DIPOLE THEORY OF HEAT PRODUCTION AND ABSORPTION IN NERVE AXON

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ABSTRACT Exact formulas are derived for the energy change of a dipole system with two energy states (or bands) in a changing field in two cases: (*a*) no dipole flip-flop and (*b*) dipole flip-flop caused by stimulation. Based on these formulas, the positive and negative heats are calculated. The results are in good agreement with experiment in case *b* but are 60-180% larger in case *a*. Furthermore, the theory shows that the negative heat cannot be less than the positive heat in case *a* but can be either way in case *b*, the latter result being found prevalent in experiment. It is concluded that nerve excitation is most likely to involve dipole flip-flop at the membrane surface. The theory is consistent in the interpretations and correlations of the electrical, optical, and thermal effects observed in nerve axon.

INTRODUCTION

One of the old phenomena observed in nerve axon is the heat production (positive heat) and absorption (negative heat) during nerve excitation (Abbott et al., 1951, 1958, 1965; Beresina and Feng, 1932; Downing et al., 1926; Feng, 1936; Feng and Hill, 1933 *a*, *b*, *c*; Hill, 1932 *a*, *b*, 1933; Howarth et al., 1968; Spyropoulos, 1965). According to the most recent work (Howarth et al., 1968), the positive and negative heats are associated with the depolarization and repolarization phases of the spike, respectively. The corrected value of the positive heat from the nonmyelinated vagus nerve of rabbit at 5°C is 24.5 μcal/g impulse, while that of the negative heat is 22.2 μcal/g impulse. The positive heat decreases with increasing temperature and the negative heat is more sensitive to the chemical environment.

There are several theories attempted to account for these nerve heats. The condenser theory was originally rejected by Hill (1932 *b*) and reexamined by Howarth et al. (1968) who again considered it unlikely. The heats of ion mixing in solution not only are much too small to provide for the observed initial heats (Howarth et al., 1968) but also pose conceptual difficulty for the origin of the negative heat (Abbott et al., 1958). The local circuit heat as calculated by Hodgkin (1951) was 10 times larger than the observed; so was the heat due to the K-Ca ion exchange at the membrane surface as estimated by Adam (1970). It is really disturbing that these nerve heats have been so stubbornly resistant to all the theoretical attempts made over a period of nearly five decades (Nachmansohn, 1966; Cole, 1968).

Very recently, there has been a great surge of dipole theory to deal with nerve problems (Almeida et al., 1971; Goldman, 1964, 1969; Hamel and Zimmerman, 1970; Wei, 1966, 1968, 1969 *a*, *b*, 1971 *a*, *b*, 1972; Wobschall, 1968). The distinct virtues of the dipole theory are its versatility and its provision of a physical mechanism for the phenomenon under question; it is possible to interpret not only electrical but also optical and thermal effects in nerve such as birefringence change (Wei, 1971 *b*) and phase transitions (Almeida et al., 1971). In this paper, we shall attempt to attack the problem of nerve heats using the dipole theory.

THEORY

Nerve excitation is brought about by the initial and sudden inward flow of Na ions (or the equivalent) to the interior of the membrane. To put it in physical terms, Wei has formulated the "force condition" (Wei, 1968, 1969 *a*, *b*),

$$f_1 + f_2 + f_3 \geq 0, \tag{1}$$

where f_1 is the electrical force on an Na ion by the dipole layer at the outer interface; f_2, the diffusional force arising from the concentration gradient of Na over the membrane; and f_3, all the other forces, be they molecular and/or externally applied. The inequality sign in equation 1 means "directed inward." This force condition is merely a statement of Newton's first law applied to Na ions. If the Na concentration gradient and hence f_2 is not to be altered, then from equation 1 there are in principle two general ways to excite the nerve, i.e., to change f_1 or to change f_3. The changing of f_1 could be achieved by dipole flip-flop upon stimulation. There are many possible means to alter or apply f_3, for example, by modifying the surface charge. Let us rewrite equation 1 using only the equality sign,

$$f_2 = |(f_1 + f_3)| = |f'|, \tag{2}$$

where f' is the effective field in the dipole layer. The effective dipole barrier to admit Na is then

$$E_0' = a|f'| = af_2, \tag{3}$$

where a is the barrier thickness. Equation 3 states that the outer barrier height (effective) must be reduced to $E_0' = af_2$ in order for nerve excitation to take place regardless of the barrier height in the resting state. Equation 3 holds if Na ions have *zero* kinetic energy. By kinetic theory, every particle should have a kinetic energy of $\frac{1}{2}kT$ per degree of freedom, that is for one-dimensional motion. Hence for the real case, the maximum excitable dipole barrier should be

$$E_0' = af_2 + \tfrac{1}{2}kT. \tag{4}$$

The generally agreeable range of E_0 in the resting state is 20–26 mv (Adam, 1970; Hamel and Zimmerman, 1970; Johnson et al., 1954; Wei, 1968, 1969 *a*). We shall take the mean, $E_0 = 23$ mv. The diffusional force f_2 for Na is given by (Wei, 1968),

$$f_2 = kT \nabla \log [N_a] = \frac{kT}{W} \log [N_a]_0/[N_a]_i , \tag{5}$$

where $[N_a]$ means Na concentration and W, the thickness of the membrane. Taking $kT = 24$ Mev (at $T = 5°\text{C}$), $[N_a]_0/[N_a]_i \sim 10$, $W \sim 100$ A, we obtain

$$f_2 = 5.5 \times 10^4 \text{ ev/cm}. \tag{6}$$

The thickness of the dipole layer is of the order of 10 A. Hence we have from equation 4

$$E_0' = 17.5 \text{ mv}. \tag{7}$$

Thus if the outer dipole barrier at 5°C is reduced to 17.5 mv either by applying an external f_3 or by dipole flip under stimulation, the Na ions would be driven inward, resulting in nerve excitation.

During nerve excitation, the effective field in the dipole layer is changing and each dipole will have its energy changed by the amount $p\mathrm{d}F$ where p is the dipole moment and $\mathrm{d}F$, the field change. Suppose that the dipoles at the membrane surface have two energy states (or bands) with opposite orientations. Then the dipole energy change in a changing field is given by

$$Q = p \int_{F_1}^{F_2} [N_1 - N_2] \, \mathrm{d}F, \tag{8}$$

where N_1 and N_2 are the dipole populations in the lower and upper states. In the following, we shall consider two cases for the calculation of Q.

Case a: No Dipole Flip-Flop

In this case, the dipole system is taken not far from equilibrium and the dipole populations may be assumed to follow the Boltzmann distribution,

$$N_1 = N_0 e^x/(e^x + e^y), \tag{9}$$

$$N_2 = N_0 e^y/(e^x + e^y), \tag{10}$$

$$x = -(E_1 - pF)/kT, \tag{11}$$

$$y = -(E_2 + pF)/kT, \tag{12}$$

where E_1 and E_2 are the energies of the lower and upper states (or bands). Substituting equations 9–12 into equation 8 and integrating, we obtain

$$Q_a = \frac{kTN_0}{2} \ln \frac{\lambda^2 U_2^2 + 2\lambda + U_2^{-2}}{\lambda^2 U_1^2 + 2\lambda + U_1^{-2}} \tag{13}$$

where

$$\lambda = \exp\,(E_2 - E_1)/kT,$$

$$U_1 = \exp pF_1/kT,$$

$$U_2 = \exp pF_2/kT.$$

To check this result, let us consider the case in which $E_2 - E_1 \gg kT$ so that only the first terms in the numerator and the denominator under ln of equation 13 are important. Then equation 13 reduces to

$$Q_a(\max) = \frac{kTN_0}{2} \ln \left(\frac{U_2}{U_1}\right)^2 = pN_0(F_2 - F_1), \tag{14}$$

which one should expect from equation 8 by letting $N_1 \simeq N_0$, $N_2 \simeq 0$. Q_a (max) is the maximum possible energy change when there is no dipole flip-flop.

Case b: Dipole Flip-Flop

If stimulation causes dipole flip-flop, the dipole system will be in nonequilibrium and the Boltzmann distribution is perturbed and hence can no longer be used. The dipole field is produced by the dipole polarization which is proportional to $(N_1 - N_2)$, hence

$$F = C(N_1 - N_2), \tag{15}$$

or

$$N_1 - N_2 = \alpha F, \tag{16}$$

where α can be determined from the initial condition (the resting state),

$$\begin{aligned} \alpha &= [N_1 - N_2]_0/F_0, \\ &= a[N_1 - N_2]_0/E_0, \end{aligned} \tag{17}$$

where a is the barrier thickness and E_0, the unperturbed barrier height. The physical situation is that under stimulation both N_1 and N_2 will change because of dipole flip-flop and consequently the dipole field changes. Substituting equations 16 and 17 into equation 8 and integrating, we obtain,

$$Q_b = \frac{pa[N_1 - N_2]_0}{2E_0}[F_2^2 - F_1^2]. \qquad (18)$$

In the case, $N_1 \sim N_0$ and $N_2 \sim 0$, we have

$$Q_b(\max) = \frac{paN_0}{2E_0}[F_2^2 - F_1^2]. \qquad (19)$$

We shall now calculate the positive heat based on equations 13, 14, 18, and 19. During the rising phase of the spike,

$$F_1 = E_0/a, \qquad F_2 = E_0'/a, \qquad (20)$$

where E_0' and E_0 are the perturbed and unperturbed barrier heights as given before, and a is the barrier thickness. Since E_0' (17.5 mv) $<$ E_0 (23 mv), $F_2 < F_1$, the Q's must be negative which means *reduction* of the dipole energy. This energy is released (or produced) to the membrane and has been called the *positive* heat in the literature. To avoid confusion in semantics, we shall disregard the algebraic sign of the Q's and use henceforth the notations Q_+ and Q_- to indicate positive and negative heats, respectively.

From equation 20,

$$F_1 = 23 \times 10^{-3}/10^{-7} = 2.3 \times 10^5 \text{ v/cm},$$

$$F_2 = 17.5 \times 10^{-3} = 1.75 \times 10^5 \text{ v/cm}.$$

Hamel and Zimmerman (1970) to fit their theory of dipole model into the experimental data, have arrived at p = 50 debye = 10^{-7} e−cm = 1.6×10^{-26} coul−cm, and S (dipole area) = 300 A^2.

A p = 50 debye would be obtained if a dipole had a charge of 1 e and a length of 10 A, both figures are acceptable. In fact, we have taken a = 10 A for the barrier thickness or dipole length. Segal (1968) has estimated 290 A^2 and 200 A^2 for the area of 1 electronic charge on the axon shear surfaces of squid and lobster, respectively, based on his surface charge measurements. Adam (1970) has used $a_0 = 23 \times 23$ A^2 for the area per "subunit" (probably protein and/or the outer layer). Thus a dipole area of 300 A^2 as given by Hamel and Zimmerman is not unreasonable. According to Keynes and Ritchie (1965), the area of membrane in a gram of rabbit vagus nerve is about 6000 cm^2. Thus in a gram of vagus nerve, there would be

$$N_0 = 6000/3 \times 10^{-14} = 2 \times 10^{17} \text{ dipoles/g},$$

at the outer surface which is accessible for thermal measurement. The value of

$\lambda = \exp{(E_2 - E_1)/kT}$ may be obtained from Wei's calculations on barrier potential and birefringence change (Wei, 1971 *b*). For a two-band dipole system, the AC barrier potential was found to almost coincide with the birefringence change when

$$r = \exp - (E_2 - E_1)/kT = 0.2,$$

that is, $\lambda = 1/r = 5$. Since $\lambda = N_1/N_2$ in the resting state and $N_1 + N_2 = N_0$, we obtain $[N_1 - N_2]_0 = 2N_0/3$ which is to be used in equation 18. To compare directly with the experimental results of Howarth et al. (1968), we take $T = 5°\text{C}$, and thus $kT = 24 \text{ Mev} = 38.40 \times 10^{-22}$ J. Substituting all the above values into equations 13, 14, 18, and 19, we obtain the *positive* heats:

Case *a*

$$Q_{a+} = 163\ \mu\text{J/g} = 39.0\ \mu\text{cal/g}, \tag{21}$$

$$Q_{a+}(\max) = 176\ \mu\text{J/g} = 42.0\ \mu\text{cal/g}, \tag{22}$$

Case *b*

$$Q_{b+} = 103\ \mu\text{J/g} = 24.7\ \mu\text{cal/g}, \tag{23}$$

$$Q_{b+}(\max) = 155\ \mu\text{J/g} = 37\ \mu\text{cal/g}. \tag{24}$$

The positive heat (corrected) from the vagus nerve of rabbit obtained by Howarth et al. (1968) was 24.5 μcal/g impulse, which is in excellent agreement with our calculated value $Q_{b+} = 24.7\ \mu\text{cal/g}$ for the case of dipole flip-flop caused by stimulation. Our results 21–24 also show:

(*a*) Q_{a+} and $Q_{a+}(\max)$ do not differ appreciably. This is expected because there will be no great change in populations if there is no dipole flip-flop.

(*b*) $Q_{a+}(\max)$ and $Q_{b+}(\max)$ differ only by 14%. This is also expected because both are under the condition $E_2 - E_1 \gg kT$ or $N_1 \sim N_0$. When E_2 is far above E_1, dipole flip is rather unlikely and case *b* should approach case *a*.

(c) Q_{b+} is much less than $Q_{b+}(\max)$. The reason is that Q_{b+} is obtained from smaller N_1 because of active dipole flip and $Q_{b+}(\max)$ from $N_1 \sim N_0$ because of rather inactive dipole flip.

The negative heat is a little more complicated. Before calculation, we need to understand what the so-called negative heat really means. In experiment, one actually measures the temperature change of the nerve fibers during and after the nerve spike. If the end temperature (T_e) after the spike is equal to the initial temperature (T_i), the negative heat (Q_-') is said to be equal to the positive heat (Q_+). If $T_e > T_i$, one takes $Q_-' < Q_+$, and if $T_e < T_i$, $Q_-' > Q_+$. T_e or $\Delta T =$

$T_e - T_i$, however, is determined by the *total* heat ΔQ remaining in the nerve fibers at the instant T_e is measured. We shall write

$$\Delta Q = C_V \Delta T = C_V(T_e - T_i), \tag{25}$$

where C_V is the specific heat of the nerve fibers; but

$$\Delta Q = bQ_+ + cQ_r - Q_-, \tag{26}$$

where Q_+ is the positive heat produced during the rising phase of the spike, Q_- is the negative heat absorbed during the falling phase of the spike with a magnitude equal to Q_+ and Q_r the energy of quantum emission due to dipole flop during the falling phase

$$Q_r = \Delta n(E_2 - E_1), \tag{27}$$

with Δn being the population change in either state by stimulation. In equation 26, b and c are the fractions of Q_+ and Q_r remaining in the nerve fibers at the end of the spike. It is to be noted that Q_+ and Q_- are the classical (nonquantal) dipole energies in a changing field and are calculated from equation 8 with integration limits (F_1, F_2) for one and (F_2, F_1) for the other, while Q_r is due to the *quantum* jump of Δn dipoles from E_2 to E_1 during the repolarization phase of the spike. The energy for the quantum jump of the dipoles during the depolarization phase is supplied from the stimulating source and hence need not be taken into account. The so-called negative heat as used and meant in the literature is actually

$$\begin{aligned} Q_-' &= Q_- - \Delta Q = 2Q_- - bQ_+ - cQ_r, \\ &= (2 - b)Q_+ - cQ_r. \end{aligned}$$

In case *a* when there is no dipole flip-flop, $Q_r = 0$ and

$$Q_{a-}' = (2 - b)Q_{a+}. \tag{28}$$

In case *b* when there is dipole flip-flop,

$$Q_b' = (2 - b)Q_{b+} - cQ_r. \tag{29}$$

Since $b \leq 1$, one sees from equation 28 that

$$Q_{a-}' \geq Q_{a+}, \tag{30}$$

or using equation 25 and 26, with $b \leq 1$, $Q_r = 0$, one finds that

$$(T_e - T_i)_a \leq 0. \tag{31}$$

Equations 30 and 31 are equivalent statements as used in the literature. Thus for case *a* when there is *no* dipole flip-flop, the end temperature of the nerve fibers after the spike cannot be higher than the initial temperature, or the negative heat will be no smaller than the positive heat. For case *b* when there is dipole flip-flop, from equation 29 the negative heat could be either way from the positive heat depending on b, c, and Q_r. Let us first calculate Q_r from equation 27 and then Q'_{a-} and Q'_{b-}. We have taken before

$$\lambda = 5 = 1/r = \exp (E_2 - E_1)/kT,$$

based on Wei's paper (1971 *b*). At $T = 5°\text{C}$, or $kT = 24$ Mev, we obtain

$$E_2 - E_1 = 38.6 \text{ Mev} = 6.18 \times 10^{-15}\,\mu\text{J} = 1.48 \times 10^{-15}\,\mu\text{cal},$$

from equation 16

$$\frac{N'_1 - N'_2}{[N_1 - N_2]_0} = \frac{F_2}{F_1} = \frac{E'_0}{E_0} = \frac{17.5}{23},$$

where $[N_1 - N_2]_0$ is the population difference in the resting state and is equal to $2N_0/3$ as given previously. Hence

$$N'_1 - N'_2 = 0.76 \times 2/3 \times 2 \times 10^{17} = 1.01 \times 10^{17},$$

since

$$N'_1 + N'_2 = N_0 = 2 \times 10^{17}$$

$$\therefore N'_1 = 1.51 \times 10^{17}/\text{g}.$$

From $[N_1 - N_2]_0 = 2N_0/3$ and $[N_1 + N_2]_0 = N_0$, we obtain

$$[N_1]_0 = 5/6 N_0 = 1.66 \times 10^{17}/\text{g}.$$

Hence

$$\Delta n = [N_1]_0 - N'_1 = 0.157 \times 10^{17}/\text{g}.$$

This is the *excess* population in state 2 acquired by dipole flipping during the rising phase. During the falling phase, this excess population will flop down, resulting in quantum emission Q_r along with Q_-, where

$$Q_r = \Delta n(E_2 - E_1) = 0.157 \times 10^{17} \times 1.48 \times 10^{-15},$$

$$= 23.2\,\mu\text{cal/g}.$$

Fraser and Frey (1968) had detected infrared emission from crab leg nerve under stimulation. By comparing with the result of Abbott et al. (1965), they estimated that 85% of the infrared emission was reabsorbed and only 15% actually radiated. This value of 0.85 is acceptable because the infrared emission is a heat wave and it takes place during the falling phase of the spike when Q_{b-} is absorbed. Thus in equation 29, we may take $c = 0.85$, $Q_r = 23.2$ µcal/g. Since Q_{b+} occurs during the rising phase which is shorter than the falling phase, probably more than half of it may be lost to the environment and a smaller part be remaining at the end of the spike. Then $b = 0.4$ may not be too far off the mark. With these values of b, c, and Q_r substituted into equation 29, and with Q_{b+} taken from equation 23, we obtain

$$Q_b' = 20\ \mu\text{cal/g}.$$

This is in good agreement with the observed value, 22.2 µcal/g by Howarth et al. (1968). For case a, with $b = 0.4$, and $Q_{a+} = 39$ µcal/g from equation 21, we have

$$Q_a' = 1.6\ Q_{a+} = 62.5\ \mu\text{cal/g},$$

which is 280% of the observed value Even if $b = 1$ (no loss of Q_{a+} at all), we would have

$$Q_{a-}' = Q_{a+} = 39\ \mu\text{cal/g},$$

that is still 170% of the value of negative heat measured.

Next, we want to find how sensitive the positive heats are to temperature change. Howarth et al. (1968) found from experiment that the ratio of the positive heat at 4°C to that at 14°C was 1.86. From our formulas, we have calculated:

$$Q_{a+}(4°\text{C}) = 165\ \mu\text{J/g} = 39.4\ \mu\text{cal/g},$$

$$Q_{a+}(14°\text{C}) = 142\ \mu\text{J/g} = 34\ \mu\text{cal/g},$$

$$Q_{a+}(4°\text{C})/Q_{a+}(14°\text{C}) = 39.4/34 = 1.16,$$

$$Q_{b+}(4°\text{C}) = 105.3\ \mu\text{J/g} = 25.17\ \mu\text{cal/g},$$

$$Q_{b+}(14°\text{C}) = 83.6\ \mu\text{J/g} = 19.8\ \mu\text{cal/g},$$

$$Q_{b+}(4°\text{C})/Q_{b+}(14°\text{C}) = 25.17/19.8 = 1.27.$$

The above results show that the ratio (1.27) in case b with dipole flip-flop is closer to the experimental one (1.87) than that (1.160) in case a without dipole flip-flop.

The sensitivity of the negative heat to the chemical environment may be judged indirectly from equation 27–29. Charged ions binding or screening the membrane surface could facilitate or hinder dipole rotations and vibrations. That is the energy difference between the two states ($E_2 - E_1$) could be modified by the chemical environment. In case *a* without dipole flip-flop, we have seen from equations 21 and 22 very little difference between Q_{a+} corresponding to $\lambda = 5 = \exp (E_2 - E_1)/T$ or $E_2 - E_1 = 38.6$ Mev and Q_{a+}(max) corresponding to $\lambda \rightarrow \infty$ or $E_2 - E_1 \rightarrow \infty$. This means that Q_{a+} is insensitive to ($E_2 - E_1$) change, so is Q'_{a-} as can be seen from equation 28. From equations 27 and 29, however, it is quite clear that Q'_{b-} is very sensitive to the change in ($E_2 - E_1$) and hence to the chemical environment. This is in accord with the findings by Howarth et al. (1968).

CONCLUSION

Based on the dipole theory, we have calculated the positive and negative heats from a dipole system with two energy states (or bands) in a changing field in two cases: (*a*) no dipole flip-flop and (*b*) dipole flip-flop caused by stimulation. Our results are: (*i*) the calculated positive and negative heats in case *b* are in good agreement with the experimental results of Howarth et al. (1968); (*ii*) the negative heat cannot be smaller than the positive heat in case *a*, contrary to the observation; (*iii*) the negtive heat in case *b* is sensitive to the chemical environment, but not so in case *a*; and (*iv*) the negative heat in case *b* has a contribution from quantum transitions of excess dipoles from state 2 to state 1. Such downward transitions should give rise to infrared emission which has been observed in crab leg nerve by Fraser and Frey (1968). From the above results, we cannot escape the conclusion that nerve excitation is most likely to involve dipole flip-flop at the membrane surface.

That case *a* cannot yield satisfactory results is not without reason. The assumption of a Boltzmann distribution is not valid when the system is under a fast changing perturbation because there is not enough time for the system to reach equilibrium at every field value. The positive heat Q_{a+}, however, calculated based upon this distribution is of the same order of the experimental value and is better than any previous estimates. The real problem lies in the negative heat (apparent) which cannot be smaller than the positive heat. This is because the heat produced from F_1 to F_2 must be equal to the heat absorbed from F_2 to F_1 in an energy conservative system. If some of the initial heat is lost to the ambient, then that amount of heat must be supplied from the nerve fibers to the dipoles during the falling phase and the end temperature would be colder than the initial temperature. The only way to get a warmer temperature at the end is to have some "excess energy" pumped in and stored during the rising phase and pumped out during the falling phase. In case *a*, such a pumping process is by no means to be expected. If there is dipole flip-flop, then in addition to the classical dipole energies Q_+ and Q_- as given by equation 8, there is a quantum energy Q_r given by equation 27 that contributes to the negative heat Q'_- (apparent) as indicated in equation 29. With this Q_r available, then the negative heat could be varied according to the experimental conditions. That is indeed borne out in experiment.

A theory is of good value if it can account for a wide range of phenomena of different nature. The dipole flip-flop mechanism has been used to interpret fundamental properties of nerve impulse (threshold, strength-duration relation, refractoriness and frequency modulation) (Wei, 1971 *a*), action potential and birefringence change (Wei, 1971 *b*), and optimum frequency for stimulation and AC thresholds under various forms of time-varying stimulations (Wei, 1972). In fact, important quantities such as λ and $(E_2 - E_1)$ used in this paper are deduced from the result of the calculations on action potential and birefringence change (Wei, 1971 *b*). Since these electrical, optical, and thermal effects are correlated in time phase, it is logical to think that the underlying molecular mechanism could be one and the same. Our detailed analysis and calculations strongly suggest that the dipole flip-flop mechanism is mainly responsible for nerve excitation and for its various forms of macroscopic manifestations.

In concluding the paper, we wish to make some remarks on the assumptions made, the choice of values for the parameters and the sensitivity of the results to the change of parameter values. The main assumption in the theory is the two-band model for the dipole energy. From physics, this is the simplest model one can take for molecular energy and thus needs no further explanation. It is also the same model used to calculate the action potential and the birefringence change (Wei, 1971 *b*). The "force condition" is not an assumption but merely a mathematical representation of Newton's law of motion. Detailed discussion of the force condition has been given previously (Wei, 1968, 1969 *b*). The two cases treated in this paper are two possible situations of dipoles under stimulation, i.e., equilibrium redistribution and non-equilibrium sudden perturbation (flip-flop). In equilibrium or near equilibrium, Boltzmann distribution is good or at least a good approximation. The calculations are straightforward involving no other assumptions than the two-band model.

The parameter values are chosen according to at least one of the following criteria: a value (*a*) obtained by and agreeable to many workers, (*b*) obtained from the latest work, (*c*) used in the dipole model on nerve problems previously, and (*d*) used in the nerve heat experiment to be compared with. No value was chosen arbitrarily with an intention to fit the data.

Elaboration of the sensitivity of the results to the change of parameter values would make sense on two conditions, (*a*) the experimental error is known with great accuracy and is within narrow limits, say ±15%, and (*b*) the values of all parameters have been well established. In the problem of nerve heats these two conditions are not fulfilled. To correct for the overlapping effect, Howarth et al. (1968) multiplied the measured positive heat (7.2 μcal/g) by a factor 3.4 and arrived at 24.5 μcal/g. With such a large error factor (340%) in experiment, there is little sense to examine the quantitative sensitivity of the theory.

The dipole theory, if only giving a better quantitative agreement with experiment than the other theories cannot simply be taken as a better or even a valid theory.

The uniqueness of the dipole theory lies in its distinct qualitative features: (*a*) it presents no conceptual difficulty for the negative heat and it offers the possibility that the negative heat can be either less or greater than the positive heat, and (*b*) it can correlate the electrical, optical, and thermal effects in nerve membrane as observed. As our theory have indicated, the second part of item (*a*) is in favor of the flip-flop mechanism. It is these qualitative features that justify the dipole theory and, furthermore, provide us a deeper understanding in the molecular mechanism of the nerve processes.

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