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NUMERICAL STUDIES OF THE FUORTES–HODGKIN LIMULUS MODEL

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In a recent paper Fuortes & Hodgkin (1964) proposed a non-linear electrical filter model for the *Limulus* (horseshoe crab) visual response. This model, with modifications to improve its agreement with the data, has been studied by means of the computer program NIH-OMR 9B21 developed by Berman, Weiss & Shahn (1962) which, given a model and a set of experimental data, finds the values of the model parameters which give a least squares fit to the data. The Fuortes–Hodgkin model consists of a cascade of identical stages, each composed of a series isolating or amplifying unit, and a shunt resistance and capacitance. The necessary non-linearity is introduced by a feed-back loop, which makes the shunt resistors decrease as the output increases. Since this model gave good qualitative agreement with the data obtained on *Limulus* (Fuortes & Hodgkin, 1964) and also with some data on the human visual system (J. G. Robson, Cambridge, personal communication) it seemed worth while to investigate its properties further by means of the computer program 9B21.

The general conclusions are that the behaviour is not, within limits, very sensitive to the number of stages in the chain—nine, ten, and eleven stage chains gave almost equally good fits. However, changing the location of the feed-back loop alters the system behaviour substantially, and the fit was greatly improved by making the shunt resistances depend not on the output of the last stage, but of the stage preceding it.

METHODS

Fuortes and Hodgkin Model. The experiments are described in detail by Fuortes & Hodgkin (1964) and Fuortes (1959), but a brief summary will be given here. The stimuli were short pulses and steps of light of varying amplitudes, and the responses were the generator potentials measured by micro-electrodes in the eccentric cells of the *Limulus* ommatidium in conditions of dark and light adaptation, at 8° C. Fuortes and Hodgkin observed that with background light, or pre-exposure, both the time constant and sensitivity of the system decreased, the latter by a far larger factor than the former. This type of relation characterizes the filter shown in Fig. 1, in which the time constant is proportional to R and the sensitivity or gain to R^{n-1}, where n is the number of stages, R the shunt resistance, and C the capacitance of each stage. The elements μ are isolating elements, having an infinite input impedance, and a gain of μ. These isolating elements are a mathematical convenience; since the behaviour of each stage is independent of the stage following

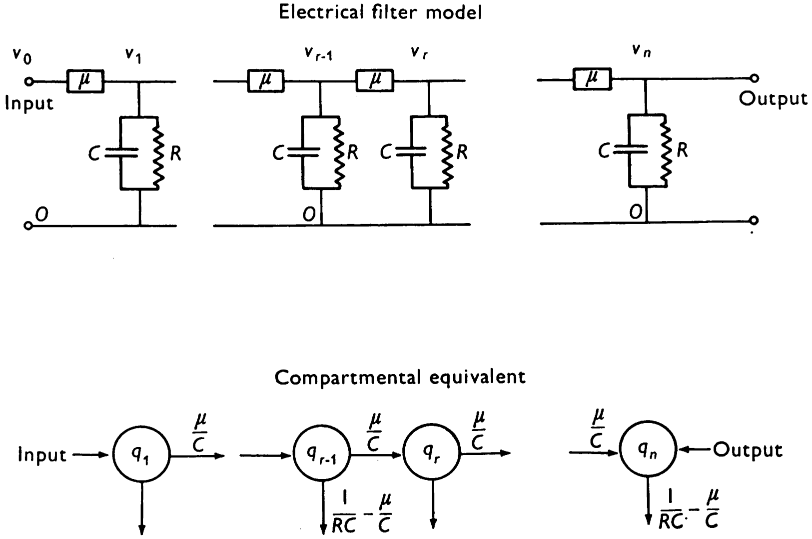

Fig. 1. Correspondence between electrical filter model, proposed by Fuortes and Hodgkin, and its compartmental equivalent, used with the 9B21 computer program.

it, the filter can be simply analysed stage by stage, starting at the beginning. The output Vn for an impulse function input, of area $v_0\Delta t$, was derived by Fuortes and Hodgkin, and is given by

$$V_n = v_0\Delta t\left(\frac{\mu}{t}\right)^n \frac{t^{n-1}e^{-t/\tau}}{(n\text{-}1)!}, \tag{1}$$

where $\tau = RC$.

If only R changes during light adaptation, then it can be shown that, for a brief flash of light, sensitivity (S) and time to maximum (t_{max}) satisfy the equation

$$S = A(t_{max})^{n-1}, \tag{2}$$

where A is a constant, and S is the ratio of peak output to input.

These equations make possible 2 independent ways of evaluating n for a system: curve fitting of a single flash to eqn. (1), or the relating of S to t_{max} for a set of curves, from eqn. (2). Fuortes and Hodgkin found that the mean value of n for a number of experiments was 10·1 using curve fitting, and 8·6 using the time-gain relation. This suggests that the resistance of most but not all of the stages changes with adaptation level. In their analysis, R is assumed to remain constant during each pulse, which is approximately true if the pulses are of low amplitude. The value of R is fixed by a previous or simultaneous exposure to a background light. Therefore the time course of changes of R, i.e. the details of the feed-back loops, need not be considered in the small input observations.

Fuortes and Hodgkin proceeded with the analysis of large inputs, arguing that the linear beginning of the response and absence of a rise after the step was turned off showed that the

R's must be controlled by the output rather than by the input. They present numerical studies done on EDSAC 2 at Cambridge which reproduce the qualitative features of the response quite well, but which, for step functions, have larger overshoots and undershoots than those observed, and which return too slowly to the resting value when the light is switched off. These responses to large amplitude inputs, during which R cannot be assumed constant, depend on the time course of the change of R, and it is this feature of the model that the present study is largely concerned with.

The NIH-OMR 9B21 program. The 9B21 computer program was originally devised as an aid to biologists studying tracer, chemical, and enzyme kinetics. The fundamental model is that of a system of compartments, connected by pathways having stated rates of flow. Any compartment can be connected to the exterior by a path in either direction. A known amount of a substance is injected into one or more compartments, and observations are made of its subsequent presence in one or any linear combination of compartments. Given the number and connectivity of the compartments, the programme will compute the value of the flow rate constants that give the best least squares fit to the observed data, compute the output of the system with those rates, and calculate the deviations between observed and computed values. The program can deal with certain types of non-linear as well as linear systems, and bypasses for the user the analytical solution of the differential equations involved. (For a full description of the program see Berman, Shahn & Weiss, 1962, and Berman, Weiss & Shahn, 1962.) The type of computation shown in Fig. 2, finding the best values of three parameters to fit the pulse and step response of a nine-stage non-linear system, took about 3½ min on an IBM 7094. Calculation of the output of this system for pre-assigned values of the parameters took 20 sec.

Correspondence between filter and compartment models. The correspondence of the compartmental model to the filter is shown by the following equations which refer to the systems shown in Fig. 1.

Filter

$$\frac{dv_i}{dt} = -\frac{v_i}{RC}+\frac{\mu}{C}v_{i-1} \qquad (i = 1, 2, \ldots, n),$$

where v_0 is the input voltage and is proportional to light intensity.

Compartmental

$$\frac{dq_i}{dt} = -(\lambda_{i+1,i}+\lambda_0)q_i+\lambda_{i,i-1}q_{i-1} \qquad (i = 1, 2, \ldots, n),$$

where q_i is the quantity in the i^{th} compartment, $\lambda_{i,i-1}$ is the flow rate constant from the i-1 to the i^{th} compartment.

Equating coefficients of corresponding terms, we have

$$(\lambda_{i+1,i}+\lambda_{0,i}) = \frac{1}{\tau} = \frac{1}{RC} = \frac{g}{C};$$

$$\lambda_{i,i-1} = \frac{\mu}{C}.$$

The conductance g is the reciprocal of the resistance, R. Since our model consists of a series of identical stages, $\lambda_{i+1,i} = \lambda_{i,i-1}$ and so finally we have

$$\lambda_{i,i-1} = \frac{\mu}{C};$$

$$\lambda_{0,i} = \frac{g}{C}-\frac{\mu}{C}.$$

This represents the linear model. The non-linearity is introduced by making g dependent on one of the q's, say q_j:

$$g = g_o(1+f(q_j)).$$

The design of the program requires that the dependence be linear.

The variables in the model structure were

(1) The length of the chain—7 to 11 stages were tried.

(2) The origin of the feed-back loop—the non-linearity was made to depend on the last compartment (as previously done by Fuortes and Hodgkin), the next to last, the second from the last, and the sixth from the last.

(3) The nature of the last compartment—it was either identical to the others, or had a constant g, not dependent on any q, adjusted independently by the programme.

For each model, the 9B21 program computed the values of the parameters to give the best fit and, as a measure of the goodness of fit, the sum of the squares of the deviations, and the average deviation per point.

The data available for the study consisted of records of responses to very short (20 msec) pulses, and to square pulses lasting about one second. The input amplitudes covered a range of approximately 4·2 log units. The extremes of the range were not included in the study, but a set of five input amplitudes covering a range of 2·4 log units was chosen, and the responses to pulses and square waves fitted. Linear analysis performed by Fuortes and Hodgkin (unpublished) had given a value of n between 9 and 10.

Initially the procedure followed was to fit simultaneously the experimental results obtained for a light pulse and a light step of the same amplitude. If the model is an accurate representation of the system, the best-fit values of the parameters for each of the five input levels should coincide, and therefore the spread in values could be considered a rough measure of the goodness of fit of the model used. However, this is not a good quantitative measure. Some studies fitted the five pulses simultaneously, and then the five steps simultaneously. This method, which gives two values for each parameter of each system, seems to yield the clearest results.

RESULTS

The location of the feed-back loop. Fuortes & Hodgkin (1964) point out that the decrease in conductance and consequent reduction in gain cannot be input controlled, because input control would result in two effects which are not observed in the *Limulus* responses. The first is non-linearity at the beginning as well as at the end of the response, and the second is a transient increase in output when the light is switched off. They concluded that gain was controlled by changes at or near the output, and therefore used output control. Their figures, as well as Fig. 2*a*, show that output control gives excessive sharpness for the pulse, and overshoot for the square wave. The overshoot is caused by too great a delay in gain reduction—if the gain is reduced sooner, the overshoot is much reduced, as is shown in Fig. 2*b* in which the conductances depended on the stage preceding the last. Figure 2*c* shows the effect of too early gain reduction (from the second from the last stage); the rise is not steep enough. An even more extreme case is shown in Fig. 2*d* with feed-back from the 4th stage. Note the rise following the light extinction.

As the origin of the feed-back loop moves from the input to the output, the initial response shifts from roughly logarithmic, approaching the steady value slowly, to the steep overshoot of the final value. The off response drifts from an initial rise to a steeper and steeper decline. The feed-back

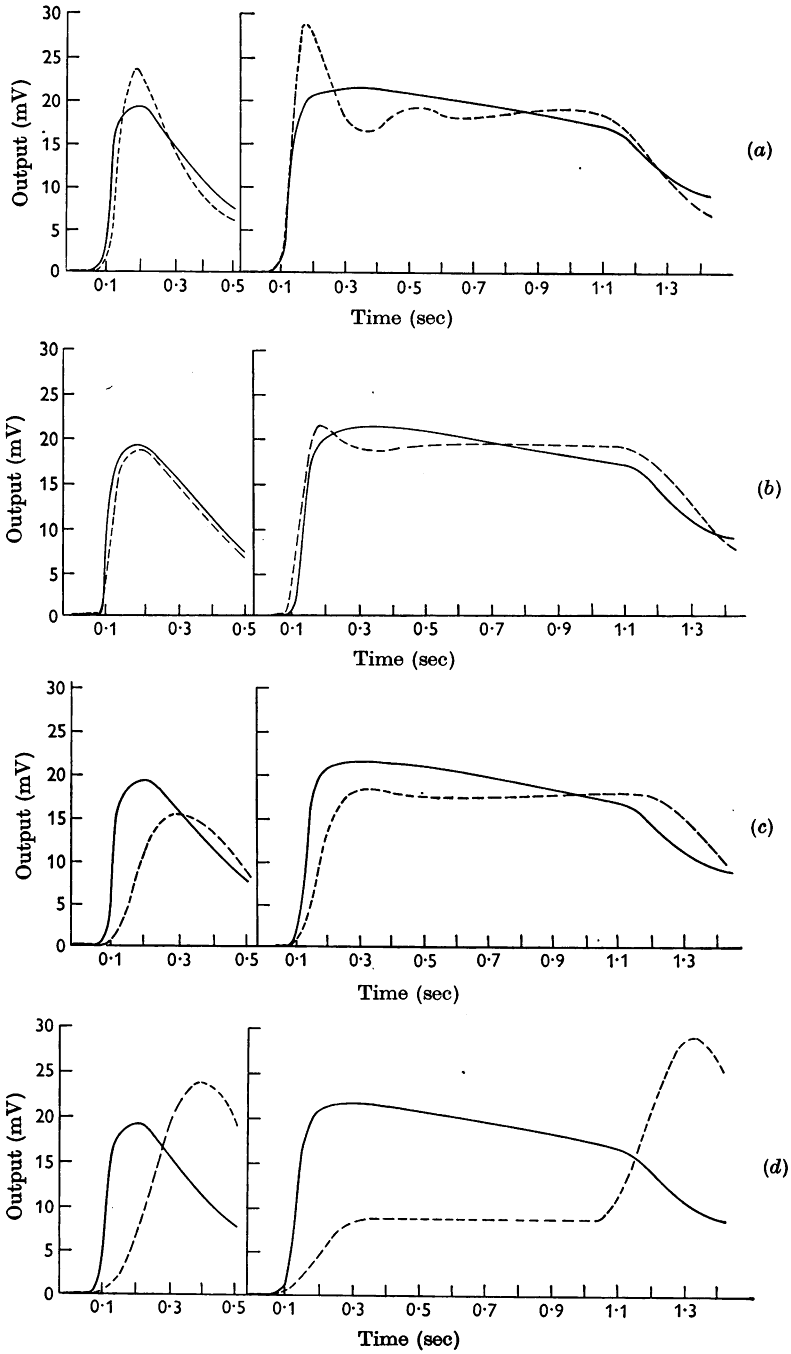

Fig. 2. Effect of location of feed-back loop on response. Chain length = 9; log input attenuation = 0·9. (*a*) Shunt conductances depend on the output of the last of nine compartments. (*b*) Shunt conductances depend on the eighth of the nine compartments. (*c*) Shunt conductances depend on the seventh of the nine compartments. (*d*) Shunt conductances depend on the fourth of the nine compartments. Solid lines indicate observed, and interrupted lines computed, responses.

loop originating at the next-to-last stage is obviously the best for this set of data.

Effect of chain length. Probably the best way to study the effect of chain length would be to fit simultaneously the five steps and pulses for each length, and compare them visually and by means of the average deviation of computed from observed values. This was impossible because the 9B21 program cannot handle simultaneously more than five different sets of data, and each pulse or step constitutes one sequence. The first method used was to fit the five pulses simultaneously, and then the five steps for chains of 7, 9, 10 and 11 stages (each with feed-back from the next-to-last stage). The value of n estimated by the methods of eqn's (1) and (2) was about 10, and the value of 7 was used to show the effect of a significant shortening of the chain. As might be expected from eqn. (2), using a value of n too small makes the change of $t_{\max}$ too great, since the least squares

TABLE 1

Chain length	D(G)	D(μ/c)	D($1/\tau$)	$\sigma_p \times 10^5$	$\sigma_s \times 10^5$
7	0·0077	0·072	0·145	0·34	0·27
9	0·0082	0·056	0·119	0·20	0·21
10	0·0	0·054	0·109	0·19	0·21
11	0·0024	0·46	0·993	0·22	0·23

fitting tends to match the sensitivity. Thus, the ratio of $t_{\max}$ for the largest and smallest pulses was observed to be 0·585. That for the 7 chain was only 0·435, while for 9, 10, and 11 the figures were 0·5, 0·538 and 0·546. The averaged squared deviations were 0·34, 0·20, 0·194 and 0·22. Thus on the basis of the 5 pulses, a value of 7 for n is inferior to 9, 10 and 11. Fitting of the five steps gave similar results.

If the model used is a perfect representation of the system, then the same set of parameters should give the best fit for both pulses and steps. Thus the discrepancies between the sets of values for the two runs, as well as the mean square deviations, can be used as a merit indication of the model. For each chain length, we have a pair of values for each of the three parameters fitted—one for the pulse run, and one for the step run. Table 1 shows the ratio of the deviation (called D(G), D(μ/c), and D($1/\tau$)) of each point of these pairs from their mean value to that mean value. The parameters are G, the non-linearity factor, μ/c, the gain factor, and $1/\tau$, the reciprocal time constant. Also shown are σ_p and σ_s, the mean square deviations per point between computed and observed values for the pulse and step runs respectively. If we rank the four chain lengths by smallness of deviations, we find that the seven chain is poorest in all but D(G), but that, as before, the differences among 9, 10 and 11 are slight, with 10 probably the best. Figure 3 shows the set of pulses for a chain of 10, with feed-back from the 9th stage, one of the best fits.

Effect of varying the last stage. Since feed-back from the penultimate stage gave the best results, it seemed reasonable to suppose that the last stage might not be affected by feed-back at all. This hypothesis was tested by making gR of the last stage independent of any voltage, and allowing the program to find its best value. The fit was poorer than that for all g's varying.

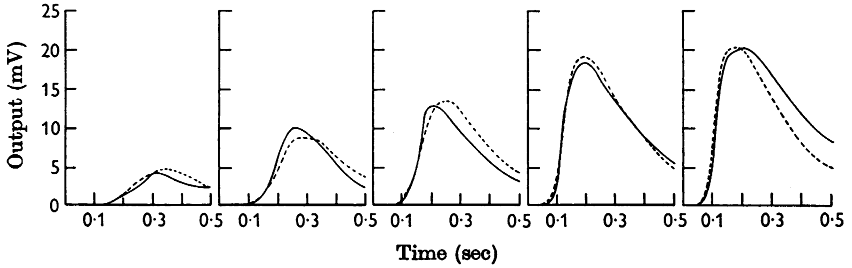

Fig. 3. Observed and computed outputs for five pulses. Chain length = 10, feed-back is from the ninth compartment. The inputs are, from left to right, log A = 3·3, 2·7, 2·1, 1·2, and 0·9 or a range of 256 to 1. Solid lines indicate observed, and interrupted lines computed, responses.

DISCUSSION

Evaluation of the model. The behaviour of the RC filter or its equivalent, the straight-chain compartmental model, is fairly easy to grasp intuitively, and describes the data reasonably well over a wide range of input amplitudes. The chief systematic error is the rapid attainment of a steady state, shown by the perfectly flat top of the computed square wave response. The gradual decrease in the observed response over the first second or more shows that there is some process with a long time constant in the system, which this model does not include. Some attempts were made to include a second feed-back loop with a longer time constant, but this computation was very lengthy, and preliminary results indicated that the expenditure was unwarranted for present purposes.

A general criticism of this model is that it does not seem to be based on any physical reality, i.e. a chain of filter stages may suggest propagation of an electrical impulse (although the isolating elements are not consistent with propagation) and a chain of compartments suggests a series of chemical reactions. In these experiments the output is measured at a point so close to the visual pigment that electrical propagation seems unrealistic and, while as many as ten chemical reactions could possibly be involved, they would not be expected to have identical time constants. In short, the physical system does not possess any obvious analogues to this model.

While it is not necessary that a mathematical model reflect the details of the physical structure it corresponds to, a model that does is more satisfying aesthetically, and more likely to suggest further research, than one which does not.

Remarks on models for non-linear systems. The property of linearity is defined in many different though equivalent ways. The fundamental definition is as follows:

If $R(s_1)$ and $R(s_2)$ are the responses to stimuli s_1 and s_2, then

$$R(as_1+bs_2) = aR(s_1)+bR(s_2).$$

This is often simplified into the statement that output is a linear function of the input. The differential equations of such a system have the property that the coefficients of the dependent variables and their derivatives do not involve the dependent variables. Both s and R are considered dependent variables, and only t is independent, according to modern usage. (That the coefficients be constant, often referred to as the condition of stationarity, is sufficient but not necessary for linearity, since coefficients involving only the independent variable will not make the system non-linear.) In the models used in this study, the non-linearity is introduced as a dependence of g on V_j in the filter model, and of $\lambda_{0,i}$ on Q_j in the compartmental model.

Any non-linear system can be considered linear if the excursions of the variables are kept small enough for the changes in the coefficients to be neglected. In our system, this is equivalent to the statement that, in a sufficiently small region, the curve of steady-state output versus input, which is approximately logarithmic, may be approximated by a straight line. These small excursions may be obtained by an input of a very low amplitude step or pulse, in which case eqn. 1 may be used. To such data the well-known methods of linear analysis may be applied. This procedure was used by Fuortes and Hodgkin in formulating their model. This type of observation also eliminates from our consideration one variable which we have found to be very significant—the location and, in general, the time course of the feed-back loop. The chain length and values of the parameters as functions of output could be established first, and then the feed-back loop fitted, which would be a simpler procedure than fitting all simultaneously. Note that at even the lower amplitudes used in these experiments the present system is non-linear. For example, the input for the second of the five pulses is 4 times that of the first, but the output is only $2\frac{1}{2}$ times as great. The difficulty with this procedure is that if preparations are somewhat noisy or unstable, low amplitude outputs are hard to read. This can be overcome by repeating the input many times, and using an automatic averaging device such as the Mnemotron computer to extract the signal from the noise. Another possibility is to use sinusoidal modulation and measure the gain and phase shift as a function of frequency. As a matter of fact, such data were available for this system. However, the 9B21 program is much better suited to the analysis of pulse than sinusoidal data, and fitting the latter was not attempted.

It seems that the best procedure for future use of the 9B21 program in fitting models of this type would be to use averaged pulses of small amplitude to determine the chain length, and then to use pulses of large amplitude and steps to determine the temporal form of the feed-back.

SUMMARY

1. The Fuortes–Hodgkin non-linear electrical filter model for visual response of *Limulus* gives a fairly good fit over a wide range of input amplitudes.

2. The behaviour of the model is rather insensitive, within limits, to the number of filter stages.

3. The behaviour is quite sensitive to the location of the feed-back loop.

4. The NIH-OMR 9B21 program is a convenient and powerful tool for the study of both linear and non-linear filter in compartmental models.

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