

Quantitative investigations of electrical nerve excitation treated as polarization

Louis Lapicque 1907 · Translated by:

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In the context of electrical excitation of nerves, one often uses the term polarization, but this remained rather vague until Nernst (1899) gave it a foundation based on chemical physics:

“According to our current knowledge, a galvanic current can in organic tissue (a purely electrolytic conductor) only cause movement of ions, i.e. concentration changes, and nothing else. We conclude that these concentration changes must underlie the physiological effect.

... It is well known that in organic tissue the composition of the aqueous solution that forms the electrolytic conductor is not everywhere the same. In particular, it is different on the inside and on the outside of the cells. The semi-permeable membranes prevent equilibration by diffusion. On these membranes, and there only, currents can lead to concentration

changes. Ions that are stopped by the membrane accumulate there, while the ions that can cross the membrane carry the current. It is here that we have to look for the basis of electric excitation.” (Nernst and Barratt 1904)

However, as the current accumulates the ions at the membrane, the diffusion acts oppositely; the net change at the membrane is the result of the opposing effects of the current and the diffusion. Nernst uses this insight to explain the physiological ineffectiveness of high-frequency alternating currents. These ideas lead, when treated in the simplest possible way, to already established equations for the polarization of metal electrodes. In the case of sinusoidal currents, one has that the net effect is inversely proportional to the square root of the frequency.¹ Experiments on the frog sciatic nerve (with platinum plated electrodes) show that between 100 and 2,000 Hz, the intensity needed to reach threshold indeed grows as the square root of the frequency (Nernst and Barratt 1904).

It is known that semi-permeable membranes placed in an electrolytic conductor can lead to a polarization, as Nernst remarks [p. 621]. This was demonstrated by Ostwald (1890). A parchment membrane is placed between a solution of potassium iron cyanide [K^+ and $Fe(CN)_6^{3-}$] and a solution of copper sulfate [Cu^{2+} and SO_4^-]. Inside the membrane a deposit of iron cyanide of copper forms. One applies a potential of about 2 V, and a current flows which decreases to about a quarter of its initial value and remains steady indefinitely. The electromotive force suppressed, a counter-electromotive force shows up. Thus we have both polarization and de-polarization.

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¹ [Note, that a passive membrane would lead to a filtering proportional to $(1 + (f/f_0)^2)^{-1/2}$, and therefore a $1/f$, not $1/\sqrt{f}$, behavior at large f .]

All these phenomena can be explained if one assumes that the potassium ions of the one solution and the sulfate ions of the other solution can cross the membrane, while the iron $\text{Fe}(\text{CN})_6$ and copper ions cannot. Indeed, one can observe a metallic copper deposit on the anode side of the membrane (Ostwald 1890).

I think that one can explain all our observations on electrical excitation by studying the membrane polarization according to Ostwald's concept, which is not very different from Nernst's. Consider a conductor made up from a solution of various electrolytes. Now, divide this conductor by a membrane that is permeable to some ions (ions I), and impermeable (or much less permeable) to other ions (ions II). If a potential is applied across the conductor, part of the current will be carried by ions I, while ions II accumulate to some limit on the two sides of the membrane, the cations on the side with the higher potential, the anions on the other side.

It is likely that complex phenomena take place at the membrane: some slow diffusion of ions II into the membrane, and maybe interaction with the membrane itself (e.g. electrostatic dyeing), etc. Despite such secondary phenomena, we can treat membrane polarization in first approximation like any polarization. The polarization of metal electrodes as well exhibit similar secondary phenomena that one might not have taken into account a few years ago. "According to Berthelot and Bouty, no electrode is fully robust or impermeable to electrolysis products" (Rothé 1904). Corrections should be studied in each case individually. In the case of nerves, still very little is known about membranes (despite recent research on the role of lipids): there are many electrolytes in a very viscous environment, due to the presence of various colloids; lime salts $[\text{CaOH}]$ probably play a special role; the myelin sheet, where present, must have a big effect. It is a very complex situation. Nevertheless, like with metallic electrodes, the first approximation is a capacitor. One should just not forget that this is an approximation.

[Equivalent circuit]

Since the capacitor has a leak, here is the schematic diagram to which one can compare what physiological experiments reveal about the law of electrical excitation (Fig. 1).

Given a capacitor K , one of its leads has zero potential, the other is connected via a resistor R with a voltage source V [p.622]. A leak resistor ρ is connected parallel to the capacitor. We assume that the threshold for excitation is reached when the capacitor is charged to a potential v .

One sees immediately that the circuit satisfies the general requirement that we derived by combining the viewpoints of Du Bois-Reymond and those of Weiss, namely: In the steady state no current passes through the capacitor. The charging occurs immediately when the contact is made. Assuming a very small inductance, the current reaches its maximal value,

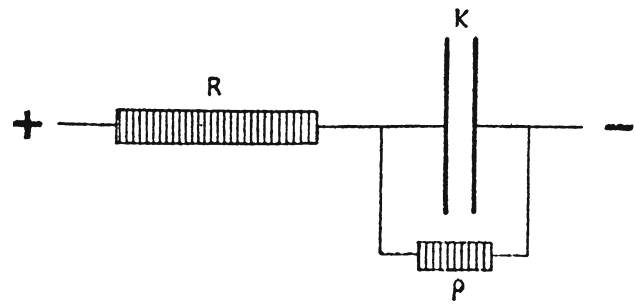


Fig. 1 [The equivalent circuit used to analyze the threshold behavior. The product ρK is the time constant.]

close to V/R , very rapidly, after which it decreases to its steady state value $V/(R + \rho)$. If R is much larger than ρ (we will see that it is generally the case in the experiments), $V/(R + \rho)$ is slightly less than V/R . This decreasing period thus affects only a very small fraction of the current if one has hundreds of $\text{k}\Omega$ s in the circuit.

Weiss, followed by us, considered this a steady state current, and from this point of view, the error was not large. However, at the contact between nerve and electrode, where the excitation is produced, represented by K and ρ , the variation [in the voltage] is major. Reduced to the above circuit, the problem is fully defined and can be mathematically analyzed exactly.²

² I had initially posed the problem, as it often happens at the beginning of a study, in an unnecessarily complicated form. For the mathematical study, I had the kind assistance of Mr. Chatanay and Mr. Levy, two students of the École Normale Supérieure who followed my course this winter. Their work was very useful to clarify the problem, and I address my sincere thanks here to them.

The simple Eq. (1), can be derived as follows: In resistor R , the current is $i = \frac{V-v}{R}$, in resistor ρ , the current is $i' = \frac{v}{\rho}$. The charge differential is $K dv = i dt - i' dt$, that is to say, $K dv = \frac{V-v}{R} dt - \frac{v}{\rho} dt = \frac{(V-v)\rho - vR}{R\rho} dt$. Or, after separating out the constants

$$\frac{K R \rho}{R + \rho} \cdot \frac{dv}{\frac{V\rho}{R+\rho} - v} = dt,$$

which one can rewrite as

$$-dt \cdot \frac{R + \rho}{K R \rho} = \frac{dv}{v - \frac{V\rho}{R+\rho}}.$$

This differential has as integral

$$A - t \frac{R + \rho}{K R \rho} = \log \left(\frac{V\rho}{R + \rho} - v \right)$$

If we assume that initially the capacitor has no charge, i.e., $t = 0$, and $v = 0$, we have for the integration constant $A = \log \frac{V\rho}{R+\rho}$, which gives $-t \frac{R+\rho}{K R \rho} = \log \left(\frac{V\rho}{R+\rho} - v \right) - \log \left(\frac{V\rho}{R+\rho} \right)$. Or, after replacing the difference of logarithms with the logarithm of the fraction, $-t \frac{R+\rho}{K R \rho} = \log \left(1 - \frac{R+\rho}{V\rho} v \right)$. That is,

$$e^{-t \frac{R+\rho}{K R \rho}} = 1 - \frac{R + \rho}{V\rho} v,$$

which then only needs to be solved with respect to v .

The potential v to which the hypothetical capacitor will be charged at a time t after the sudden application of the voltage V is given by

$$v = V \frac{R}{R + \rho} \left(1 - e^{-t \frac{R+\rho}{R\rho K}} \right). \tag{1}$$

However, the experimental quantities that one measures are the duration t and the necessary voltage V to reach threshold in that duration. From the previous equation one derives (p. 623)

$$V = v \frac{R + \rho}{R} \frac{1}{1 - e^{-t \frac{R+\rho}{R\rho K}}}.$$

Noting that R is known and constant, while K , ρ , and v are assumed constant, we can set

$$v \frac{R + \rho}{R} = \alpha, \quad \frac{R\rho K}{R + \rho} = \beta.$$

After substitution, we get

$$V = \frac{\alpha}{1 - e^{-t/\beta}},$$

which is to be compared with Weiss' equation $V = a/t + b$ [see accompanying preceding introduction].

In both formulas one obtains the constants for a given experiment from two measurement of V for two values of t . Using the new formula, one needs two values of t , one double the other, to be able to solve the system of equations. Given

$$V_1 = \frac{\alpha}{1 - e^{-t'/\beta}}, \quad V_2 = \frac{\alpha}{1 - e^{-t''/\beta}},$$

where V_1 , V_2 , t' , and t'' are numerical values, one needs to know α and β [p. 624]. Setting $e^{t'/\beta} = x$, then if $t'' = 2t'$, $e^{t''/\beta} = x^2$. After substitution into the above equations and subtracting one from the other, we obtain a second degree equation with one unknown. Solving it towards x , one finally finds after all simplifications, $x = \frac{V_2}{V_1 - V_2}$ (the other root of the equation is 1). From which one gets

$$\beta = t' \frac{\log e}{\log V_1 - \log(V_1 - V_2)}.$$

We will use these two parameters to compare the two formulas with the experiments. But afterward we will have to examine the physical quantities, both real and hypothetical, that are combined in these two parameters.

At this point it is worthwhile to point out that in overall form the new equation that we derived for a capacitor with leak, is identical to the one we would obtain without leak. For the latter, $v = V (1 - e^{-t/(RK)})$, from which $V = \frac{v}{1 - e^{-t/(RK)}}$. Setting $v = \alpha$ and $RK = \beta$, one arrives at the same equation. But study of the parameters would reveal contradictions with the experiment. For instance, adding or removing a resistor in the driving circuit [i.e. changing R], would not change the required voltage, but would change

the time constant. In reality the opposite is true, and that is consistent with the full equation, as we shall see.

Despite the fact that Weiss' equation (a hyperbolic) and the one I propose (a logarithm) are different, both are convex curves. Both diverge near $t = 0$, while for long durations both run parallel to the x -axis and reach a constant value. In small regions the curves look very similar, but for large durations, the curves diverge, with the hyperbole going below the logarithm.

I recall that in the preceding paper, my main criticism of Weiss' equation concerned the constant b , which is difficult to interpret physically and leads to a too low value for the threshold voltage for long durations (Lapicque 1907, p. 570). In contrast, the logarithmic equation extrapolates very satisfactorily in this direction. We will show this using an example experiment from a paper by Weiss [p. 625]. It is the only experiment that gives V for $t = \infty$. (The time is expressed in centimeters, which corresponds to 1/13,000s. The voltages are in arbitrary units, likely on the order of millivolts. The resistance R was about 0.5 MΩ.)

Experiment of 6 December 1900 (Weiss 1901)

From durations 4 and 12 I extracted for Weiss' equation, the values $a = 168$ and $b = 21$. From durations 8 and 16 I extracted for the logarithmic equation, $\alpha = 29.5$ and $\beta = 6.3$. (Durations 6 and 12 gave $\alpha = 29.5$ and $\beta = 6.5$.) For $t = \infty$, Weiss' equation becomes $V = b$; mine becomes $V = \alpha$.

Duration	Voltage		
	Observed	$\frac{a}{t} + b$	$\frac{\alpha}{1 - \exp(-t/\beta)}$
3	82	77	78
4	63	63	62.5
6	49	49	48
8	41	42	41
12	35	35	34.5
16	32	31.5	32
∞	30	21	29.5

For duration 3, the experiment is certainly poor; the duration is too short to ignore onset transients. For the next durations, both equations match the experiments equally well. For $t = \infty$, Weiss' equation deviates considerably. My equation, fitted using short durations, matches very well without any correction.

If the experiment encompasses somewhat longer durations, as is generally the case for Weiss' experiments, the logarithmic equation cannot follow the experimental data. The parameters extracted using different durations will then vary systematically with duration.

Example: Weiss experiment of December 19

Duration	4	6	8	10	12	14	20	40
Observed voltage	185	142	123	112	103	97	86	77

We obtained the following values:

Calculated with	β	α
4 and 8	5.8	92
6 and 12	6.2	87
10 and 20	8.3	78
20 and 40	9.4	76

On the contrary, Weiss' formula gives for the constants a and b values that vary only from 62 to 65 for b , and from 46 to 49 for a [p. 626]. This formula therefore seems closer to the experiment, especially given that the slight deviations from the formula do not appear systematic.

However, let us plot, rather than V , the values of the product $V \cdot t$ which are predicted by Weiss' formula to lie on a straight line; this is sensitive to smaller deviations. We see that the straight line going through the point with duration 40 and points corresponding to the shortest durations leaves the point with duration 20 below it.

This deviation would not matter, if it occurred once. However, such an inflexion occurs in almost all Weiss' experiments that he has published, as well as those he was kind enough to communicate to me during the very amicable conversation that we have been having, orally or through mail, since several years on the law of excitation.³ This small deviation interested me, since it seemed to indicate that the curve is convex, as in the logarithmic formula. The curve, using for the parameters found for durations 20 and 40, is plotted in Fig. 2.

I found such curvature, more or less pronounced, in my own experiments. Until then, I had considered them sufficiently well described by a straight line. However, I have redone particular experiments to characterize the curvature further. To do this, it was first necessary to get more data for the longer durations, in the part of the curve in which I suspected an upward convexity [p. 627]. Secondly, it was desirable to decrease as much as possible the resistance of the circuit, in such a way as to obtain excitation with the smallest voltage possible.

³ Weiss himself also noted this inflexion. I had asked him for the data on the toad, because I had great trouble to admit that in this animal the larger voltages did not deflect the curve towards the origin. On sending me the data on April 26th 1903, Weiss noted as a curious fact an inflexion between durations 10 and 15. At that time, we did not find any interpretation and neither him nor me gave the matter further thought.

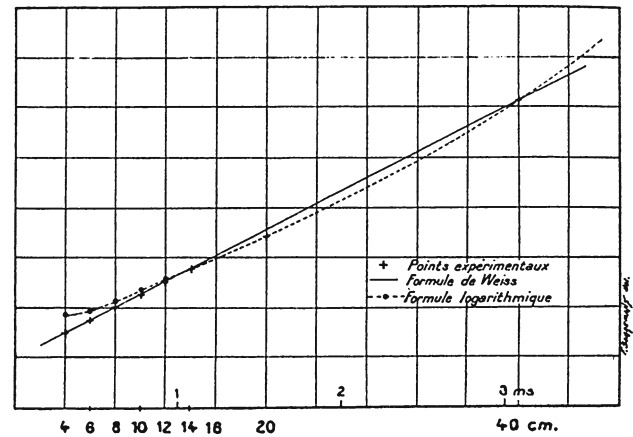


Fig. 2 [Plot of the threshold voltage times duration ($V \cdot t$) versus duration (t). Solid line Weiss' law $V \cdot t = a + bt$; dashed line Lapique's formula: $Vt = \frac{at}{1 - \exp(-t/\beta)}$.]

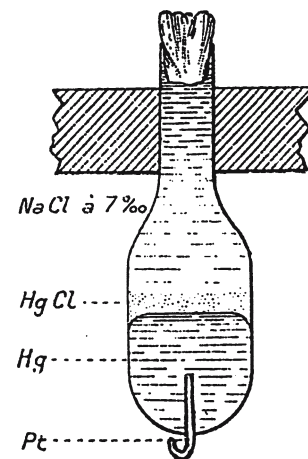


Fig. 3 [The electrodes used by Lapique.]

[Methods]

Concerning this second point, I have built unpolarizable electrodes with a weak resistance, with mercury, calomel [Hg Cl] and physiological solution; the drawing (Fig. 3) should give the reader the idea. A pair of those electrodes, with small plugs of filter paper on which the nerve rests, have a resistance of about $7k\Omega$ (instead of the $50k\Omega$ for the model with the same chemical elements that I usually use). I checked several times that these electrodes are practically unpolarizable in the conditions in which I use them, as follows: with the two plugs of filter-paper being in direct contact, I applied several tens of mV to the circuit, i.e. the order of magnitude used in such experiments. The galvanometer deflected with its usual speed and stayed absolutely constant. On the other hand, when un-damped and working ballistically the galvanometer, upon applications of constant voltage lasting 1, 2,

and 3 ms, gave deflections that are approximately in a 1, 2, 3 ratio.

In the remaining part of the circuit there is only a resistance of $5k\Omega$. Since the nerve is interposed for a length of 3–4 mm, we have a total resistance of 30–40k Ω which comes from the most part (2/3 approximately) from the nerve. Concerning stability of the results, this last point is obviously very unfavorable—the least variation of resistance in the nerve provokes an appreciable variation of the current. Our goal of understanding polarization forces us to accept at the same time a relatively big influence on other phenomena, such as drying out, or temperature changes. One needs to try to eliminate such perturbations with more rigor than usually.

After experimenting, I came to place the experimentalist with the whole experiment (except the ballistic interrupter with its fulminate rifle, which emits unpleasant smoke in a restricted space) in a big incubator. [fulminate is an explosive based on fulminic acid]. This still allows us to maintain a small wet chamber around the nerve. The temperature was set several hours in advance. Alive frogs to be used in the experiment, electrodes, instruments, all was placed in advance in the incubator such as to be in equilibrium. Lumbar nerves have to be dissected up to the spinal cord; placing the sciatic nerve on the electrodes, we thus operate on a region far removed from the section of cylinder-axis. Furthermore, one should not take measurements made during the first minutes after the section into account.

To obtain a sufficiently large and accurate series of threshold measurements using the ballistic circuit breaker, about an hour is needed. In spite of all precautions, the threshold measured after that time differs from the one measured at the beginning. To eliminate annoyances of this type, each series of measurement was made twice, in both directions; i.e. after going from the longest to the shortest duration, we went from the shortest to the longest [p. 628]. Or we took alternatively a long duration and a short duration. In that way we can rule out the effect of progressive alteration of the nerve on the measured duration or voltage.

With the used resistance, one needs extremely small voltages. To manage those with precision, we established half a volt across a plated iridium bridge of one meter long, which is well calibrated and has a precise contact slide (instrument by Fritz Köhler, used for the Kohlrausch method [a method to measure conductance of electrolytes using a Wheatstone bridge]). Every millimeter is thus equivalent to half a millivolt. The contacts are carefully made, and a calibrated voltmeter with a precision of 0.1 V allows to verify the voltage across the bridge from time to time.

The determination of the threshold for a current of indefinite duration is done at the end of the experiment, for fear that such long applications produce permanent alterations, but immediately after the measurement of the threshold for the longest duration.

Experimental results

Here are a few experiments. Experimental values are reproduced in the order in which they were obtained. Times are expressed in cm of the rheotome (27 cm = 1 ms), voltages in mm of the bridge (1 mm = 0.5 mV) [see preceding introduction]. All experiments are on the gastrocnemius muscle [muscle of the back lower leg] of the frog (*Rana Esculenta*) excited through the sciatic nerve.

Experiment of March 10, temperature 18°C.

<i>t</i>	81	27	67	18	40	9	54	9
<i>V</i>	135	200	137	240	170	360	145	370
<i>t</i>	67	54	40	27	19	9	81	∞
<i>V</i>	145	150	180	200	245	380	144	143

Given the order in which these data have been collected, it would seem illegitimate to take the average of the two values of *V* taken for each value of *t*. But it is also interesting to note that the seven first, as well as the seven last measurements show clearly the curvature that appeared in Weiss' experiments (Fig. 4). As this curvature is obtained with two apparatuses that only have their principle in common and is independent on the order in which durations are applied, the curvature is therefore due to the law of excitation.

The following series have been made symmetrically to allow for a more correct use of means. I was able to further reduce the deviations [p. 629].

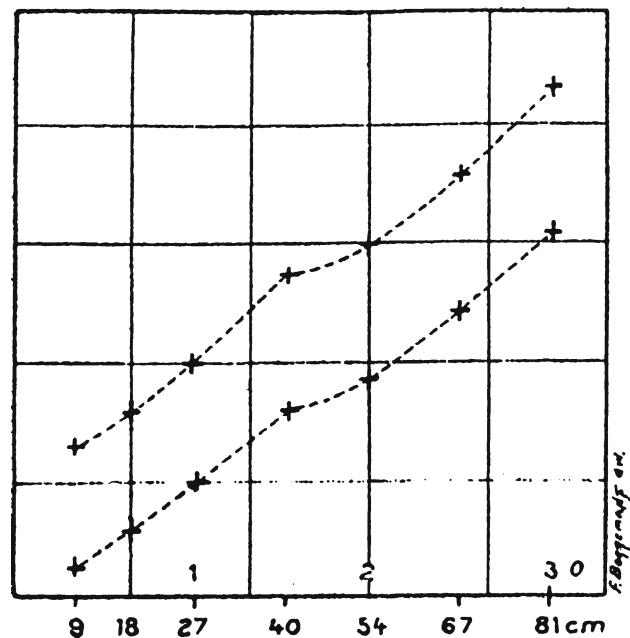


Fig. 4 [Plot of the threshold voltage times duration ($V \cdot t$) versus duration (t). The two curves are from the same experiment, but differ because of experimental drift.]

Experiment of 15 March, temperature 12.5°C

<i>t</i>	81	67	54	40	27	18	9
<i>V</i>	58	62	66	76	91	115	175
<i>t</i>	18	27	40	54	67	81	∞
<i>V</i>	115	92	77	70	67	64	63

The mean gives, with durations in ms,

<i>t</i>	$\frac{1}{3}$	$\frac{2}{3}$	1	1.5	2	2.5	3
<i>V</i>	175	115	91	76	68	64	61

For $t = \infty$, we take V to be one unit below the value for $t = 3$, i.e. 60.

Here, the experimental data points expressed as $V \cdot t$ deviate only slightly from a straight line. The curvature, though recognizable, is not very pronounced. It seems to hold generally in experiments at low temperature. Weiss' formula captures very well the seven measurements at limited duration. The parameters take the values $a = 44$, $b = 46.5$; the deviation between the value of b and the voltage for the long duration current is here quite large (almost 25%).

In reality, the lower limit of the voltage is reached at 3 ms, as shown by the experiment. For all longer durations, Weiss' formula would give rise to more pronounced deviations. Indeed, instead of 60, it gives for $t = 5$, $V = 55$ (a deviation of 10%) and for $t = 10$, $V = 51$ (almost 20%). We see that there is no need to do a sophisticated extrapolation to disprove the formula that only works in a limited range.

On the contrary, if one takes the logarithmic formula with $\alpha = 59$, $\beta = 1$ (ms) we find too large values for the shortest durations (the deviation being smaller than 15%), but a better agreement from 1ms to infinity.

Duration	Observed voltage	$V = \frac{44}{t} + 46.5$	Deviation (%)	$V = \frac{59}{1 - \exp(-t)}$	Deviation (%)
0.33	175	178	+2	208	+19
0.66	115	111.5	-2	125	+8
1	91	90.5	0	93	+2
1.5	76	75	-1	76	0
2	68	68.5	+1	68	0
2.5	64	64	0	64	0
3	61	61	0	62	+1.5
∞	60	46.5	-22	59	-1.5

In spite of the very small deviation between the experimental values and Weiss formula for all measured durations, on a graph it is easy to see which formula corresponds best to reality (Fig 5) [p. 630].

The value of Vt , according to the logarithmic formula tends to αt [for large t]; hence the curve is asymptotically a straight line going through the origin. Weiss' law, represented by the straight line $a + bt$, crosses the straight line αt with a pronounced angle. Above the crossing point, experimental values are approximately constant, i.e. they follow αt and not $a + bt$.

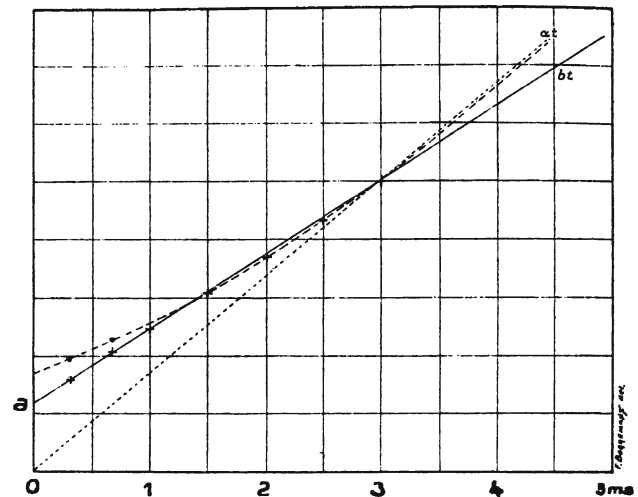


Fig. 5 [Plot of the threshold voltage times duration ($V \cdot t$) versus duration (t). Solid line Weiss' law, dashed line Lapicque's equation, short-dashed asymptote of Lapicque's formula for large t , given by $Vt = \alpha t$.]

However, in reality, most experiments show that our formula stemming from an ideal capacitor can accurately follow the experimental curve only in a very restricted range. Here are the values of the constants of the logarithmic formula, taken directly from the experiment below:

Durations	β	α
0.33 and 0.66	0.51	84
1 and 2	0.93	60
1.5 and 3	1.07	57

The parameters in the table were obtained combining the two last values, so as to obtain a reasonable agreement on the largest set of durations. The value of 57 for α presents a smaller deviation than one could expect. This deviation is more pronounced when temperature is higher [p. 631].

Experiment of March 13, temperature 24.5°C.

<i>t</i>	81	67	54	40.5	27	18	9
<i>V</i>	111	112	115	125	154	185	270
<i>t</i>	18	27	40.5	54	67	81	∞
<i>V</i>	190	156	127	115	113	112.5	112

In this series of experiments, done at a relatively high temperature, the duration 3 ms (81 cm) is relatively long. For this duration, we see that the necessary voltage becomes asymptotically close to its minimal value. From these very similar values we obtain the mean as:

<i>t</i>	9	18	27	40.5	54	67	81
<i>V</i>	270	187	155	126	115	112.5	112

From duration 1 to 3, experimental values for $V \cdot t$ show a pronounced convexity (Fig. 6). It has not been possible to find constants for which the logarithmic formula exactly fits that curve. All theoretical curves built from the formula are less curved and give too small values, either for duration 1, or

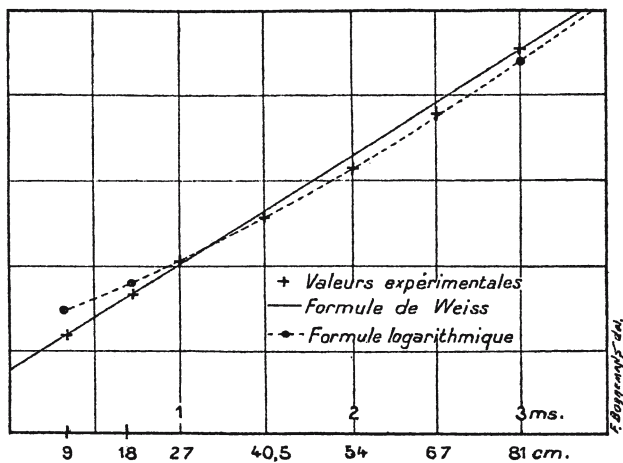


Fig. 6 [Similar experiment as Fig. 5, but at higher temperature.]

duration 3. For theoretical reasons I accept this last deviation. In the scale of experimental durations, except for the shortest duration, we obtain deviations which are of the same order as the ones given by Weiss law. Both do not exceed 5%.

Observed Duration	voltage	Deviation $V = \frac{60}{t} + 92$	(%)	Deviation $V = \frac{103}{1 - \exp(-t/0.9)}$	(%)
0.33	270	272	0	327	+21
0.66	187	182	-2.5	197	5.5
1	155	152	-2	154	0
1.5	126	132	+4.5	127	0
2	115	122	+6	115	0
2.5	112.5	116	+3	110	0
3	112	112	0	107	-4.5
∞	111.5	92	-18	103	-7

[Discussion]

We have therefore shown that for the sciatic nerve on the frog the part of the experimental curve between 0.3 and 3 ms, treated by Weiss as a straight line, is actually a non-linear curve. However, treating the excitation as charging of a capacitor leads to a formula that shows systematic deviations for both short and long durations. These deviations are very pronounced for very short intervals, but are smaller for longer durations.

It seems to me that these systematic deviations confirm that the involved phenomenon is indeed polarization [p. 632]. We have treated this polarization like an ideal capacitor, with a perfectly well determined capacitance. However, we know that such a description is only approximate for platinum electrodes in any electrolytic solution. The polarizability is only a fictitious quantity, measured as the ratio between the difference of potential V between the electrodes and the charge. This ratio varies both with charge time and with voltage, and

therefore the polarizability has a well-defined meaning only in the limit, $v = 0$ and $t = 0$ (Bouty 1894).

If the same line of reasoning applies to the polarization of a membrane (most likely, the difference with a capacitor is even more pronounced here), it is clear we will not find data that fits exactly with electrostatic capacity. It would be premature to investigate if the observed deviations can be explained by secondary phenomena associated to polarization, since here we do not know what these secondary phenomena are. For the moment, from the physical point of view, it is wise to content oneself with this first-order approximation. However, from the physiological point of view, there is a number of experimental facts that should agree with the proposed formula.

For this discussion it is necessary to return to the formula that represents the theory of the membrane polarization. With the two parameters α and β we have studied the formula as an empirical formula, comparing it to data obtained in some given experimental conditions. However, both constants represent a set of physical quantities, some hypothetical, some experimentally modifiable. We have to check what happens to the formula when we vary one of these quantities, and to compare the results with experiment.

Let us recall the formula that gives the threshold voltage V as a function of the duration t :

$$V = v \frac{R + \rho}{\rho} \cdot \frac{1}{1 - \exp\left(-\frac{R + \rho}{KR\rho}t\right)} \tag{2}$$

and we set

$$\alpha = v \frac{R + \rho}{\rho}, \quad \beta = \frac{KR\rho}{R + \rho} \tag{3}$$

The constants corresponding to physical quantities are v , K , ρ and R . In the schematic apparatus that we have used, R is the sum of the resistances of the circuit external to the capacitor [p. 633].

In the experiments of excitation of the nerve (we consider here only the sciatic nerve of the frog), these resistances can be divided in three types: (1) the sum of the resistances in the excitation circuit, (2) the intrinsic resistance of the part of the nerve interposed between the electrodes, the nerve is considered to be an electrolytic conductor to which Ohm’s law can be applied; (3) a membrane resistance at the anode, with an undefined form, that behaves in part as a polarization resistance.

The sum of 1 and 2 is always much larger than 3. One cm of nerve, taken in the sense of 2, has a resistance of 50–60 k Ω . The unpolarizable electrodes, which are part of 1 have a resistance which is greater. Furthermore, there are always additional resistances which can be sometimes very large. In Weiss’ experiments, the total resistance of the circuit was often 800 k Ω .

As a general rule, in experiments of electrical excitation of the nerve, the resistor is on the order of $10^5 \Omega$, while the resistance of the membrane at the anode is on the order of 10^4 . Compared to the sum, we can therefore neglect the part of this last resistance which is due to polarization. Overall R is therefore on the order of several hundreds $k\Omega$.

In the schematic apparatus, ρ is the leak resistance between the two leads of the capacitor. In the nerve, it [ρ] is the resistance of the membrane in immediate contact with the cylinder-axis in front of the cathode. It is only a part of the membrane resistance in this area. It is an unknown quantity, and it varies as a function of the contact area of the electrode (see below). However, according to the physical picture that we have introduced here, in given experimental conditions, it has a well-defined value, that is certainly in most cases smaller than $10^4 \Omega$. R is therefore much larger than ρ .

1. We will first examine the excitability for a sudden application of a constant current. The formula applies when we insert $t = \infty$; $e^{-t/\beta}$ tends towards zero, and V becomes equal to α , i.e. $v \frac{R+\rho}{\rho}$.

Influence of resistances. Since R is much larger than ρ , $\frac{R+\rho}{\rho} \approx \frac{R}{\rho}$. Since V and ρ are assumed constant, we see that V will be approximately proportional to R . This means that if we add or subtract resistances (without inductance) to the excitation circuit, we will need to increase or decrease the voltage approximately in proportion to the increase or decrease of the total resistance. This is what is observed.

Influence of cathode area. We know that the contact area of the active electrode has a considerable importance. Du Bois-Reymond said that the excitation is a function of the *density* of the current, which is equivalent to say that the necessary current to excite grows as the contact area. Let us consider the membrane that corresponds to the resistance ρ . This membrane is a conductor of constant length, but variable cross section [p. 634]. Let r be its resistance per unit section. For a cross section s , the total resistance is $\rho = r/s$. Inserting this expression in $V = vR/\rho$ yields $V = vRs/r$; we see that V grows with the surface.

2. Let us return to the temporal aspect of the function, i.e. the fact that time appears in a logarithmic fashion. β appears as a time scale in this formula. It seems that physiological considerations on this parameter, to which I ascribe the utmost importance, will then appear in a more concrete fashion—it will be the equivalent of the ratio a/b of the constants in Weiss formula, a ratio whose physiological variations I have already studied in various cases.

The expression $\frac{1}{1-e^{-t/\beta}}$ goes rapidly to 1 when t/β grows. For $t = 3\beta$, its value is 1.055; for $t = 4\beta$, it becomes 1.02. This means that, in ordinary experimental conditions, the influence of duration on threshold voltage be negligible as

soon as $t = 3\beta$. In case of the gastrocnemius muscle of the frog excited by the sciatic nerve, according to the above mentioned values, β is approximately 1 ms. Three milliseconds is therefore the duration after which the process corresponding to the threshold for constant current is practically over. It is exactly the value that I gave previously calculating the ratio $a : b$ in Weiss' formula.

We should now examine the possible variations of the several physical quantities that enter in the coefficient β . We can write $\beta = K\rho \frac{R}{R+\rho} \cdot \frac{R}{R+\rho}$ has a value very close to 1, since ρ is much smaller than R . It follows that in practice, in nerve excitation experiments, $\beta = K\rho$, the product of a capacity and a resistance, which is indeed a time. Here, it is the product the capacity of the membrane times the resistance of this membrane. This product is constant, for any considered surface; indeed, capacity grows with the surface, while resistance decreases inversely proportional to it.

It follows that if we vary the contact area of the active electrode, we will change the voltage necessary to the excitation, as we just saw, but not the temporal aspect of excitation. In addition, if we vary the resistances of the circuit, i.e. R , either adding or subtracting resistances, or applying current through a varying length of the nerve, the factor $\frac{R}{R+\rho}$, stays always very close to 1. It follows that $\beta = K\rho \frac{R}{R+\rho}$ will not be appreciably affected by any modification of the experimental apparatus. That is what I indeed found in numerous experiments [p. 635].

This temporal aspect, measured as the $a : b$ ratio, was always approximately constant, even though each of the two parameters depended greatly upon the arrangement of the electrodes (Mr & Mrs Lapicque 1906). This invariance can be very well explained by the idea that membrane polarization is the mechanism of electrical excitation. The product $K\rho$, i.e. the polarizability and the resistance per unit area, depends on the organization of the considered nerve: on the width and nature of the membrane, on the composition of the electrolytic solution, on the colloidal solution etc. Furthermore, it varies with temperature, hydration, etc, but is absolutely independent on the conditions in which the excitation is given.

This temporal aspect is therefore a fundamental property of excitable tissue, nervous or other. I already insisted on this point of view in various previous works. Therefore, the physical interpretation that I reach today gives a precise meaning to several important previously known facts on excitability, facts that I did not consider when building this interpretation. It seems to me a reason to consider it a step in the direction of realism.

The most serious problem that currently remains, is that the equation does not explain the inefficiency of slowly increasing currents [to excite the nerve]. This is a hiatus, not an objection. One should recognize that these ineffective currents increase *very slowly*, compared to the timescales con-

sidered here; they are of another order. It is possible that the explanation can be found in the necessary correction terms. However, it is preferable to wait for the results of further experiments that I propose to do.

Postscript: While this paper was at the printer, I have been able to create a strongly polarizable membrane using substances common to the physiological milieu (parchment between a sodium phosphate solution and a calcium chloride solution). A preliminary study of this polarization shows notable deviations from the equation of a charging capacitor; the deviations are exactly of the size and direction required to explain the excitation of nerves.

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