VII. Principles of Electrophysiology with Special Reference to the Heart

Electrical Fundamentals

Maxwell's equations

$$\text{curl } \underline{E} = -\frac{\partial}{\partial t}\underline{B} \qquad \text{div } \underline{E} = \rho$$

$$\text{curl } \underline{B} = \underline{J} + \frac{\partial}{\partial t}\underline{E} \qquad \text{div } \underline{B} = 0$$

$\underline{E}$ = electric field

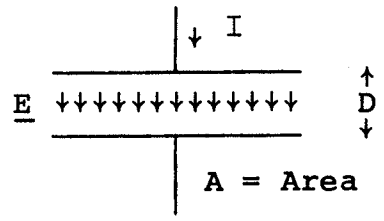
$\underline{B}$ = magnetic field

ρ = charge density

$\underline{J}$ = current density

Remark: $\frac{\partial}{\partial t}\underline{E}$ = "displacement current". This term was added by Maxwell to Faraday's laws in order to secure conservation of charge. If $\frac{\partial \rho}{\partial t} + \text{div } \underline{J} = 0$ and $\text{div } \underline{E} = \rho$, then $\text{div}\left(\underline{J} + \frac{\partial}{\partial t}\underline{E}\right) = 0$. This shows that there is some field $\underline{X}$ such that $\text{curl } \underline{X} = \underline{J} + \frac{\partial}{\partial t}\underline{E}$. The static law $\text{curl } \underline{B} = \underline{J}$ suggests that $\underline{X}$ is the magnetic field.

Capacitor:



In the wire we have current; in the space, displacement current. Since $\text{div}\left(\underline{J} + \frac{\partial \underline{E}}{\partial t}\right) = 0$ the <u>total</u> current flux is the same along the wire and in the space.

$I = A \frac{dE}{dt} = \frac{A}{D} \frac{dV}{dt}$, where V = ED = voltage across capacitor. Hence the equation of a capacitor $I = C \frac{dV}{dt}$ and the fact that capacitance is proportional to A/D.

In biological membranes $D \approx 100$ Å and the capacitance is typically 10^{-6} farads/cm^2.

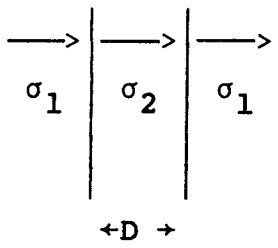
Conducting medium:

In a classical conductor $J = \sigma E$ (in ionic solutions this may have to be modified by a diffusion term). Then $\text{div } \underline{J} = \sigma \text{ div } \underline{E} = \sigma\rho$. But $\frac{\partial \rho}{\partial t} + \text{div } \underline{J} = 0$. Hence

$$\frac{\partial \rho}{\partial t} = - \sigma\rho \Rightarrow \begin{cases} \text{Space charge decays away} \\ \text{exponentially in a uniform} \\ \text{conductor leaving a condition} \\ \text{of } \underline{\text{electroneutrality}}. \end{cases}$$

The leaky capacitor:

Consider a slice of thickness D, conductivity σ_2 , between two semi-infinite media of conductivity σ_1 . We shall use $\sigma_2 << \sigma_1$. Let the total current density (including displacement current) be $J_0(t)$.

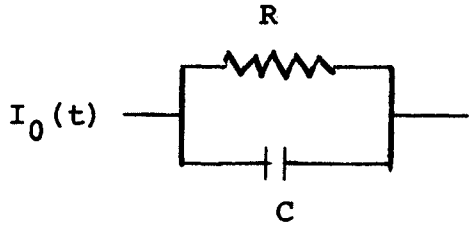


$$J_0(t) = J_1 + \frac{\partial E_1}{\partial t} = J_2 + \frac{\partial E_2}{\partial t}$$

$$= \sigma_1 E_1 + \frac{\partial E_1}{\partial t} = \sigma_2 E_2 + \frac{\partial E_2}{\partial t}$$

With $J_0(t)$ fixed, as $\sigma_1 \to \infty$, $E_1 \to 0$. This is the case of interest. Let $A\, J_0 = I_0$.

$$I_0(t) = \frac{\sigma_2 A E_2 D}{D} + \frac{A}{D}\frac{\partial E_2 D}{\partial t} = \frac{1}{R} V + C \frac{dV}{dt}$$



Remark: Although there are no physical plates on the capacitor formed by the slice of medium of low conductivity, nevertheless the interfaces act like plates in the sense that they store charge. This comes about because of the discontinuity in field across the interface. The integral form of $\operatorname{div} \underline{E} = \rho$ then requires a surface charge density at the interface. More generally, one can show that non-uniform conductivity yields a possible site for charge storage.

$$0 = \frac{\partial \rho}{\partial t} + \operatorname{div} \underline{J} = \frac{\partial \rho}{\partial t} + \operatorname{div} \sigma \underline{E}$$

$$= \frac{\partial \rho}{\partial t} + \sigma \rho + \underline{E} \cdot \nabla \sigma \ .$$

Work of Concentration:

The immediate source of energy for the electrical events of interest is the concentration differences of various ions across the cell membranes. The internal and external concentrations are essentially time independent, since the changes that occur during activity are (1) small and (2) rapidly restored through the expenditure of metabolic energy.

In dilute solutions the work involved in the transport of n ions from concentration $c_1 \rightarrow c_2$ can be calculated exactly as though the ions were molecules of an ideal gas. Thus we have

$PV = nkT$ ideal gas law

P = pressure

V = volume

n = # of molecules

k = Boltzmann constant

T = absolute temperature

Isothermal compression of the gas yields

$$dV = - \frac{nkT}{P^2} dP$$

$$dW = - P\, dV = nkT \frac{dP}{P} = d \log P \,, \qquad dW = \text{work of compression.}$$

$$W_{1\rightarrow 2} = nkT \log \frac{P_2}{P_1}$$

Let $\frac{n}{V} = C$, the concentration of molecules. Then $P = ckT$, and

$$W_{1\rightarrow 2} = nkT \log \frac{C_2}{C_1} .$$

Now suppose we arrange things so that an electric field will perform work W_0 per molecule in moving molecules from region 1→2. We get equilibrium when the work done by the electric field just equals the concentration work. Then

$$W_0 = kT \log \frac{C_2}{C_1} .$$

If q is the charge per molecule and V is the voltage difference (measured with region 1 positive), then

$$qV = kT \log \frac{C_2}{C_1} .$$

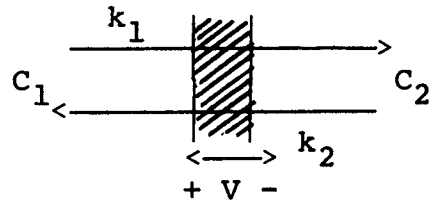
or

$$\boxed{\frac{C_2}{C_1} = e^{qV/kT}}$$

Let $\beta = \frac{q}{kT} \cong \frac{1}{25 \text{ mv}}$ (mv = millivolts).
This quantity sets the scale for electrical phenomena in biology.

Whenever the actual voltage differs from the equilibrium potential for a given ion, then there will be a net flux of that ion across the membrane. The actual magnitude of the flux cannot be calculated without a more detailed model. For illustrative purposes, we here consider the case where the motions of the individual ions are all independent:

Ionic Fluxes



If the ions move independently* the current carried by them must have the form

$$I = q(k_1(V)C_1 - k_2(V)C_2) ,$$

* This assumption is not too restrictive but would be violated by a mechanism involving a saturated carrier.

where the rate constants k_1 and k_2 depend on the voltage. The functions $k_1(V)$, $k_2(V)$ are not arbitrary but are restricted restricted by thermodynamics. Thus the requirement that we have equilibrium (I = 0) when

$$\frac{C_2}{C_1} = e^{\beta V}$$

yields

$$\frac{k_1(V)}{k_2(V)} = e^{\beta V}$$

Therefore

$$I = q\, k_1(V) C_1 \left(1 - \frac{C_2}{C_1} e^{-\beta V}\right) .$$

Let $V_0(C_1,C_2)$ be the potential such that concentrations C_1,C_2 are in equilibrium. Then

$$\frac{C_2}{C_1} = e^{\beta V_0}$$

$$I = q\, k_1(V) C_1 \left(1 - e^{-\beta (V-V_0)}\right)$$

It is not possible to choose $k_1(V)$ independent of V_0 such that the foregoing current voltage relation is linear for all V_0 (i.e., for all concentrations).

However, we can construct $k_1(V)$ to get a linear current-voltage relation for a particular V_0. Let

$$k_1(V) = \frac{A(V-V_*)}{1-e^{-\beta (V-V_*)}}$$

$$k_2(V) = \frac{A(V-V_*)e^{-\beta V}}{1-e^{-\beta (V-V_*)}}$$

Then

$$I = \frac{qA(V-V_*)}{1-e^{-\beta(V-V_*)}} C_1\left(1 - e^{-\beta(V-V_0)}\right)$$

when $V_0 = V_*$ we get $I = q\, C_1 A(V-V_*)$ and this displaced linear current voltage relation holds for all C_1, C_2 such that $C_2/C_1 = e^{\beta V_*}$.

The construction of $k_1(V)$, $k_2(V)$ in the foregoing was not based on physical considerations, but purely as an exercise to see whether a linear current voltage relation (for some ionic concentrations) is consistent with independent movement of ions. (The squid giant axon exhibits linear current voltage relations -- over what range of concentrations? -- but other tissues do not). We now inquire whether a simple physical model can predict the functions chosen above.

Drift-Diffusion in a Constant Field

Suppose a region of membrane of length L in which I, E are independent of X. Then

$$I = -qD\left(\frac{\partial C}{\partial X} + \beta C \frac{\partial \phi}{\partial X}\right) = -qD\left(\frac{\partial C}{\partial X} - \beta CE\right)$$

where D = diffusion coefficient

ϕ = potential $\left(-\frac{\partial \phi}{\partial X} = E\right)$.

Remark: The origin of the foregoing equation is as follows: The flux due to diffusion is $-D\frac{\partial C}{\partial X}$. The flux due to drift is μCE, where μ is the mobility of ions in the field. The

fact that $\mu = \beta D$ where $\beta = q/kT$ was noticed by Einstein, who derived it by applying the condition $I = 0$ at thermodynamic equilibrium. With $I = 0$, we have

$$\frac{1}{C}\frac{\partial C}{\partial X} + \frac{\partial}{\partial X}\beta\phi = 0 \Rightarrow \log C + \beta\phi = \text{constant}$$

which is consistent with thermodynamics only if $\beta = \frac{q}{kT}$.

Our equation can be written

$$-\frac{\partial C}{\partial X} + \beta CE = \frac{I}{qD} = \text{constant}$$

$$\Rightarrow \quad C = C_A + C_B e^{\beta EX} \quad \text{where } C_A = \frac{I}{qD\beta E}.$$

Assuming the concentrations are known at $x = 0$ and $x = L$ we have

$$C(0) = C_A + C_B$$

$$C(L) = C_A + C_B e^{\beta EL}$$

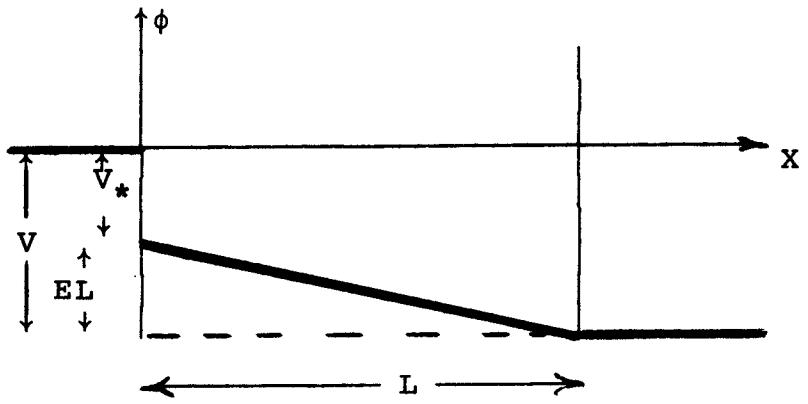
Solve for C_A and hence for I:

$$C_A\left(e^{\beta EL}-1\right) = C(0)e^{\beta EL} - C(L)$$

$$I = qD\beta EC_A = qD\beta E\left[\frac{C(0)e^{\beta EL}-C(L)}{e^{\beta EL}-1}\right]$$

Note that when $C(0) = C(L)$, this expression is linear in E. This corresponds to the case $V_* = 0$ considered above. Thus we can easily get linearity for equal concentrations. To get linearity for unequal concentrations is harder. We have to

assume that there is a fixed dipole layer on one side of the membrane with potential drop V_* as indicated below.



Then equilibrium across the dipole layer implies $C(0) = C_1 e^{\beta V_*}$. At the interface with no dipole layer the potential and hence the concentrations are equal. $C(L) = C_2$. The expression for I is therefore

$$I = \frac{qD\beta}{L} e^{\beta V_*} C_1 EL \left\{ \frac{e^{\beta EL} - \frac{C_2}{C_1} e^{-\beta V_*}}{e^{\beta EL} - 1} \right\}$$

<u>If</u> $\frac{C_2}{C_1} = e^{\beta V_*}$ then

$$I = \frac{qD\beta C_2}{L} EL = \frac{qD\beta C_2}{L} (V - V_*) .$$

Thus a membrane with a fixed dipole layer on one side will yield a linear current voltage relation for a particular ratio of concentrations. With no dipole layer, linearity holds only when $C_1 = C_2$. These conclusions are for independent movement of ions in a constant field.

Hodgkin-Huxley Equations*

We begin with the ordinary differential equations for current through a patch of membrane. The partial differential equations for conduction of the action potential will be discussed below.

Hodgkin and Huxley postulate that the total current through a membrane patch in squid giant axon can be partitioned as follows:

$$I_0(t) = g_{Na}(V-E_{Na}) + g_K(V-E_K) + g_L(V-E_L) + C\frac{dV}{dt}$$

where the first three terms give the ionic current, and the fourth gives the capacitive current, and where:

g = ionic conductance

E = ionic equilibrium potential

V = membrane potential

C = membrane capacitance

Na = sodium

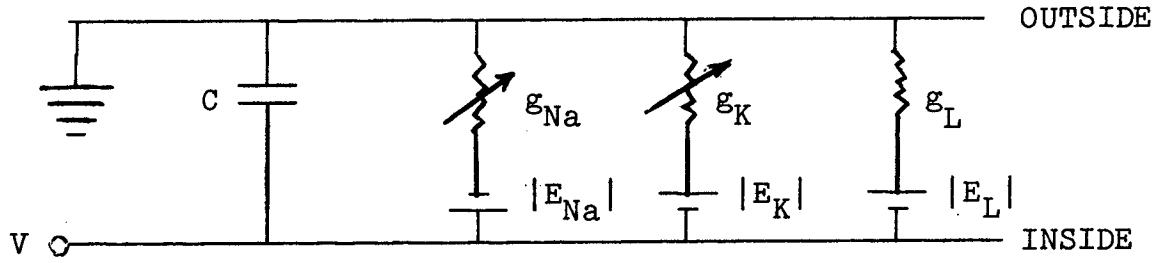
K = potassium

L = "leakage", i.e., currents due to ions other than Na^+, K^+.

The equation given above may be summarized by the equivalent circuit.

---

* Hodgkin, A. L. and Huxley, A. F.: A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve. J. Physiol (London) 117 500 (1952).



The "batteries" E_{Na} , E_K , E_L have e.m.f.'s which are determined by the appropriate ratios of ionic concentrations. For example

$$E_{Na} = kT \log \frac{[Na^+]_e}{[Na^+]_i} > 0$$

$$E_K = kT \log \frac{[K^+]_e}{[K^+]_i} < 0$$

e = external, i = internal.

(Since L refers to "other ions" the expression for E_L will be more complicated.) These quantities are, to an excellent approximation, time independent.

Interesting dynamics arises in the model stated above because the Na^+ and K^+ conductances vary with voltage and time.

The postulated dynamics of these quantities is as follows:

$$g_{Na} = \overline{g_{Na}}\, m^3 h$$

$$g_K = \overline{g_K}\, n^4$$

$$\frac{dm}{dt} = \frac{1}{\tau_m(V)} \left(m_\infty(V) - m\right)$$

$$\frac{dh}{dt} = \frac{1}{\tau_h(V)} \left(h_\infty(V) - h\right)$$

$$\frac{dn}{dt} = \frac{1}{\tau_n(V)} \left(n_\infty(V) - n\right)$$

These equations have as a consequence that g_{Na} and g_K approach equilibrium values which depend on voltage if the voltage is held constant long enough. On the other hand, these conductances cannot change suddenly but approach their equilibrium values at a finite rate.

The Membrane Patch as a Two-State Device *

The quantities n, h are slowly varying in comparison with m, v. This suggested to Fitzhugh that one might get some insight into the qualitative aspects of membrane behavior by studying the properties of the equations outlined above with n, h constant. Here we shall illustrate this procedure in an especially simple limiting case, when m-dynamics are so fast that $m = m_\infty(v)$ at each instant. Moreover we shall assume that $m_\infty(v)$ has the form

$$m = m_\infty(V) = \begin{cases} \alpha(V-E_0) , & V > E_0 \\ 0 , & V < E_0 \end{cases}$$

If the total current through the membrane is zero, we have:

* This analysis is a simplified version of FitzHugh, R: Mathematical Models of Excitation and Propgataion in Nerve; in ed: H. P. Schwan, Biological Engineering, New York: McGraw Hill, 1969, p. 1 ff.

$$- C \frac{dV}{dt} = \bar{g}_{Na} \alpha^3 h(V-E_0)^3(V-E_{Na}) + \bar{g}_K n^4(V-E_K) + \bar{g}_L(V-E_L) .$$

Define the quantities g_1 , E_1 as follows.

$$g_1 = \bar{g}_K n^4 + \bar{g}_L$$

$$g_1 E_1 = \bar{g}_K n^4 E_K + \bar{g}_L E_L .$$

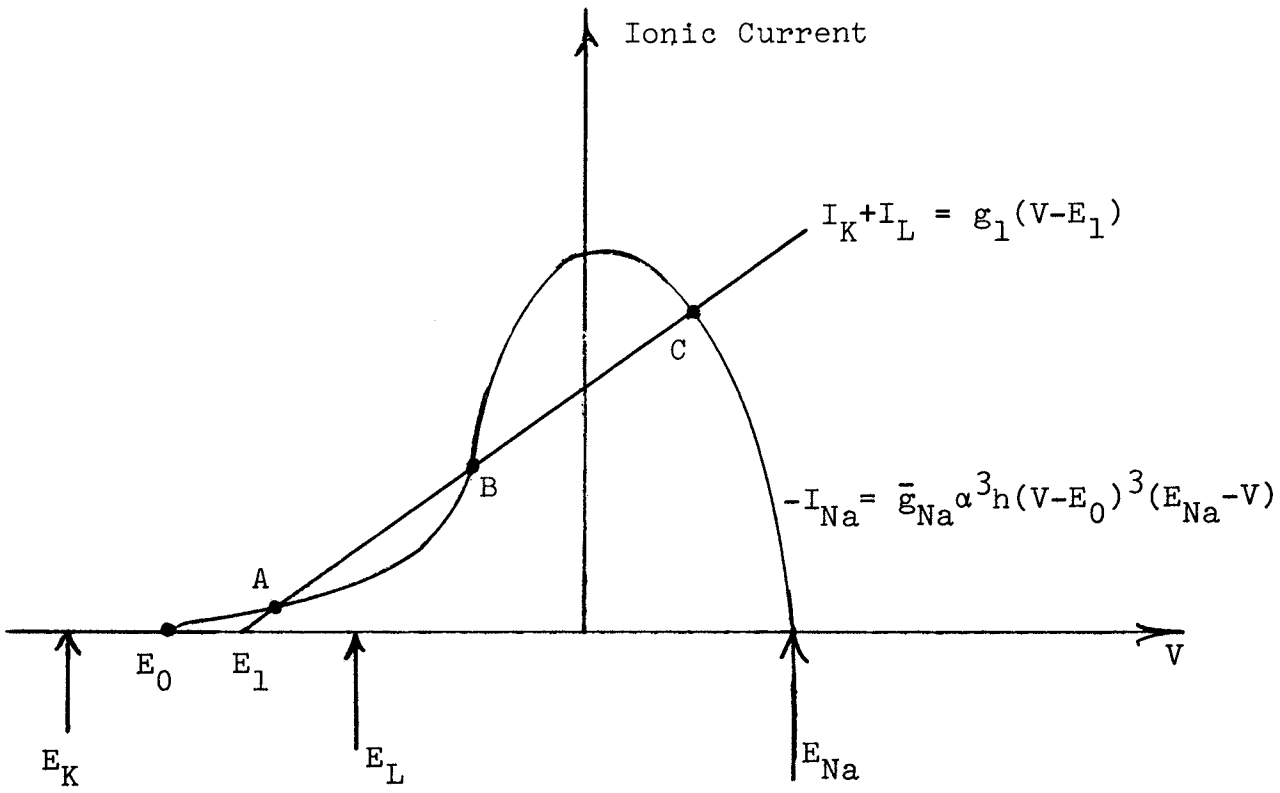
Then

$$\bar{g}_K n^4(V-E_K) + \bar{g}_L(V-E_L) = g_1(V-E_1)$$

and

$$C \frac{dV}{dt} = \bar{g}_{Na} \alpha^3 h(V-E_0)^3(E_{Na}-V) - g_1(V-E_1) .$$

We now indicate graphically where the equilibrium ($dV/dt = 0$) values of V lie. In constructing the graph we use $E_K < E_1 < E_L < 0 < E_{Na}$. Also we assume that $E_K < E_0 < E_L$.



The points A, B, C are the points where dV/dt = 0. Reference to the sign of dV/dt in the neighborhood of these points shows that A and C are stable, while B is unstable. If V > B, V → C, but if V < B, V → A. Therefore B is a " threshold", spearating two stable states which may be called the <u>resting state</u>, A, and the <u>excited state</u> C.

If we now permit the parameters n, h (and hence (E_1,g_1) to vary, then the stable equilibria and the threshold will move. Increasing n or decreasing h shifts the line I_K+I_L up and to the left relative to the I_{Na} curve. This decreases V_A and V_C ,

but increases V_B. At certain critical values of the parameters the threshold and the excited state collide and disappear leaving only the resting state. The opposite phenomenon happens with decreasing n or increasing h. If the latter processes are continued the threshold collides with the resting state leaving only the excited state.

To the picture given above we must add the fact that n, h are not really independent variables but obey equations of the form

$$\frac{dn}{dt} = \frac{1}{\tau_n(V)} [n_\infty(V) - n]$$

$$\frac{dh}{dt} = \frac{1}{\tau_h(V)} [h_\infty(V) - h]$$

where $n_\infty(V)$ is an increasing function, and $h_\infty(V)$ is a decreasing function. Thus the ON state of the membrane ultimately turns itself OFF by driving n up and h down to the point where the ON state collides with the threshold and disappears. The fact that n is high drives $E_1 \to E_K$ so that the OFF state reached immediately after excitation is more negative than the original resting state.

The membrane will be inexcitable if n is sufficiently large or h sufficiently small that only the OFF state exists, and it will be difficult to excite if the threshold is near the excited state even though the excited state still exists. These two situations are called absolute and relative refractoriness, respectively.

Hyperpolarization (holding the membrane at a more negative potential than usual) can lead to an action potential upon release from the influence of the hyperpolarizing current. This is because n is temporarily depressed by the hyperpolarization to the point where only the excited state exists.

In nerve the excited state has only a brief existence, and one may question the usefulness of describing the membrane as a two-state device. In heart, by contrast the excited state is prolonged and its stability can be proved by direct experiment. The application of a modified form of the Hodgkin-Huxley theory to heart is discussed in the next section.

Adaptation of Hodgkin-Huxley Theory to Heart

This adaptation was accomplished by Noble and Tsien* in a series of papers the main conclusions of which will be summarized here:

(i) The initial depolarization (turn-ON) of the cardiac cell is accomplished by a rapid inward movement of Na^+ ions obeying the same kinetics as in nerve.

(ii) Repolarization is delayed in comparison with nerve for general reasons:

(a) There is a slowly activated channel for inward current which passes either Na^+ or Ca^{++} ions and which remains activated after the fast Na^+ channel has been inactivated by the fall in h.

(b) The potassium current-voltage relation is instantaneously nonlinear; it rectifies in the inward going direction and this fact limits the outward potassium current during the plateau.

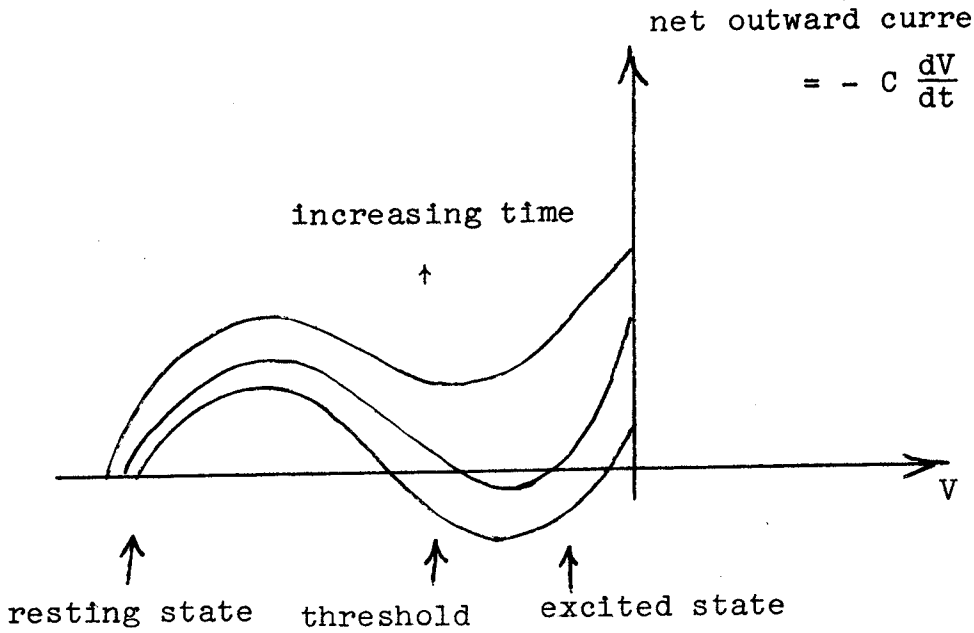
(c) The activation of the potassium current is delayed in comparison with nerve.

Remark: The slowly activated channel which passes either Na^+ or Ca^{++} ions is probably the channel responsible for excitation -

* D. Noble and R. W. Tsien:
The Kinetics and Rectifier Properties of the Slow Potassium Current in Cardiac Purkinje Fibers. J. Physiol. (London) 195, 185-214 (1968);
Outward Membrane Currents Activated in the Plateau Range of Potentials in Cardiac Punkinje Fibers. J. Physiol. (London) 200, 205-231 (1969);
Reconstruction of the Repolarization Process in Cardiac Pinkinje Fibers Based on Voltage Clamp Measurements of Membrane Current. J. Physiol. (London) 200, 233-254 (1969).

contraction coupling, and the competition between Na^+ and Ca^{++} for this channel probably explains the dependence of the strength of contraction on the ratio $[Ca^{++}]/[Na^+]^2$ in the extracellular fluid. (See discussion of Ca^{++} kinetics, above.) Thus the prolonged repolarization process is an essential feature of contraction in heart muscle. The fact that the prolongation is greatest in the ventricle is therefore not surprising.

(iii) During the plateau (the prolonged excited state), the instantaneous current voltage relations change with time as shown below. The change is due to the gradual activation of an outward potassium current. As a consequence of this change, the excited state collides with the threshold and disappears. Direct experimental evidence for the existence of a threshold for repolarization and measurements of its time course



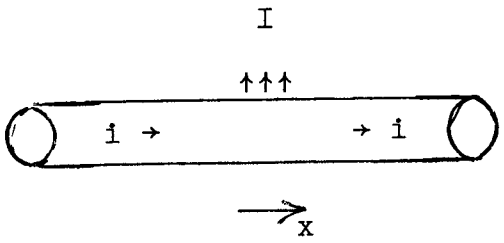
were obtained by Vassalle.*

(iv) The pacemaker potential (in cells where it exists) is essentially the same as the afterpotential of the nerve impulse. Immediately following activity, potassium current is higher than normal and the potential is low. Turning off of the potassium current leads to a rise in potential which is responsible for pacemaker activity.

In summary, the comparison between heart and nerve appears to be as follows. The fast Na^+ current obeys essentially the same kinetics, but the inactivation of this Na^+ channel is followed by the prolonged activation of a second channel which passes both Na^+ and Ca^{++} ions and is probably responsible for excitation-contraction coupling. The outward potassium current is more slowly activated in heart than in nerve; it consists of more than one component and its instantaneous current-voltage relation is like that of a rectifier pointing inward. A component activated by potentials in the plateau region is responsible for repolarization, a slower component activated by similar potentials is responsible for effects of the interval between beats on the duration of the action potential, and the turning-off of a component similar to that found in nerve is responsible for the pacemaker potential.

* Vassalle, M.: An analysis of Cardiac Pacemaker Potential by Means of a Voltage Clamp Technique. Am. J. Physiology 210 1335-1341, 1966.

Nonlinear Wave Propagation *



Consider a cell with:

i = longitudinal current

r = resistance per unit length

I = transmembrane ionic current per unit length

V = membrane potential (inside with respect to outside)

C = capacitance per unit length.

The equations for this system are:

$$ri = -\frac{\partial V}{\partial x}$$

$$C\frac{\partial V}{\partial t} - I = -\frac{\partial i}{\partial x}$$

Eliminating i we obtain

$$C\frac{\partial V}{\partial t} - I = \frac{1}{r}\frac{\partial^2 V}{\partial x^2}$$

If I were known, this would be an inhomogeneous form of the heat equation; in fact, however, I is determined from the Hodgkin-Huxley equations for a membrane patch, which we can generalize as follows:

---

* Cohen, H. Nonlinear Diffusion Problems, in ed: A. H. Taub, Studies in Applied Mathematics, Prentice Hall, Englewood Cliffs, N. J., 1971.
Rinzel, J. and Keller, J. B. Traveling Wave Solutions of a Nerve Conduction Equation, Biophysical J. 13, 1313-1337 (1973).

$$I = I(S_1 \ldots S_N, V)$$

$$\frac{dS_k}{dt} = f_k(S_k, V) \ .$$

It is instructive to consider some very simple examples of equations of this type with traveling wave solutions. More interesting examples are discussed in the references cited above.

Transition State Wave Form:

$$\text{Suppose} \quad I = -gV + \begin{cases} 0 \ , & V < a \\ I_0 , & V > a \end{cases} .$$

We seek traveling wave solutions $V(t + x/\theta)$ with velocity θ for the equation

$$C \frac{\partial V}{\partial t} - I = \frac{1}{r} \frac{\partial^2 V}{\partial x^2}$$

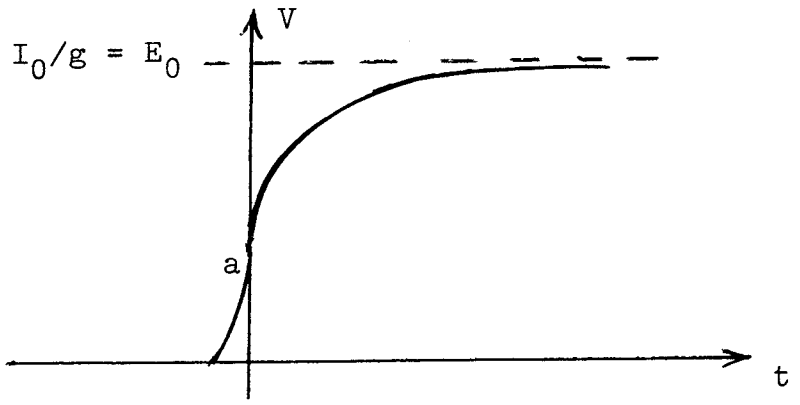
Such a solution will obey the ordinary differential equation

$$CV' + gV - \begin{cases} 0, & V < a \\ I_0, & V > a \end{cases} = \frac{1}{r\theta^2} V''$$

Look for solutions of the form

$$V = \begin{cases} ae^{\lambda t} \ , & t < 0 \ , \quad \lambda > 0 \\ ae^{\mu t} + E_0(1-e^{\mu t}) \ , & t > 0 \ , \quad \mu < 0 \end{cases}$$

where $E_0 = I_0/g$ (see figure next page).



This solution is a "change of state" wavefront, traveling to the left with velocity θ. Each section of the line is brought to threshold a by diffusion, whereupon it turns on and drives itself to the excited state E_0.

The condition of finite longitudinal current in the line leads to V' continuous at t = 0, and hence

$$a\lambda = a\mu - E_0\mu$$

$$\frac{\lambda-\mu}{-\mu} = \frac{E_0}{a} = \gamma$$

(We shall refer to γ as the " threshold ratio". Large γ means that the threshold is low relative to the excited state.)
λ,μ are the roots of

$$\frac{1}{rC\theta^2} z^2 - z - \frac{g}{C} = 0$$

$$\lambda,\mu = \frac{1 \pm \sqrt{1+\alpha}}{\frac{2}{rC\theta^2}}, \qquad \alpha = \frac{4g}{rC\theta^2}$$

$$\lambda > 0 , \quad \mu < 0$$

Therefore

$$\gamma = \frac{\lambda-\mu}{-\mu} = \frac{2\sqrt{1+\alpha}}{-1+\sqrt{1+\alpha}}$$

$$(2-\gamma)\sqrt{1+\alpha} = -\gamma \Rightarrow \gamma > 2$$

$$(2-\gamma)^2(1+\alpha) = \gamma^2$$

It follows that

$$\alpha = 4\,\frac{\gamma-1}{(\gamma-2)^2}$$

and

$$\theta^2 = \frac{g}{rC^2}\,\frac{(\gamma-2)^2}{(\gamma-1)}\,, \qquad 2 < \gamma < \infty$$

Thus propagation becomes very slow as the excited state is depressed (fixed threshold) and fails entirely when $E_0 < 2a$.

Remark: The procedure used above was to assume propagation at velocity θ and to find a bounded smooth solution for the ordinary differential equation,

$$CV' - I = \frac{1}{r\theta^2}\,V'' \,.$$

Such a solution only exists for special values of θ, as determined above. On the other hand if we fix θ in advance and integrate this equation starting from $t = -\infty$ (as one might attempt numerically if the expression for I were more complicated) the following situation arises. For $t < 0$ we have the solution $ae^{\lambda t}$, $\lambda > 0$. At $t = 0$, to continue the solution with V and V' continuous we need in general a solution of the form

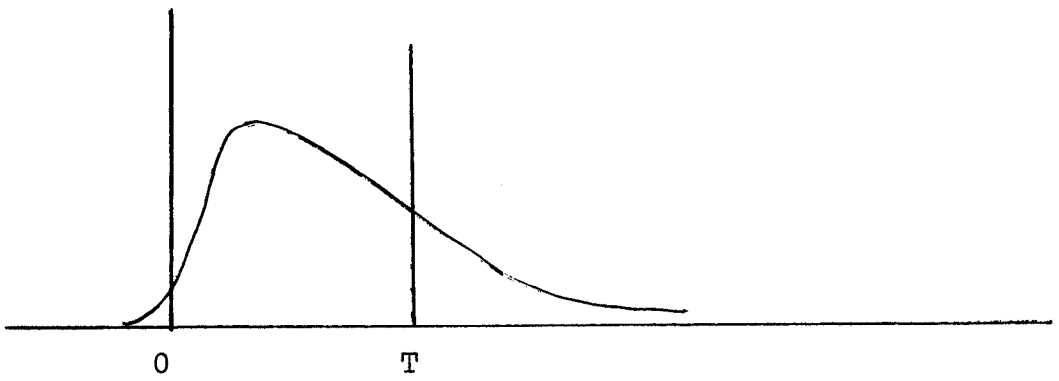
$$V = b_1 e^{\lambda t} + b_2 e^{\mu t} + E_0(1-e^{\mu t}) , \qquad t > 0.$$

There are enough conditions to determine b_1, b_2 as functions of θ (recall that λ, μ depend on θ). The correct values of θ are those for which $b_1(\theta) = 0$, since only these remain bounded as $t \to \infty$. This is an indication that any attempt to solve $CV' - I = \frac{1}{r\theta^2} V''$ by integrating forward in time with some incorrect value of θ will lead solutions which fly off to $\pm \infty$ (depending in the present case on the sign of $b_1(\theta)$) following the onset of the action potential. This is precisely the experience which Hodgkin and Huxley had, in fact they determined θ by searching between values which led to increasing solutions and those which led to decreasing solutions.

Pulse-Shaped Nonlinear Waves

If a simple model of the cardiac action potential is sought, it should as a minimum requirement have the capability of turning off as well as on. Consider the same equations as previously, but suppose that the active current turns off after a time interval T following the initial crossing of threshold. Then we seek a solution of the following form.

$$V = \begin{cases} a_1 e^{\lambda t} & , \quad t < 0 \\ a_2 e^{\mu t} + a_3 e^{\lambda t} + E_0 & , \quad 0 < t < T \\ a_4 e^{\mu t} & , \quad T < t \end{cases}$$



Continuity at $t = 0$ and $t = T$ of V and V' yields the four equations:

$$a_1 = a_2 + a_3 + E_0$$

$$a_1\lambda = a_2\mu + a_3\lambda$$

$$a_2 e^{\mu T} + a_3 e^{\lambda T} + E_0(1-e^{\mu T}) = a_4 e^{\mu T}$$

$$a_2\mu e^{\mu T} + a_3\lambda e^{\lambda T} - E_0\mu e^{\mu T} = a_4\mu e^{\mu T} .$$

In addition we have $a_1 = a$, and λ, μ as functions of θ. After considerable algebra, the equation for θ becomes

$$\left(1 + \frac{\mu\gamma}{\lambda-\mu}\right)\left(e^{\lambda T}-1\right) = 1$$

If $T \to \infty$ (and λ does not tend to zero), then we get solution only by requiring

$$\frac{\mu\gamma}{\lambda-\mu} \to -1 \quad \text{where} \quad \gamma = \frac{E_0}{a} \quad \text{as above.}$$

This is the same expression as for the change of state waveform. Thus, for large T, the wave speed is determined mainly by the properties of the front which "pulls" the rest of the wave along.

It would be of great interest for heart physiology to solve simple nonlinear diffusion equations of the type outlined above for cases in which the properties of the fiber depend on x. For example, one might consider a case in which E_0 is reduced drastically along a short segment of fiber. The reason for this is that experimental preparations which appear to correspond to this situation have been produced which exhibit many of the features of disturbed wave propagation which actually occur in diseased hearts. The next section will discuss these effects briefly.

Disturbed Conduction in Heart

This section is a brief discussion of some experimental results* which are of the utmost importance in understanding abnormal rhythms of the heart.

In this work the typical experiment was performed on a bundle of Purkinje fibers (the conduction tissue of the heart). A short segment of the bundle of fibers was depressed by the application of high external K^+ concentration. Effects seen with this preparation include the following:

(i) Block. A stimulus applied at one end may fail to pass the depressed segment.

(ii) n:1 block. A certain fraction of stimuli may pass (e.g. every other stimulus) the fraction typically depending on the frequency of stimulation.

(iii) One-way block. Stimuli of a given frequency may pass in one direction but fail to pass in the other.

(iv) Echo. A stimulus may pass the depressed segment with considerable delay and the excitation of the tissue beyond the depressed segment may be sufficiently strong to re-excite the tissue on the original side sending out an echo.

---

* Cranefield, P. F., Klein, H. O., and Hoffman, B. F. Conduction of the Cardiac Impulse. I. Delay, Block, and One-Way Block in Depressed Purkinje Fibers. Circ. Res. 28 199, 1971.

Cranefield, P. F. and Hoffman, B. F. Conduction of the Cardiac Impulse. II. Summation and Inhibition. Circ. Res. 28, 220, 1971.

Cranefield, P. F., Wit, A. L., and Hoffman, B. F. Conduction of the Cardiac Impulse. III. Characteristics of Very Slow Conduction. J. Gen. Physiol. 59 227, 1972.

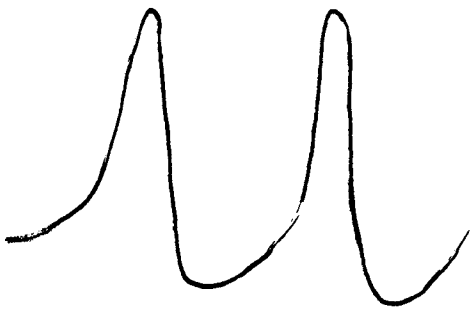
(v) Circus movement. If a ring of tissue is created with a short segment exhibiting one-way block, then a stimulus entering the ring near the site of block can initiate a wave which travels repetitively around the circuit.

These phenomena appear to be the basis of many abnormal rhythms in the heart which occur following damage to a small piece of tissue. They also present an interesting challenge, since a theory of conduction in the heart ought to be able to predict these phenomena as a consequence of depression of a short segment of fiber.

Remark: Since the experimental preparation contains many parallel fibers which branch, it may not be possible to construct a single fiber theory which reproduces the phenomena. One-way block would seem particularly hard to predict, but if the pattern of depression is asymmetric such a result would seem possible even in a single fiber.

Self-Synchronization of the Cardiac Pacemaker

The heart beat is originated in the sinoatrial node, a region of cells which have the capability of depolarizing spontaneously toward the threshold firing, and then recovering. Their action potential is smoother than that of the rest of the heart, suggesting that the cells lack the fast Na^+ channel. This suspicion is confirmed by the failure of tetrodotoxin to



block pacemaker activity in the sinoatrial node.*

The question naturally arises how the different cells coordinate their activity so that the whole sinoatrial node fires at the same frequency and (except for conduction delays) in phase. The simplest explanation is that the cell which is inherently fastest drives all the others by bringing them to the threshold, but this view requires that in principle one can identify at any instant a single cell which is driving the heart. Moreover it suggests that injury to a single cell could set off a rapid heart rate. A more reasonable design would be a population of cells with weaker coupling, in which synchrony emerges as a consequence of the interaction and in which the overall frequency was a property of the population of cells, rather than any single cell.

In this section we discuss a population of weakly interacting "pacemakers". The model we use was discussed by Knight** in the context of the nervous system. He discusses the interaction of a cell with a given periodic stimulus. We shall begin with this case but consider also the case where the "stimulus" depends on the population behavior of the cells in question.

Consider our "oscillator" or "pacemaker" characterized by state x, $0 \leq x \leq 1$. Let x satisfy

$$\frac{dx}{dt} = -\gamma x + S_0 + S(t) \geq 0$$

but when $x = 1$ the oscillator "fires" and jumps back to $x = 0$.

---

* Brooks and Lu, The Sinoatrial Pacemaker of the Heart, Thomas, Springfield, Ill. 1972.

** Knight, B. W. Dynamics of Encoding in a Population of Neurons, J. Gen. Physiol. 59, 734-766, 1972.

Regard S_0, γ as the intrinsic properties of the oscillator, and $S(t)$ as an external stimulus.

Let $\{t_n\}$ = set of times when oscillator fires. For $t_n \leq t \leq t_{n+1}$,

$$x(t) = \int_{t_n}^{t} e^{-\gamma(t-t')} f(t')\, dt'$$

where $f(t) = S_0 + S(t)$

The equation for the firing times is therefore

$$1 = \int_{t_n}^{t_{n+1}} e^{-\gamma(t_{n+1}-t')} f(t')\, dt'$$

Let $S(t) = \lambda\, g(t)$ (λ small), so that $f(t) = S_0 + \lambda\, g(t)$. Then

$$1 = \frac{S_0}{\gamma}\left(1 - e^{-\gamma T_n}\right) + \lambda \int_{t_n}^{t_{n+1}} e^{-\gamma(t_{n+1}-t')} g(t')\, dt'$$

where $T_n = t_{n+1} - t_n$.

Assume

(1) g is a periodic function with period T and mean zero

(2) γ is small.

Then

$$1 = S_0 T_n + \lambda \int_{t_n}^{t_{n+1}} g(t')\, dt' - \lambda\gamma \int_{t_n}^{t_{n+1}} (t_{n+1}-t')\, g(t')\, dt'$$

Let $G(t) = \int^{t} g(t')\, dt'$, and choose the constant of integration

so that G has mean zero. Since g has mean zero, G is periodic with period T. Integrate by parts to obtain

$$1 = S_0 T_n + \lambda \int_{t_n}^{t_{n+1}} g(t')\, dt' + \lambda\gamma \int_{t_n}^{t_{n+1}} G(t')\, dt' + \lambda\gamma\, T_n\, G(t_n)$$

$$\boxed{1 = [S_0 + \lambda\gamma\, G(t_n)]T_n + \lambda \int_{t_n}^{t_{n+1}} h(t')\, dt'}$$

where $h(t) = g(t) + \gamma\, G(t)$ is a periodic function with period T and mean zero.

We have thus found an implicit recursion relation for the firing times when an arbitrary periodic stimulus $\lambda\, g(t)$ is applied. Seek a solution of this recursion of the form $t_{n+1} - t_n = T$, the period of the stimulus. If $t_{n+1} - t_n = T$, then

$$\int_{t_n}^{t_{n+1}} h(t)\, dt = 0 \quad .$$

Also $G(t_n) = G(t_0)$. Hence we have

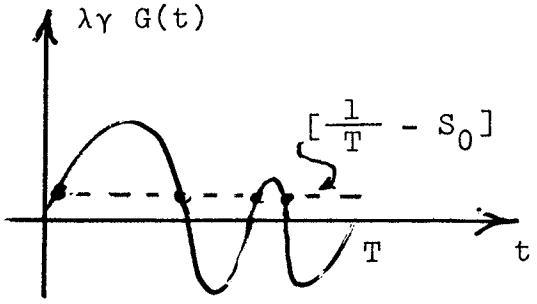
$$1 = [S_0 + \lambda\gamma\, G(t_0)]T$$

or

$$\lambda\gamma\, G(t_0) = \left[\frac{1}{T} - S_0\right] .$$

Since $G(t)$ has mean zero, one can find t_0 such that this

equation is satisfied provided that $\lambda\gamma$ is sufficiently large. There will typically be an even number of such phases t_0 where the oscillator can fire in step with the stimulus.



Note that the amplitude required to get solutions (to capture the oscillator) is proportional to the disparity between the natural frequency of the oscillator and the frequency of the stimulus.

The stability of the points of equilibrium phase will now be checked. Let

$$t_n = t_0 + nT + \delta_n$$

$$t_{n+1} = t_0 + (n+1)T + \delta_{n+1}$$

$$t_{n+1} - t_n = T + (\delta_{n+1} - \delta_n)$$

Computing the variation of

$$1 = [S_0 + \lambda\gamma\, G(t_n)]T_n + \lambda \int_{t_n}^{t_{n+1}} h(t')\, dt'$$

about a solution with the property $T_n = T$, $G(t_n) = G(t_0)$ we have

$$0 = [S_0+\lambda\gamma\ G(t_0)](\delta_{n+1}-\delta_n) + \lambda\gamma\ G'(t_0)\delta_n T + \lambda h'(t_0)(\delta_{n+1}-\delta_n)$$

$$\left[\frac{1}{T} + \lambda h'(t_0)\right](\delta_{n+1}-\delta_n) = -\lambda\gamma\ G'(t_0)\delta_n T$$

$$\delta_{n+1} = \left[1 - \frac{\lambda\gamma\ G'(t_0)T}{\frac{1}{T} + \lambda h'(t_0)}\right]\delta_n$$

For small enough λ, stability is controlled by the sign of G', with $G' > 0$ giving stability. Thus in the typical case, half the solutions will be stable and half unstable.

A population of oscillators can thus be driven by a periodic signal to fire at one or more definite points in the cycle of the given signal. We now consider a case where the signal is not imposed from the outside but arises in the population of oscillators itself.

Consider a collection of N oscillators of the type described above, each characterized by $dX_k/dt = - X_k + S_0$, $0 \leq X_k \leq 1$. When $X_k = 1$, X_k jumps to zero. When a given oscillator fires it pulls the others up by an amount ε/N, or pulls them up to firing, whichever is less.

For this system one can state the following conjectures:
(1) For arbitrary initial conditions, the system approaches

a state in which all the oscillators are firing synchronously. (2) This remains true even when the oscillators are not quite identical. Here we shall demonstrate only (1), and that only for the case N = 2 with small ε, γ. An interesting fact which emerges even from this simple case is that the desired convergence depends on the product $\varepsilon\gamma$. It is thus in some sense a cooperative effect between the coupling and the dissipation; convergence disappears when either the coupling or the dissipation is removed.

Let N = 2. Without loss of generality, start the system with $X_1 = 0$, $X_2 = \alpha$. The equations for $X_1(t)$, $X_2(t)$ are

$$X_1(t) = \frac{S_0}{\gamma}\,(1-e^{-\gamma t})$$

$$X_2(t) = \alpha\, e^{-\gamma t} + \frac{S_0}{\gamma}\,(1-e^{-\gamma t})\ .$$

Let t_A be the first firing time, $X_2(t_A) = 1$.

$$1 = \frac{S_0}{\gamma} - \left[\frac{S_0}{\gamma} - \alpha\right] e^{-\gamma t_A}$$

$$e^{-\gamma t_A} = \frac{\frac{S_0}{\gamma} - 1}{\frac{S_0}{\gamma} - \alpha} = \frac{S-1}{S-\alpha} \quad \text{where} \quad S = \frac{S_0}{\gamma}$$

$$1 - e^{-\gamma t_A} = 1 - \frac{S-1}{S-\alpha} = \frac{1-\alpha}{S-\alpha}$$

$$X_1(t_A^-) = S\left[\frac{1-\alpha}{S-\alpha}\right]$$

$$X_1(t_A^+) = S\left[\frac{1-\alpha}{S-\alpha}\right] + \varepsilon/2 \qquad (N= 2)$$

We are now in essentially the same state as initially, but with new α, and the oscillators interchanged. Therefore, to follow the system ahead in time consider the recursion

$$\alpha_{n+1} = S\left[\frac{1-\alpha_n}{S-\alpha_n}\right] + \varepsilon/2$$

Let $\beta = 1/S$, $\varepsilon_0 = \varepsilon/2$. Then

$$\alpha_{n+1} = \left[\frac{1-\alpha_n}{1-\beta\alpha_n}\right] + \varepsilon_0$$

$$\alpha_{n+2} = \left[\frac{1-\alpha_{n+1}}{1-\beta\alpha_{n+1}}\right] + \varepsilon_0$$

Regard α_n as fixed, and consider the function $\alpha_{n+2}(\beta,\varepsilon_0)$. This function has the properties

$$\alpha_{n+2}(0,\varepsilon_0) = 1 - \alpha_{n+1}(0,\varepsilon_0) + \varepsilon_0 = 1 - (1-\alpha_n+\varepsilon_0) + \varepsilon_0 = \alpha_n$$

$$\alpha_{n+2}(\beta,0) = \frac{1-\alpha_{n+1}(\beta,0)}{1-\beta\alpha_{n+1}(\beta,0)} = \frac{1-\left[\frac{1-\alpha_n}{1-\beta\alpha_n}\right]}{1-\beta\left[\frac{1-\alpha_n}{1-\beta\alpha_n}\right]} = \frac{\alpha_n(1-\beta)}{(1-\beta)} = \alpha_n$$

Thus if we expand α_{n+2} about α_n as a series in β, ε_0, then the lowest order terms will have the form

$$\alpha_{n+2} = \alpha_n + A\beta\varepsilon_0$$

where $A = \dfrac{\partial^2 \alpha_{n+2}}{\partial\varepsilon_0\,\partial\beta}(0,0)$.

$$\frac{\partial}{\partial\beta}\,\alpha_{n+2} = \frac{\partial\alpha_{n+2}}{\partial\alpha_{n+1}}\,\frac{\partial\alpha_{n+1}}{\partial\beta} + \frac{\partial\alpha_{n+2}}{\partial\beta}$$

$$\left.\frac{\partial\alpha_{n+2}}{\partial\alpha_{n+1}}\right|_{\beta=0} = -1$$

$$\left.\frac{\partial\alpha_{n+2}}{\partial\beta}\right|_{\beta=0} = (1-\alpha_{n+1})\alpha_{n+1}$$

$$\left.\frac{\partial\alpha_{n+1}}{\partial\beta}\right|_{\beta=0} = (1-\alpha_{n})\alpha_{n}$$

$$\left.\frac{\partial\alpha_{n+2}}{\partial\beta}\right|_{\beta=0} = -(1-\alpha_{n})\alpha_{n} + (1-\alpha_{n+1})\alpha_{n+1}$$

$$\frac{\partial}{\partial\varepsilon_0}\left[\left.\frac{\partial\alpha_{n+2}}{\partial\beta}\right|_{\beta=0}\right] = (1-\alpha_{n+1})\,\frac{\partial\alpha_{n+1}}{\partial\varepsilon_0} - \frac{\partial\alpha_{n+1}}{\partial\varepsilon_0}\,\alpha_{n+1}$$

But $\dfrac{\partial\alpha_{n+1}}{\partial\varepsilon_0} = 1 \Rightarrow A = 1 - 2\alpha_{n+1}(0,0)$.

But $\alpha_{n+1}(0,0) = 1 - \alpha_n$.

$$A = 1 - 2(1-\alpha_n) = 2\alpha_n - 1 .$$

It follows that

$$\alpha_{n+2} = \alpha_n + 2\varepsilon_0\beta(\alpha_n - \tfrac{1}{2}) .$$

Note that

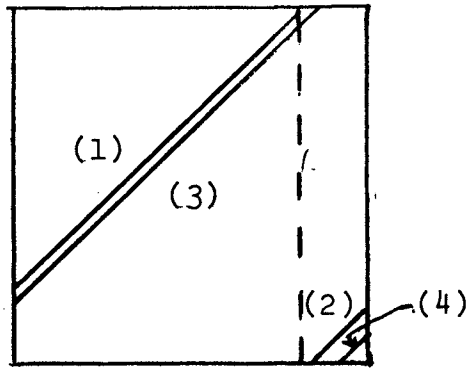
$$\alpha_n > \tfrac{1}{2} \Rightarrow \alpha_{n+2} > \alpha_n$$

$$\alpha_n < \tfrac{1}{2} \Rightarrow \alpha_{n+2} < \alpha_n .$$

α is therefore driven toward zero or one ➡ the oscillators are driven together (the equilibrium at $\alpha = \frac{1}{2}$ is unstable).

P. Ungar has given the following geometric interpretation. The pair of oscillators is represented by a point (X_1, X_2) on a doubly periodic square.

The coordinates are stretched so that each oscillator moves uniformly, hence the trajectories are straight lines with slope 1. Because of the stretching the size of the jumps depends on X. What we have just proved is that the trajectory approaches the diagonal of the square:



To treat the N-oscillator case by the recursion method one could proceed as follows. At the nth firing we have a vector of N-1 values of α: $\alpha_n^{(1)} \ldots \alpha_n^{(N-1)}$. These satisfy the following recursion

$$\alpha_{n+1}^{k+1} = \min\left(1, \frac{\alpha_n^k(s-1)+s(1-\alpha_n^{N-1})}{(S-\alpha_n^{N-1})} + \varepsilon/N\right)$$

where $\alpha_n^0 = 0$. Note that the expression

$$\frac{\alpha_n^k(S-1) + S(1-\alpha_n^{N-1})}{S - \alpha_n^{N-1}}$$

reduces to 1 when k = N-1, as it should since the oscillator N-1 is the next to fire.

In any event this theory is elementary compared with the real situation. In particular each oscillator has been assumed to be coupled with all of the others, so that spatial effects have been ignored. Nevertheless, we have the beginnings here of a theory of the self-organization of the heartbeat.