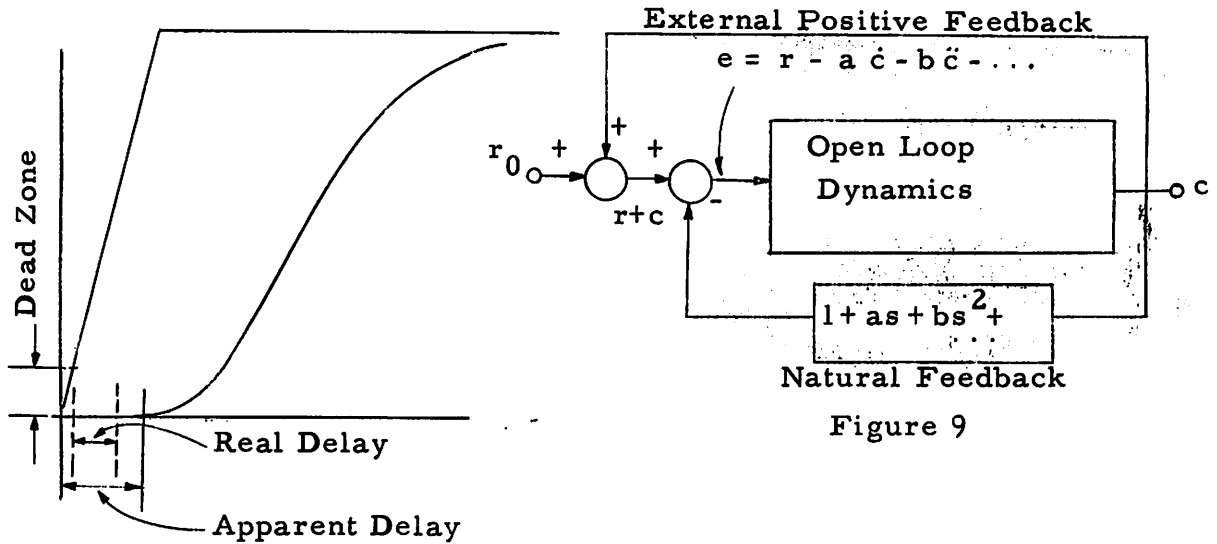
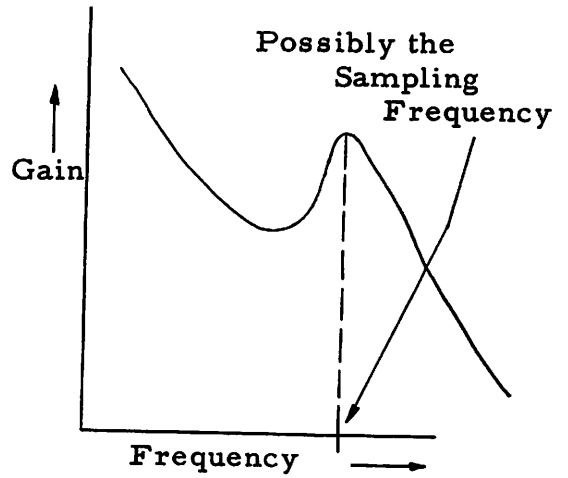


Figure 8

Figure 9

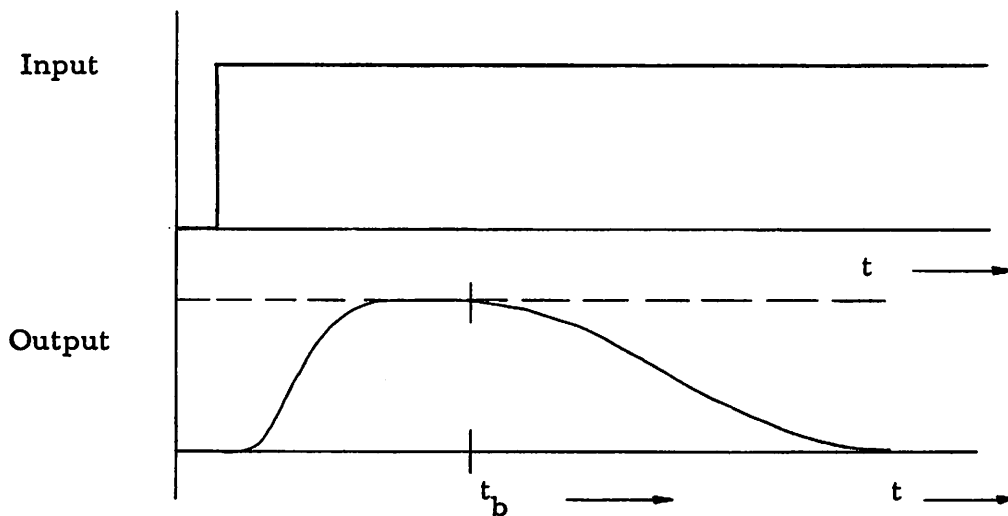


Figure 10. Pupillary reflex to light intensity plus retina adaption (t_b)

Journal of the American Society of Mechanical Engineers, Vol. 78, No. 1, 1956, pp. 1-10.

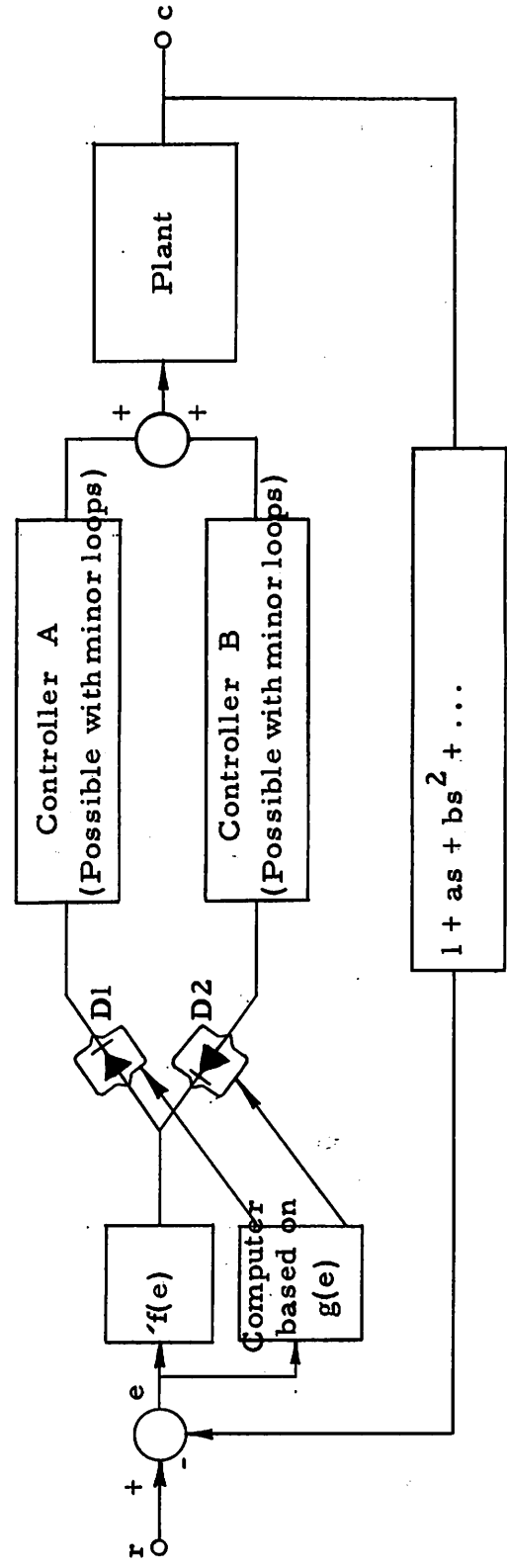
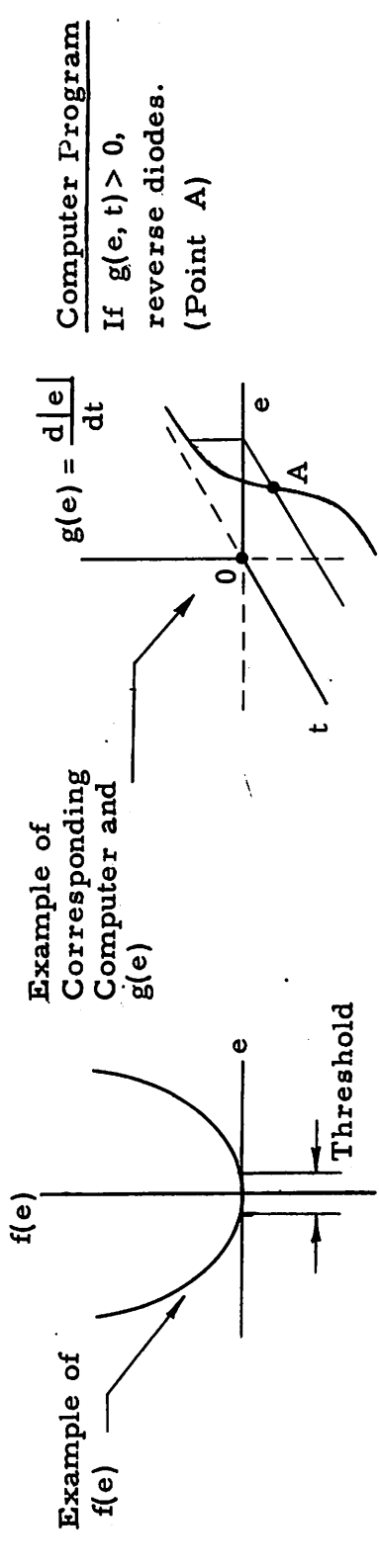


Figure 11. A general form for models of biological control systems