RHYTHMICITY IN NEURON-LIKE LINES

BY

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THESIS

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INTRODUCTION

A great deal of effort has been made in the empirical investigation of the electrical properties of animal neurons and in the synthesis of neural analogs. In both cases studies have been largely confined to the case of the propagation of a single pulse, lasting only a few milliseconds. Such behavior is often referred to as 'all or none' response. Essentially, it represents one 'bit' of information. Only by repetitive behavior is the information capacity of the line increased. It is the intention of this paper to delve into the possibilities of recurrent as opposed to 'all or none' behavior of these lines when d.c. voltage inputs are applied.

To undertake this study, two well established models will be utilized. The first, which is based solely on laboratory findings is the Hodgkin-Huxley[1] model of the giant squid axon. The second is the Neuristor[2] model which is itself based upon a simplification of the Hodgkin-Huxley model. Both models are reasonably consistent with empirical data. Both will be employed to investigate different modes by which recurrent or rhythmical behavior can be achieved.

In this endeavor we shall approach our problem from an engineering standpoint. We will examine possible modes of repetitive discharge as purely electrical phenomena, and appeal to our knowledge of electrical circuit theory.

[1] A. L. Hodgkin, A.F.Huxley, "A quantitative description of membrane current and its application to conduction and excitation of nerve,",Journal of Physiology, vol. 117, pp. 500-540; August, 1952.

[2] J. Nagumo, S. Arimoto, S. Yoshizawa, "An active pulse transmission line simulating nerve axon," Proceedings of the IRE, vol. 50, no. 10, pp. 2061-2070; October 1962.

Experimental data with animal neurons known as receptor cells indicate that these lines respond to d.c. input voltages (referred to as generator potentials) with a <u>train</u> of spike-like pulses. It is generally acknowledged that the pulse frequency varies directly with the input voltage, (though frequency may gradually decline or adapt). Yet histological examination shows that the receptor cell has characteristics similar to all nerves though its response is not the same. It is logical that we begin our investigation of rhythmicity by first looking at neuron-like lines, both physiological and electrical in nature.

THE NEURON-LIKE LINE

There are of course other models that we might choose to elaborate on. Let us therefore define descriptively the properties of the neuron-like line in general. Here we might select a variety of characteristics associated with some animal neuron. Thus the following definition is somewhat arbitrary. The neuron-like lines to be discussed will have these properties:

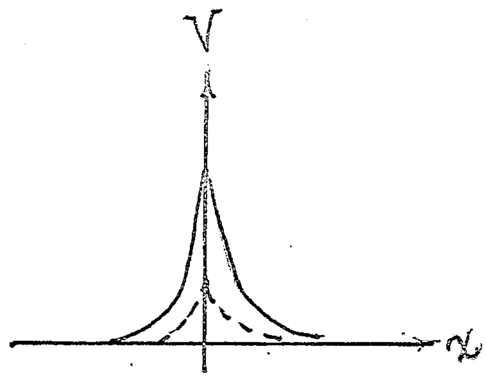
1. Distributed parameters; which are uniform with respect to distance.
2. Bidirectional characteristics (except for end point discontinuities).
3. 'All or none' action potential response.

Some explanation of the third property is in order. In a few words, such a line, when excited at any point along its length, will respond in one of two (all or none) manners, depending upon the magnitude and duration of the excitation:

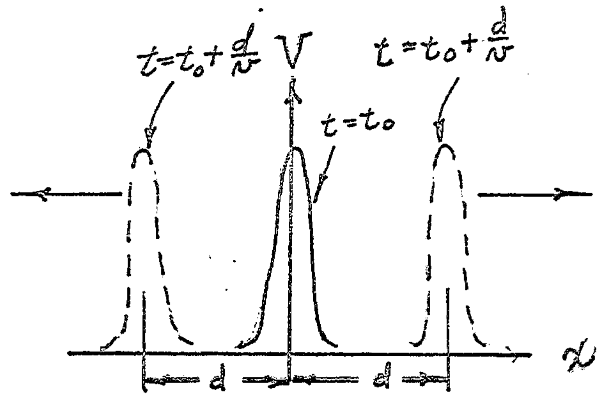
a. (none)- Below the so-called 'threshold' level of excitation.

b. (all)- Above the threshold level of excitation, an 'action potential' wave with a shape which is independent of the level of excitation, propagates away from the point of excitation in both directions at a uniform velocity.

The animal neuron axon and certain of its analogs such as the Neuristor have all of the above properties. Such lines behave linearly and passively with high attenuation at sub-threshold levels, and nonlinearly and actively with zero attenuation at super-threshold levels. These lines 'fire' electrically much the same as fuses when heated above some ignition point, but they are recoverable after a brief 'refractory' period to their original state.



Sub-threshold propagation



Superthreshold propagation

V= line voltage

x= line distance

t_o= time at which excitation is applied

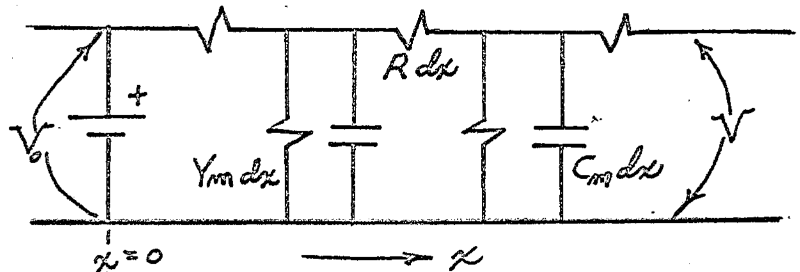
v = velocity of propagation

Fig. 1. Propagation of the action potential.

THE LINEAR SUB-THRESHOLD LINE

Electrotonic Spread

Now that we have some notion of the neuron-like line, let us proceed to study analytically a typical line. Below threshold depolarization (line voltage) the line behaves passively as a uniform cable having a simple linear model.[3]



V_o= applied depolarization voltage

C_m= shunt capacitance/unit length

R = series resistance/unit length

Y_m= shunt conductance/unit length

Fig. 2. Linear, sub-threshold neuron circuit model.

In the steady-state we may neglect the effects of distributed shunt capacitance so that an applied voltage, V_o at $x=0$ decays exponentially according to the relation,

$$V = V_o \exp + x(RYm)^{-1/2} \qquad x < 0 \qquad (1)$$

$$V = V_o \qquad x = 0 \qquad (2)$$

$$V = V_o \exp - x(RYm)^{-1/2} \qquad x > 0 \qquad (3)$$

This exponential variation is referred to in electrophysiology as electrotonic spread and we shall investigate it in greater detail later.

[3] P. Bard, et al, "Medical Physiology, " pp. 921-922, C. V. Mosby Company, St. Louis, Mo; 1961.

THE NONLINEAR SUPER-THRESHOLD LINE

Hodgkin-Huxley and Neuristor Models

Now let us consider what occurs when the applied voltage V_o exceeds the threshold level, $V_o > V_{th}$. Strictly speaking, corresponding to $V_o(t)$ we encounter $V_{th}\ (V_o(t))$; that is, the threshold is a function of the way in which V_o varies with time (accommodation).

In this case our neuron line becomes active; it 'fires'; our linear model breaks down, and an action potential propagates in both directions down the line. This break-down has been studied extensively by Hodgkin and Huxley (and others). Their nonlinear model presents analytical difficulties, but it is subject to a number of reasonable simplifications.

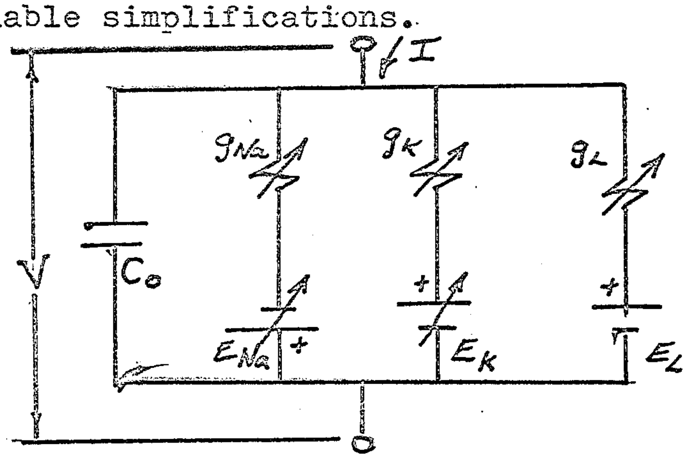


Fig. 3. Hodgkin-Huxley neuron circuit model.

The above model represents many years of experimental work with the giant squid axon. The equations which describe this model are given below. Although little use will be made of them, they are presented to indicate the complexities inherent in our study of neuron behavior. Total membrane current is given by[4]

$$I = C_o\mathring{V} + \bar{g}_{Na} m^3 h (V - E_{Na}) + \bar{g}_K n^4 (V - E_K) + \bar{g}_L (V - E_L) \tag{4}$$

$$\mathring{m} + (\alpha_m + \beta_m) m = \alpha_m \tag{5}$$

[4] A.L. Hodgkin, A.L. Huxley, op. cit.

$$\mathring{h} + (\alpha_h + \beta_h)h = \alpha_h, \quad \mathring{n} + (\alpha_n + \beta_n)n = \alpha_n \tag{6}$$

$$\alpha_m = .1\,(V+25)\left[\exp\left(\frac{V+25}{10}\right) - 1\right]^{-1} \tag{7}$$

$$\beta_m = 4\exp\left(\frac{V}{18}\right), \quad \alpha_h = .07\exp\frac{V}{20} \tag{8}$$

$$\beta_h = \left(\exp\left[\frac{V+30}{10}\right] + 1\right)^{-1} \tag{9}$$

$$\alpha_n = .01(V+10)\left[\exp\left(\frac{V+10}{10}\right) - 1\right]^{-1} \tag{10}$$

$$\beta_n = .125\exp\left(\frac{V}{80}\right) \quad \left\{\begin{array}{c}\text{where } \mathring{x} = \frac{\partial x}{\partial t} \\ t = \text{time}\end{array}\right\} \tag{11}$$

The above was derived entirely from empirical results.

From these 'space clamp' equations (V=constant) the propagation of an action potential is obtained by assuming a wave equation solution and applying successive approximations (method of Hartree) to these partial differential equations. The method is obviously laborious and it gives us essentially no insight into possible modes of rhythmical behavior. This model will however be useful later at least qualitatively.

Perhaps the best electrical analog to the above model is the Neuristor. Theoretically, such a line is constructed of distributed elements exhibiting R,L,C and nonlinear characteristics (e.g. tunnel diode behavior). The Neuristor is often based upon the following mathematical model (Bonhoeffer-van der Pol,[5] BVP).

$$J = \frac{1}{c}\mathring{\mu} - w - (\mu - \mu^3/3) \tag{12}$$

$$c\mathring{w} + bw = a - \mu \tag{13}$$

where a, b, and c are constants satisfying the relations.

$$1 > b > 0, \quad c^2 > b, \quad 1 > a > 1 - 2/3\,b \tag{14}$$

[5] R. FitzHugh, "Impulses and physiological states in theoretical models of nerve membrane," Biophysical Journal, vol. 1, pp. 445-466; July 1961.

and the variables u,w and j in the above correspond to the pair of variables (V,m), (h,n) and I in the Hodgkin-Huxley equations. An electronic simulator of the BVP model is shown below.[6]

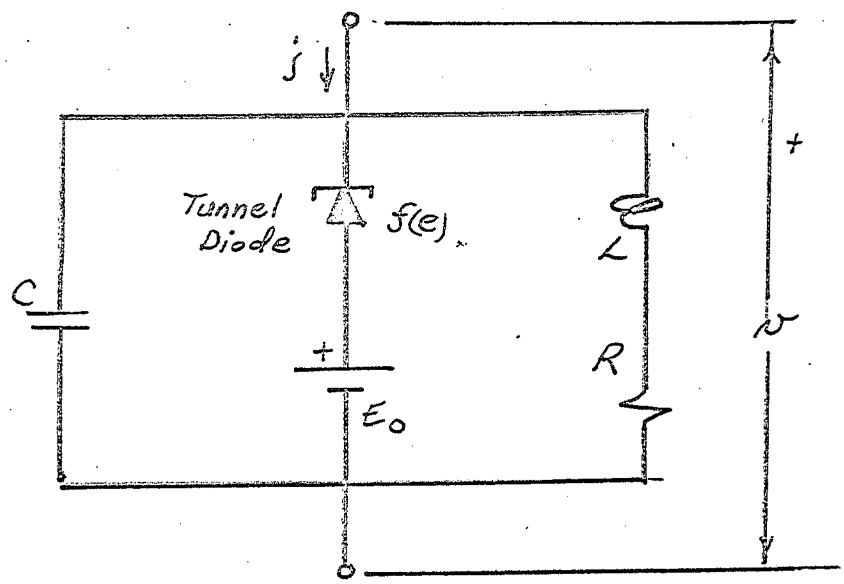


Fig. 4. One version of the tunnel diode discrete element neuristor.

6 J. Nagumo, S. Arimoto, S. Yoshizawa, op. cit.p. 2063.

RHYTHM

Now that we have acquired some familiarity with the basic properties and structure of neuron-like lines, we can begin probing into their rhythmical characteristics. Our dictionary defines rhythm as: "Movement characterized by regular measured or harmonic recurrence of stress, beat, sound, accent, or motion; as the rhythm of the pulse." More specifically we shall confine ourselves to rhythmical response under input voltage control. It is by the process of voltage controlled modulation of pulse frequency that quantitative information is transmitted along the animal neuron. This voltage controlled form of oscillation must be distinguished from fixed frequency oscillation such as one finds in animal neurons after the removal of calcium (decalcification). In the later case, oscillations are independent of any input voltage and the system is said to be unstable.

RHYTHMICITY AS A STABILITY PROBLEM

Lyapunov's Second Method

It is only natural to consider rhythmicity in terms of stability. For-

Rhythmicity implies Instability

The type of oscillations we are considering actually represent conditional instability. That is, instability which is dependent upon input voltage. If the input voltage is removed, no oscillations occur, but if an input above threshold is applied, then pulsations are present and their frequency increases with input voltage.

To test whether our system is capable of rhythmical response, we can appeal to stability criteria. Is the system stable? If the system is stable, it must have a Lyapunov function L ($\underline{s}$)[7] where $\underline{s}$ denotes the state vector. Thus in both Hodgkin-Huxley and neuristor equations we can seek out a scalar L ($\underline{s}$) such that:

$$L(\underline{s}) > 0 \quad , \; L'(\underline{s}) < 0 \quad , \text{ when } \underline{s} \neq \underline{s}_e \; , \; L'(\underline{s}) = \frac{dL}{dt} \tag{15}$$

where $\underline{s}_e$ is the equilibrium state and

$$L(\underline{s}_e) = L(\underline{s}_e) = 0 \tag{16}$$

If we are able to find L ($\underline{s}$), then unending rhythmicity is not possible. This does not exclude rhythmicity of a transient nature (i.e. adapted response). If we are unable to find an L ($\underline{s}$), this does not of course imply that one does not exist and that the system is unstable. To establish instability, we require a new scalar function, call it $\daleth$ ($\underline{s}$) such that

$$\daleth(\underline{s}) > 0, \quad \daleth'(\underline{s}) > 0 \quad , \text{ when } \underline{s} \neq \underline{s}_e \tag{17}$$

$$\text{and} \quad \daleth(\underline{s}_e) = \daleth'(\underline{s}_e) = 0 \tag{18}$$

We are lead immediately to Lyapunov's Second Method here, because of its complete generality in dealing with nonlinear systems. The difficulty lies in its application. Also, assuming that some $\daleth$($\underline{s}$) exists, we are still <u>unable</u> to say

$(\ni \daleth(\underline{s}) \Longrightarrow \text{instability}) \Longrightarrow \text{rhythmicity}$

(instability <u>does not</u> imply rhythmicity)

[illegible] the case)

It is necessary to [illegible] our models more closely for rhythmical tendencies.

7 R.E. Kalman, J. E. Bertram, "Control system analysis and design via the 'second method of Lyapunov'," Journal of Basic Engineering, Transactions of the ASME, pp. 371-400; June 1960.

MODES OF OSCILLATION

As we can see, knowing that a line is unstable does not in itself identify the type of instability and the mechanism by which recurrent response is possible. There are, however, several modes of oscillation that we might consider. To motivate later development, the following are suggested.

Take the relaxation oscillator for example. In essence a relaxation oscillator is a nonsinusiodal waveform generator. A typical relaxation device involves the repeated charge and discharge of an energy storing component, such as an inductor or capacitor through a nonlinear electronic switch such as a tunnel diode. The simplest circuit that we might imagine is a series R-C configuration with the capacitance shunted by some device which discharges the capacitance at some critical voltage.

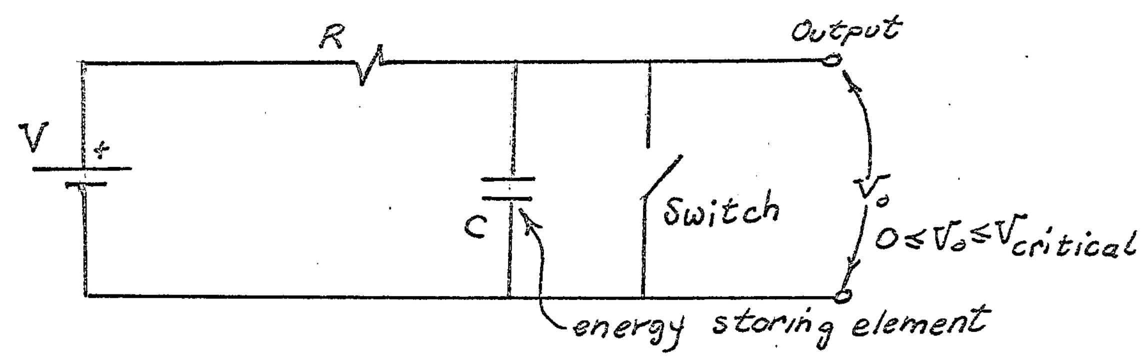


Fig. 5. Simple R-C discharge oscillator.

We note that the output frequency of this circuit will increase with V, as C charges to the critical voltage more rapidly with increasing V.

Neuron-like lines do contain series R, shunt C and nonlinear 'switching' properties, but these are all distributed. It is required that we elaborate further before accepting oscillations of the relaxation type in neuron-like lines.

Yet another form of oscillation that we might associate with any distributed line involves line resonance. Consider the situation when a line is shorted at both ends. If it is lossless, then we know immediately that it is resonant at odd half-wave lengths. Consider next the case of a neuron-like line which is terminated in other than its characteristic impedance. (We have not defined the correct termination for such a nonlinear line but let us assume for the moment that it exists). Assume also, that at some point in the line behind its termination, another reflection is possible. Then we might again say that our line is resonant. The frequency is given by

$$f = v/2d \qquad (19)$$

where f = pulse frequency

v = pulse propagation velocity, assumed constant

d = length of line between reflection points

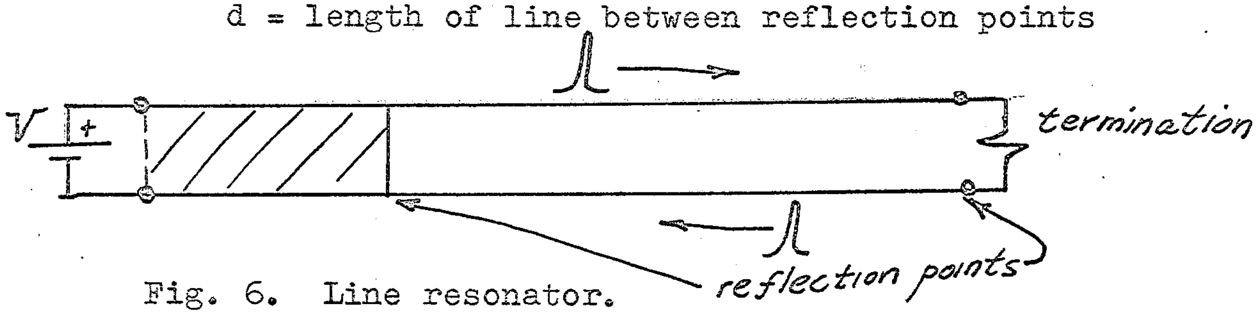


Fig. 6. Line resonator.

Also assume that the left-end reflection point is under voltage control. Nothing has been said about how this resonant line condition can be achieved in neuron-like lines. This shall be discussed at some length later.

Perhaps the most obvious oscillator is that which employs direct feedback. No further elaboration on this mode is necessary. However, it is difficult to see how feedback loops can develop in a distributed line with uniform characteristics. Secondly, how can the frequency of a closed loop oscillator be under voltage control?

Here, let us assume that our line exhibits continuous feedback. Allow external <u>uni-directional</u> feedback from an endpoint discontinuity into the line along its length. Also, let there be regeneration (looping back) at some point on the line which is under voltage control.

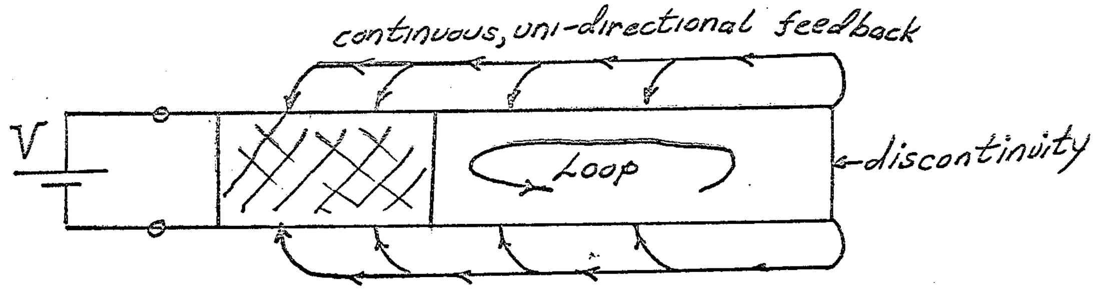


Fig. 7. Continuous feedback oscillator.

Admittedly, the concept of continuous feedback is difficult to accept, but we shall, however, not reject it as a possibility.

CIRCUIT APPROXIMATIONS

At this stage, it is necessary to turn to the neuron-like models themselves for true insight into the mechanisms by which some of the above modes of oscillation are realizeable. To be completely rigorous we should appeal directly the sets of differential equations which describe these models. Such a procedure is, however, frought with difficulties. In both cases analytical solutions are generally unattainable so that we must rely entirely upon numerical techniques and computer solutions. Any manipulation of these equations will only compound our problem.

Secondly, it is not our purpose here to obtain numerical results of limited applicability. Thus we must obtain algebraic results without analytical solutions.

To solve this dilemma, a number of simplifying assumptions will be made. This procedure will be followed entirely out of necessity. To test the validity of these assumptions we must avail ourselves of quantitative information which we shall not deal with here in this paper.

APPROXIMATION 1 R-C DISCHARGE via THE HODGKIN-HUXLEY MODEL

There are of course many simplifications of the neuron-like line that we might make without stretching the imagination too far. Let us first investigate a reasonable approximation of the Hodgkin-Huxley model.

This model represents one section of the neuron line which is space clamped at a constant voltage. An incremental extrapolation should include series resistance as well as shunt conductance and susceptance.

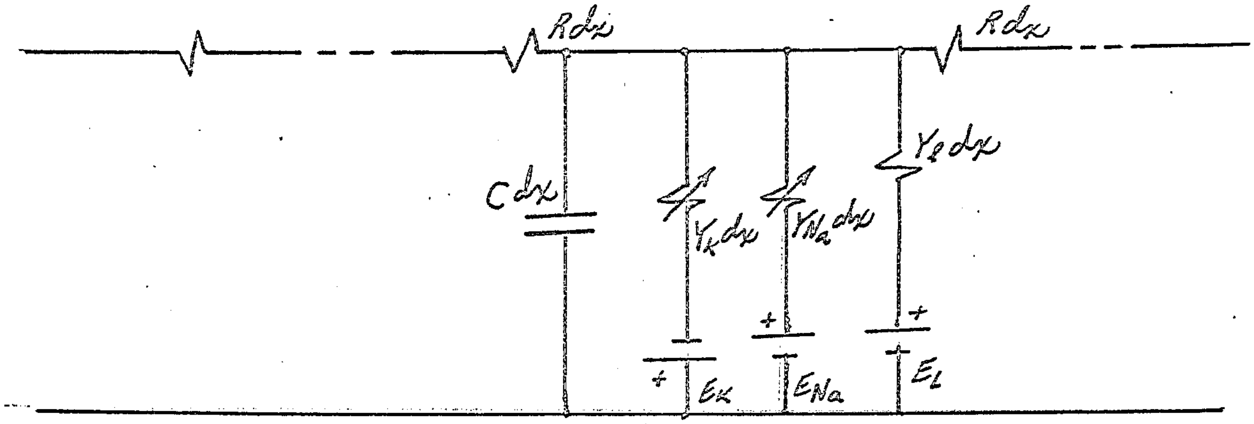


Fig. 8. Incremental extension of Hodgkin-Huxley circuit model.

This infinitesimal circuit reduction is achieved by spacially chopping the Hodgkin-Huxley circuit down to a width dx and then coupling it to similar sections with series resistance Rdx.

It should be noted that the shunt conductances have fixed biasing voltages (equilibrium potentials, E_{Na}, E_k, E_l). This was done because each of the conductances was isolated experimentally and it was discovered that the equilibrium potentials were essentially independent of applied voltage.

For convenience we may combine all the conductance branches into one equivalent Y and an equivalent series voltage E. It must be noted that both Y and E are nonlinear. In the original model

E_K and E_{Na} are opposite in sign, thus allowing the line voltage to reach zero and reverse (which it does do during activation) when Y_K and Y_{Na} vary sufficiently. To achieve the same response with one source, requires that it too be nonlinear and bipolar.

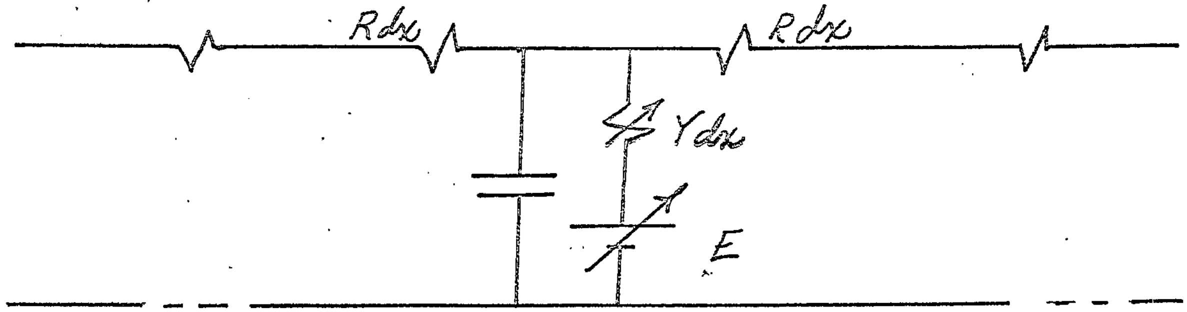


Fig. 9. Reduction of Hodgkin-Huxley incremental model.

Now that we have simplified the model somewhat, let us apply a voltage V_o which is above threshold, over some region on the left. It must be remembered that Y is a nonlinear function of V(x). This is suggested by the sketch below for the case of the propagated action potential.[8]

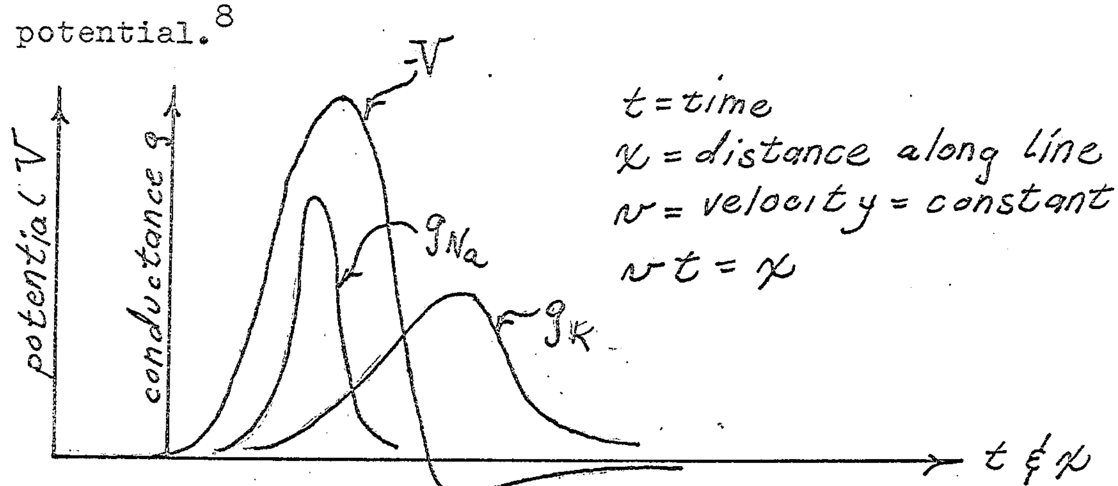


Fig. 10. Action potential fluctuations.

The above is not quantitative, but it does clearly suggest that shunt conductance increases sharply with V. It is reasonable to assume that series resistance R is linear since the longitudinal voltage component is normally small. Although the transverse voltage V may be large, on the basis of experimental evidence, C is relatively constant.

[8] A.L. Hodgkin, A. F. Huxley, op. cit., p. 500.

It is most important that we take note of the fact that both R and C parameters are constant, independent of the line voltage V.

For small perturbations about some equilibrium point we may linearize the line parameters, gradually tapering their characteristics with respect to distance to conform to the line voltage.

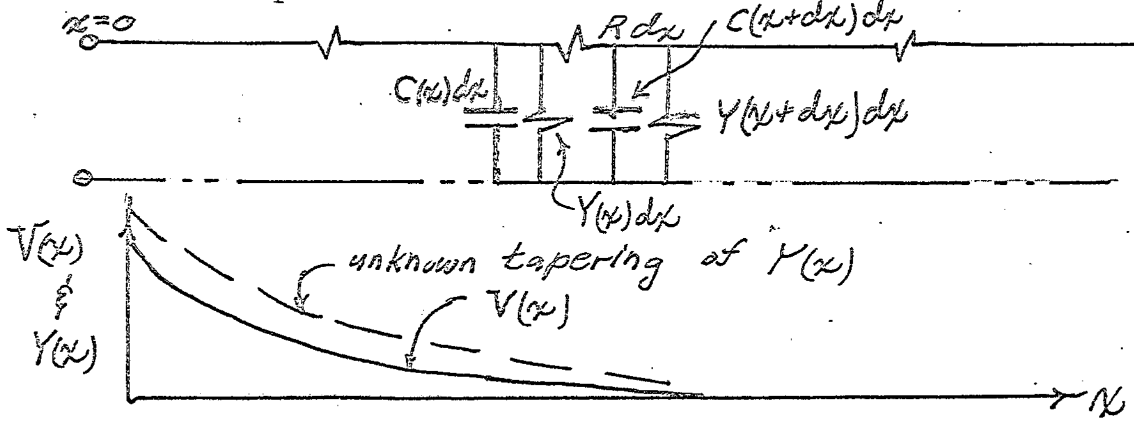


Fig. 11. Line parameter tapering.

The source E is removed in this model as we are assuming small perturbations. From left to right we expect to find constant R and C and decreasing Y. Thus we might divide the line artifically into three segments:

1. where Y is large relative to R, Y >> R

   followed by a segment

2. where R is larger than Y, R > Y

   followed by a segment

3. where Y is negligible and shunt capacitance is important

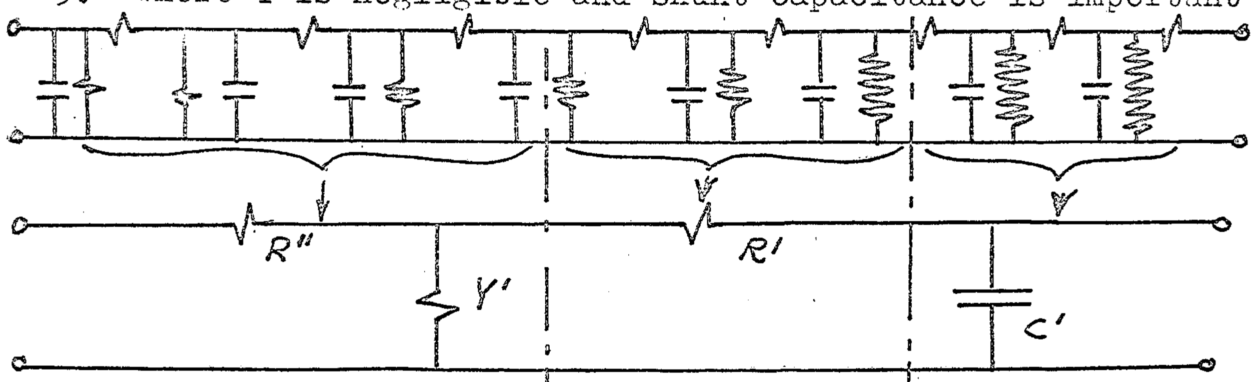


Fig. 12. Approximate line segmentation.

NOTE: The third section effective capacitance C' should approach a limit as $x \to \infty$ due to series resistance R.

Thus we have in a very crude fashion developed an R-C approximation of an above-threshold line. We do not possess sufficient evidence to justify this approximation. If we do accept this approximation, it becomes easy to see how a relaxation oscillator develops out of the model. It is only necessary to have C' alternately charge and discharge to have recurrent behavior. This will occur during the propagation and recovery phases of the action potential.

The concept here is that of a super-threshold line on the verge of firing, which is triggered by an R-C discharge.

It is interesting to note the properties of the R-C discharge circuit.

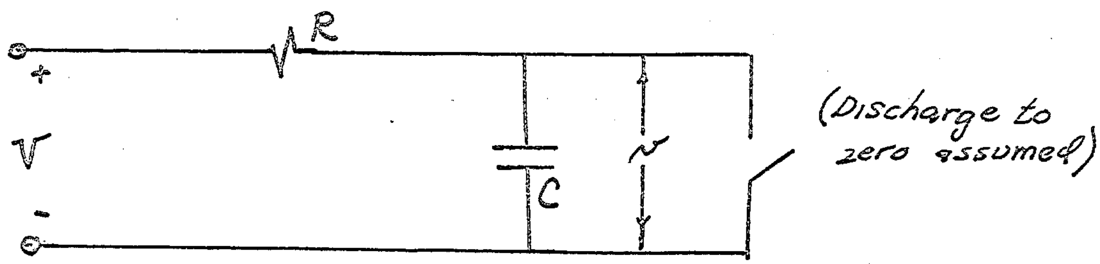


Fig. 13. R-C discharge oscillator.

C is discharged when $v = V_f$

for $v \leq V_f$ we have

$$v = V(1 - \epsilon^{-t/RC}) \tag{20}$$

As an infinite series the exponential term is given by

$$\epsilon^{-t/RC} = 1 - t/RC + t^2/2!R^2C^2 - t^3/3!R^3C^3 + \ldots \tag{21}$$

which is approximated by

$$\epsilon^{-t/RC} \cong 1 - t/RC \tag{22}$$

when $t/RC \ll 1$

$$v \cong \left(\frac{V}{RC}\right) t \tag{23}$$

when $v = V_f$

$$t = \frac{V_f RC}{V} = \text{period of pulsation} \tag{24}$$

As the frequency varies directly with the applied voltage:

$$f = \text{frequency} \cong V\left(\frac{1}{V_f RC}\right) \tag{25}$$

This is the relationship that one commonly finds experimentally between generator potential V and pulse frequency f in the receptor cell.

THE R-C DISCHARGE APPROXIMATION AND STRENGTH - DURATION CURVES

Let us take another look at the implications of our R-C discharge approximation model.

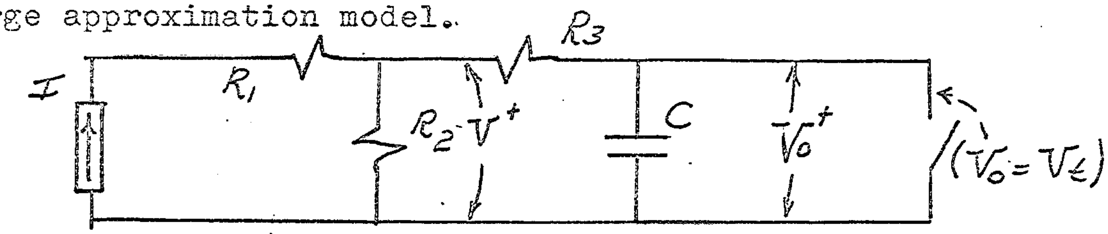


Fig. 14. R-C discharge oscillator with current input.

Assuming R2 < < R3 we have immediately

$$V \cong R_2 I = constant \tag{26}$$

and the output voltage is

$$V_o = V(1 - e^{-t/RC}) \tag{27}$$

or

$$\frac{V_o}{1 - \epsilon^{-t/RC}} = V \tag{28}$$

and at the time of discharge $V_o = V_t$

$$V = \frac{V_t}{1 - \epsilon^{-t/RC}} = IR_2 \tag{29}$$

$$I = \frac{V_t}{R_2}\left[1 - \epsilon^{-t/RC}\right]^{-1} \tag{30}$$

We have arrived at a relation between a constant excitatory current and the time required to 'fire' the device. But this is completely analagous to the empirical expression for nerve stimulation which is

$$I = I_{rh}\left[1 - \epsilon^{-t/K}\right]^{-1} \tag{31}$$

"The value of K depends on various parameters of the fiber. Some of these are membrane capacity, the length constant and the critical level of depolarization of the membrane required for excitation."[9]

[9] Bard, et al, op. cit., p. 925.

APPROXIMATION 2 LINE RESONANCE

Concept of Heightened Excitability

As a second approach let us continue with a study of actual line resonance. In this case it is worthwhile to look into the neuristor line. With this line we can most readily gain some insight into wave propagation and repeated reflection accompanying line resonance. To eliminate difficulties inherent in any study of a nonlinear distributed line, we shall begin with an approximation of the neuristor consisting of lumped parameters and relays.

Basically, we may construct such a line by connecting a string of monostable multivibrators, each capable of firing the succeeding one with a finite delay.[10]

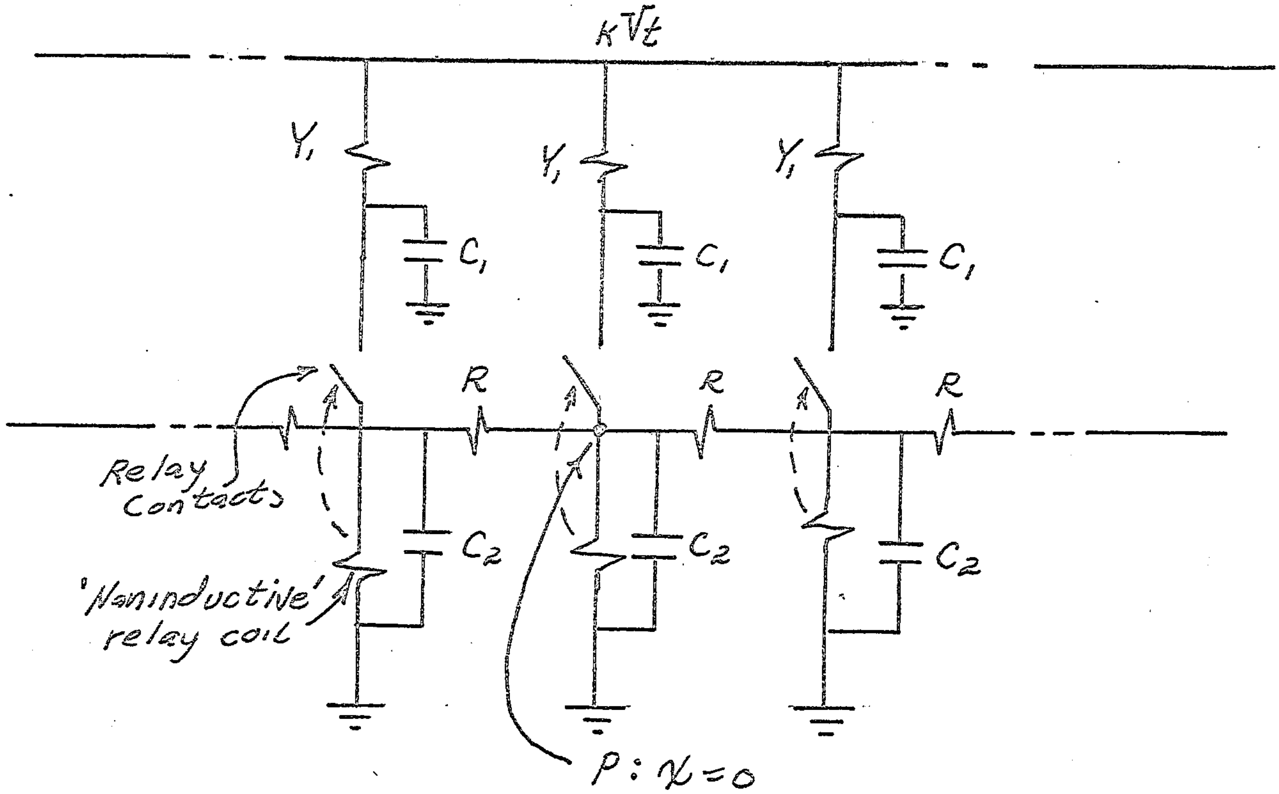


Fig. 15. Relay approximation of the Neuristor

[10] H. D. Crane, "Neuristor-a novel device and system concept," Proceedings of the IRE, vol. 50, no. 10 p. 2049, October 1962.

This model, although a gross simplification of neuron-like characteristics will for the present serve our purpose.

Suppose a voltage V is applied at point P. As long as $V < V_t$, the relay actuating voltage, V will decay electrotonically along the line. However, when $V(0) > Vt$ the relay contacts close and kV_t, the voltage to which C_1 is charged is suddenly impressed at P (for $C_2 << C_1$). For k sufficiently greater than 1, succeeding relays on each side of point P will have a chance to fire and the disturbance will propagate. Note C_2 is introduced to achieve a propagation time delay.

At this point it would be profitable to review the properties of the neuristor line. It is uniform, nonlinear and conceptually at least there is no reason why it can not be distributed, (Although in practice, we must realize the difficulty involved in reducing a lumped parameter network to its transmission line extension).

When the line is made active, an action potential traverses the line without attenuation and at some finite velocity. All this is in accord with current concepts of the physiological neuron. In fact a neuristor model using lumped R,C,L and Tunnel diodes has been experimentally synthesized which conforms closely to a simplified Hodgkin-Huxley neuron model.

Now we might ask ourselves if there is some way of modifying the Neuristor to achieve repetitive discharges of pulses under input voltage control. The answer is yes, if we are willing to accept the introduction of some form of retarded feedback into our original model. To see how this is possible, let us return to the simple R, C. relay line.

Designating V, applied at point P as the input, let us consider the response of the line for $x \geqslant 0$ for sub- and super-threshold V, ($V < V_t$ and $V \geqslant V_t$). From earlier discussion, we have that V spreads electrotonically for $V < V_t$, (disregarding initial transients due to circuit capacitance). Let V exceed V_t and as we have shown a single propagated action potential results. Note that it is not recurrent, but we must not overlook the fact that if V is maintained constant during and after the action potential we will have an electrotonic spread along the line leaving one section of the line from $x=0$ to $x=x_t$ above threshold and the section $x=x_t$ to infinity below threshold but in a state of heightened excitability.

From $x=0$ to $x=x_t$ by definition $V(x) \geqslant V_t$ and the relay contacts are closed. In the steady state the line is simplified as below.

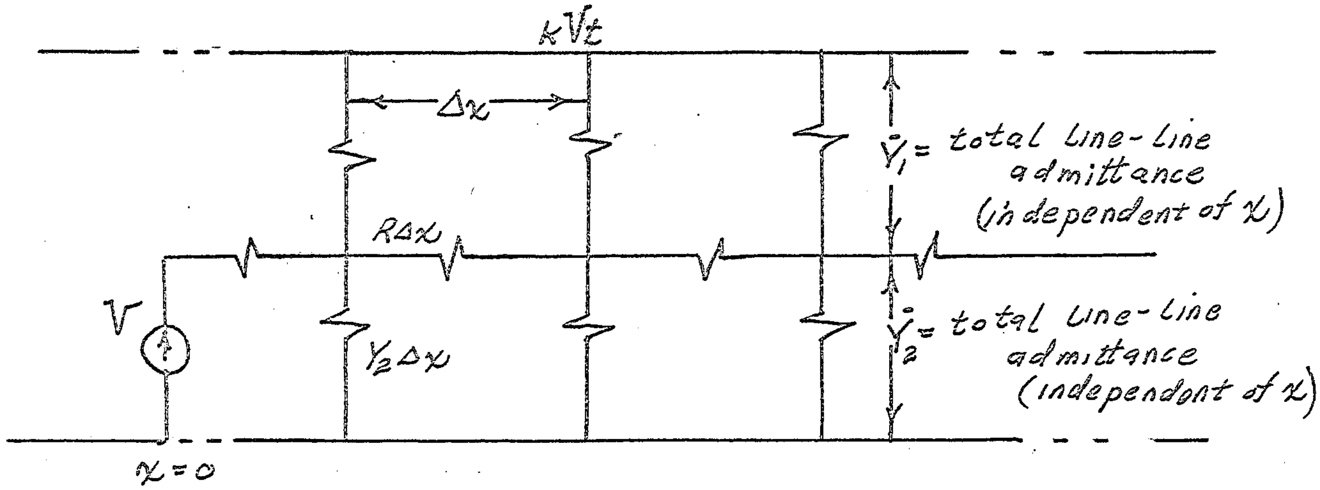


Fig. 16. Resistance network of 'relay' Neuristor.

This line is linear for $V(x) \geqslant Vt$ so we can justifiably superimpose the effects of the distributed source voltage kV_t and the input voltage V for any point $0 \leqslant x \leqslant x_t$

$$V(x) \simeq \frac{\bar{Y}_1}{\bar{Y}_1 + \bar{Y}_2} kV_t + V_s^V(x, 0) \qquad (32)$$

assuming Δx small; i.e. line ~ distributed

where

$$V_s^V(x, 0) = V e^{-\gamma x}, \quad \gamma = \sqrt{(Y_1 + Y_2)R} \qquad (33)$$

= line voltage at x, due to V at $x=0$

Note that to determine the independent effects of V and the energy source kV_t we let each in turn be zero and add the responses. When $kV_t = 0$ we have:

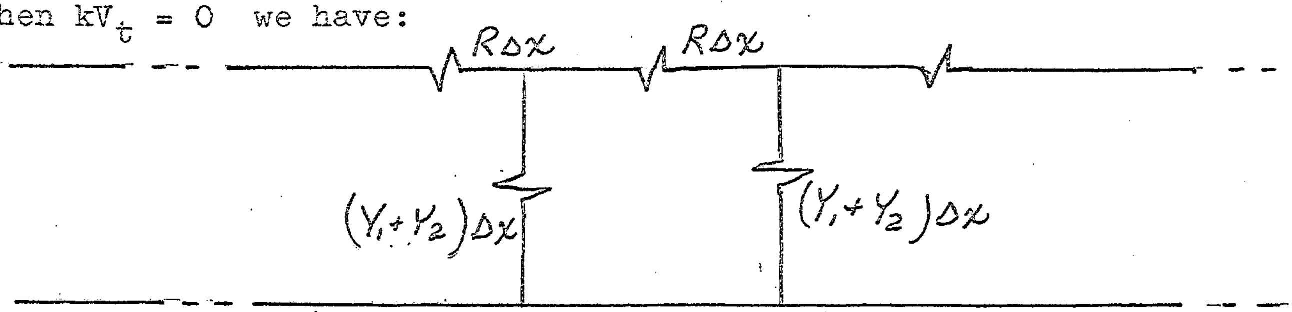


Fig. 17. Reduction of resistive network.

$$V_{s_0}^{V}(x, o) = V \epsilon^{-\gamma x} \tag{34}$$

By Superposition

$$V(x) \cong V \epsilon^{-\gamma x} + \frac{\bar{Y}_1}{\bar{Y}_1 + \bar{Y}_2} kV_t - \frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} kV_t \epsilon^{-\gamma x} \tag{35}$$

$$= \left(V - \frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} kV_t\right) \epsilon^{-\gamma x} + \frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} kV_t \tag{36}$$

Note: $\frac{kV_t \bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} < V_t$

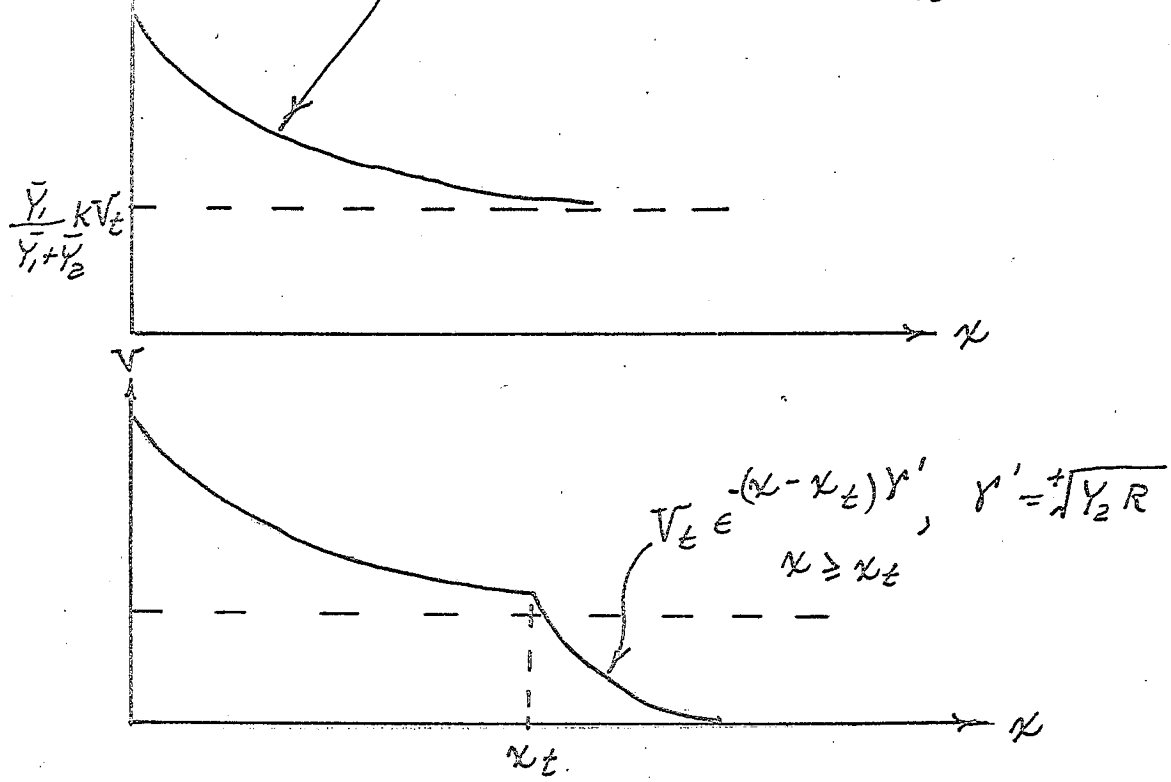


Fig. 18. Voltage along relay Neuristor Line

$$V(x) \cong \left[\left(V - \frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} k V_t \right) \epsilon^{-\gamma x} + \frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} k V_t \right] \left[1 - U(x - x_t) \right] + U(x - x_t) V_t e^{-\gamma'(x - x_t)} \tag{37}$$

where

$U(x-x_t)$ = unit step function at $x = x_t$

At x = xt

$$V(x_t) = V_t = \left(V - \frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} k V_t \right) \epsilon^{-\gamma x_t} + \frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} k V_t \tag{38}$$

And solving for xt

$$\epsilon^{\gamma x_t} = \frac{V - \frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} k V_t}{V_t \left(1 - \frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} k \right)} \tag{39}$$

$$x_t = \frac{1}{\gamma} \left[\ln \left(V - \frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} k V_t \right) - \ln V_t \left(1 - \frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} k \right) \right] \tag{40}$$

Let

$$\frac{1}{\gamma} \ln V_t \left(1 - \frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} k \right) = C_1 \quad (\text{independent of } V) \tag{41}$$

$$\frac{\bar{Y}_1}{\bar{Y}_1+\bar{Y}_2} k V_t = C_2 \tag{42}$$

So that

$$x_t = \frac{1}{\gamma} \ln (V - C_2) - C_1 \tag{43}$$

The 'resonant' length is then

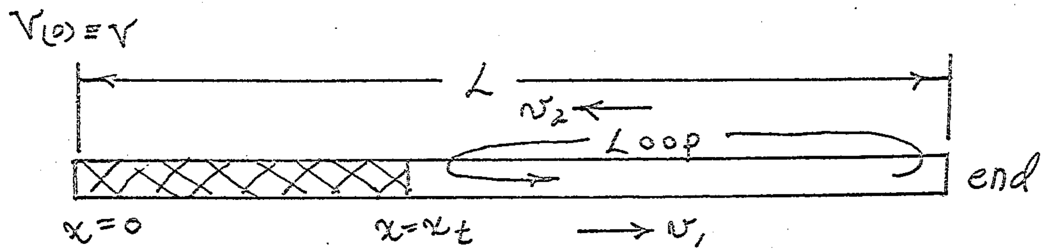


Fig. 19. Internal Line resonance.

Assuming that there is reflection exactly at $x = x_t$ and $x = L$ the frequency will be

$$f = \left[\frac{L - x_t}{v_1} + \frac{L - x_t}{v_2} + delay_1 + delay_2 \right]^{-1} \quad (44)$$

where v_1 = wave velocity to right

v_2 = wave velocity to left via return path

f = frequency

time $delay_1$ = rebound delay at $x = xt$

time $delay_2$ = rebound delay at $x = L$

without endpoint delays

$$f = \left[\frac{L - x_t}{v_1} + \frac{L - x_t}{v_2} \right]^{-1} = \left[L - x_t \right]^{-1} \frac{v_1 v_2}{v_1 + v_2} \quad (45)$$

Feedback Possibilities

The above development is applicable for both continuous external and internal reflection types of feedback discussed earlier. As a reminder, in the continuous external feedback case the loop is completed by continuous uni-directional coupling and v_1 and v_2 may be different. Also in the case of repeated internal reflection v_1 must equal v_2.

It remains to examine the conditions at the end points where delays are possible. The action potential wave traveling to the right at velocity v_1 meets a discontinuity at the extreme right. If it is to be reflected back along the line itself, there must be a delay there so that the region immediately behind the wave can recover (capacitors C_1 in the relay neuristor model are discharged). If on the other hand there is continuous feedback, an external loop must begin at this point. In this case the external looping must be uni-directional or else small multiple loops will appear and voltage control will be lost.

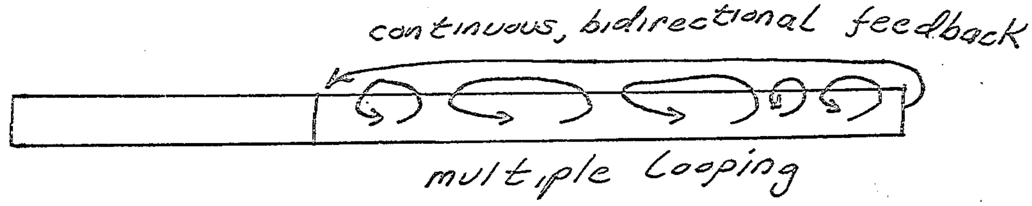


Fig. 20. Continuous feedback oscillator.

Wave reflection also occurs near the point $x=x_t$, because the line is in a condition of heightened excitability. A return signal of sufficient magnitude traveling to the left will reexcite the line initiating a new pulse wave to the right. With continuous feedback, the return signal level is determined by the characteristics of the feedback path (whether it has active or passive elements, with or without gain) For the case of internal reflection the return signal spreads electrotonically with or without attenuation accordingly, as it is below or above threshold respectively. It is assumed that this process of oscillation does not cease as long as V is maintained.

INHIBITORY INFLUENCES ON RHYTHMICITY

Further Investigation of the Neuristor

Up to this point we have been greatly concerned with generation of pulses (action potentials) along the neuron-like line, but for completeness we should also be interested in mechanisms by which such discharges are inhibited. Obviously, removal of the input will prevent rhythmical pulsations from happening, but it is also quite possible to have a super-threshold input and in addition one or more inhibitory inputs which prevent or diminish the tendency for discharges to occur.

To illustrate possible mechanisms for this phenomena let us investigate two modes of inhibition. Perhaps the most obvious method of excitatory-inhibitory control is by direct summation of inputs as shown below.

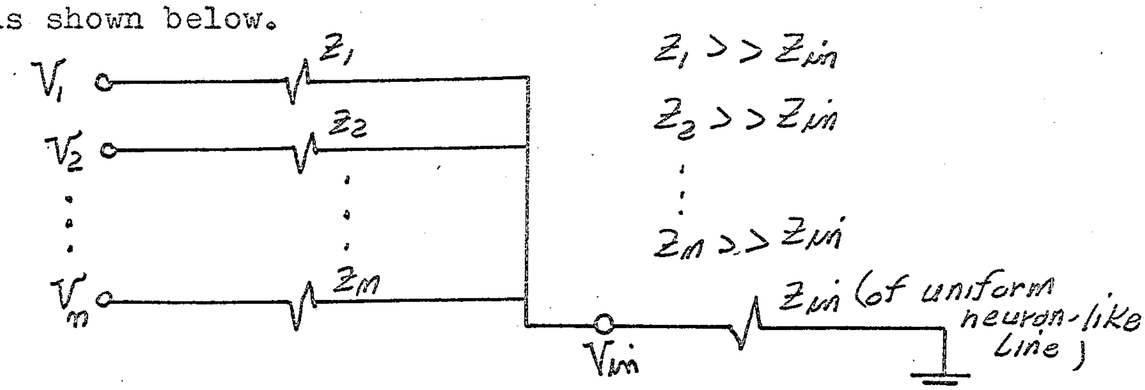


Fig. 21. Resistive adder.

This system requires that the inputs be applied at the same point on the line and that the inputs greatly exceed the output V_{in} for strictly additive properties to exist.

There is quite a different method of inhibition which requires a new point of application. Consider for a moment one version of the neuristor discrete-element line. There are several possible line structures that might be chosen but this one is purposely

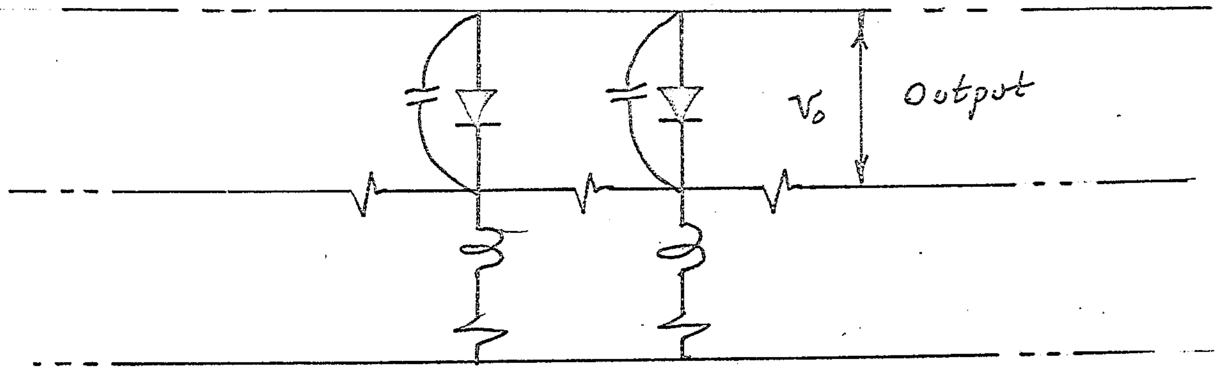


Fig. 23. One version of the neuristor.

selected to illustrate the following. If we ignor the effects of L and C the line may be broken into the section below.

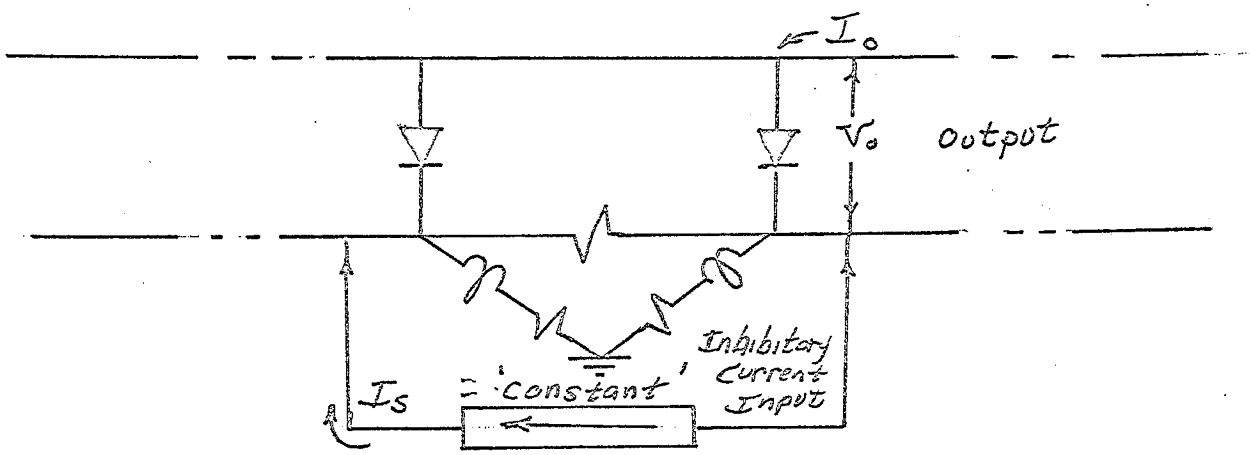


Fig. 24. One form of Inhibitory Input.

This segment as seen from the output terminals has tunnel diode characteristics with controlled negative resistance a function of the externally applied inhibitory input current. The effect of varying I_s on the output characteristic is illustrated by the family of curves given below.[11]

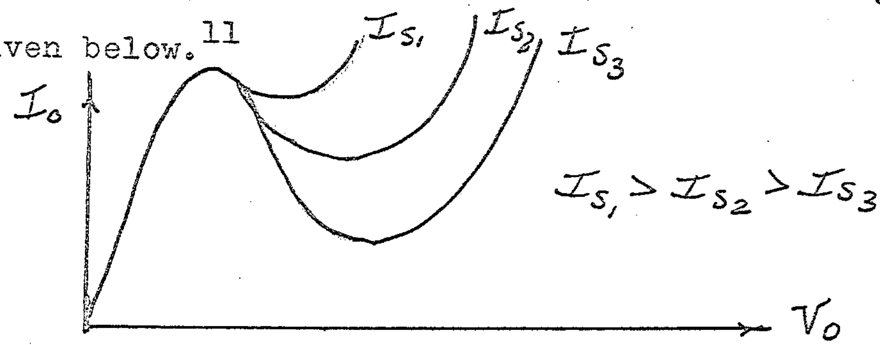


Fig. 25. Tunnel diode characteristics as a function of a control current.

11 S.P. Gentile, "Basic Theory and Application of Tunnel Diodes," D. Van Nostrand, New York; pp. 300-302; 1962.

We note immediately the increase in 'valley' current with increasing inhibitory current I_s. It should be obvious that this represents a decrease in gain for this segment of the line.

If I_s is sufficiently large an action potential reaching the segment will be attenuated to the level where no further activation of the line is possible and thus it will completely block the signal.

On the other hand, if V is applied at approximately the same point as I_s the inhibitory effect of I_s will not be absolute and it merely will raise the apparent threshold.

Obviously there are other disturbances which might be introduced on the line to inhibit its transmission. The above are but two conceivable examples.

STATISTICAL VARIATION OF RHYTHM

Shot Noise

Given an input V and a series of inhibitory currents and/or voltages we assume that the output response of our neuron-like line is thus uniquely determined. It is generally the rule that in actual experimental studies of receptor cell response one encounters random pulse frequency and amplitude variations which we have not anticipated for the simple electrical analog. Up to now such phenomena have not been considered important, but the effects of randomness in the physiological system are worthy of attention. It is spontaneous neural activity, actually a form of noise which stimulates and heightens the receptivity of the system. Also random statistical fluctuations are an important factor in limiting the relative accuracy of the pulse frequency coded neural signals.

It is reasonable to suspect that our distributed neuron-like line will be subject to fluctuations in parameters along its length as a function of applied voltage and time. We know that all electronic discrete components possess random variations and are therefore generators of noise of one form of another. What we do know of distributed parameter circuitry suggests that this noise problem is universal. However, relative magnitude must be noted in these variations.

It is generally accepted that in the neuron longitudinal resistance/unit length and shunt capacitance/unit length are 'virtually' independent of applied voltage, (as noted earlier). We would therefore be cautioned to look elsewhere for sources of noise. The natural parameter to suspect is the nonlinear one. In the neuristor the logical choice is the parameter with tunnel diode characteristics.

It is during the tunneling process that shot noise manifests itself. Shot noise is believed to be the result of carriers deflected from the barrier when unlike charges of equal energy levels are not on opposite sides of the barrier. It is also recognized in electron tubes as the result of the irregular impact of electrons on the plate of the tube. Similarly we might expect shot noise during ionic conduction across a neural membrane.

At the low frequencies of neuron-like lines (in the audio range) tunnel diode noise is almost entirely shot noise while thermal noise is present in significant amounts only at high frequencies, too high above the normal response of such lines. Shot noise is inversely proportional to frequency (over a wide range) and an increasing function of voltage.[12]

It is not unreasonable for us to include such phenomena as shot noise in our neuron-like line model.

[12] S. P. Gentile, Ibid., p. 251.

SUMMARY

After familiarizing ourselves with the neuron-like line and specifically with the Hodgkin-Huxley model, we tried to point out some of the road-blocks to straight-forward analysis in our understanding of rhythmical behavior. Powerful 'tools' such as Lyapunov's Second Method were not readily applicable to this problem. As an alternative we searched for a number of network simplifications, based upon quantitative assumptions which we left without justification.

Before actually probing into the neuron-like line, we considered possible mechanisms by which oscillatory behavior could be achieved, thus motivating later discussion. As a first approach, we examined the Hodgkin-Huxley circuit model. Here the shunt conductance was seen to vary with respect to distance away from the point of input application. This variation was used to fabricate a roughly equivalent R-C series configuration. From this model a frequency vs. voltage dependence was established with neuron excitation strength-duration characteristics.

In an entirely different manner we next pursued the notion that transmission line resonance was a possible mode of oscillation. to this end we utilized a simplified discrete element, piece-wise linear approximation of the Neuristor transmission line. Our analysis showed that the voltage along such a line delays exponentially with respect to distance, with different asymptotes for segments of the line above and below threshold voltage. Near the transition point the line was on the verge of initiating an action potential. Although the actual stability at this point was not considered, it was reasoned that a returning pulse of sufficient magnitude would elicit a new action potential. Thus this heightened excitability could furnish the necessary wave regeneration for repetitive behavior. Both internal line reflection and external return signals were included in our study of line resonance. In the later case we introduced the concept of continuous feedback.

At this point we considered negative influences upon rhythmicity and the effect of multiple inputs both excitatory and inhibitory. Pulse blocking was studied for the case of the tunnel diode Neuristor. We concluded with a consideration of statistical variation and noise.

CONCLUSION

UNSOLVED PROBLEMS

It must be realized that almost any simplification that we might desire to make of the complex neuron-like line is likely to mislead us. As previously stated it is only out of necessity that we are compelled to perhaps over-simplify our model. Ultimately it is required that all conclusions reached be investigated experimentally and/or analytically in the most realistic model we have.

Thus if we suspect some feedback mechanism, for example, in the animal receptor cell, it might be useful to study the effect of breaking the feedback loop, if this is possible. Unfortunately, nerve studies are difficult or impossible in all but the largest cells such as the giant squid axon due to the problems inherent in manipulating tissue measured in micron dimensions.

With neuristor lines we are confronted with the problem of physical realizability. Here it is required to synthesize non-linear distributed parameter lines. The synthesis of lumped parameter networks with nonlinear properties, even with the aid of computer facilities, is indeed a formidable task. Transform methods are only useful for piecewise-linear networks so that ultimately we must work exclusively in the time domain.

Then again, assuming that the synthesis problem has been completely resolved theoretically on paper, it then remains to develop the component characteristics and circuitry to carry out the design. Then we may desire to develop a distributed model in the laboratory. Neuristor development awaits technological breakthroughs in distributed circuitry.

It is hoped that this work will encourage others to expand neuron analogs so that new comparisons can be made with their animal counterparts.

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