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ILLUMINATIONS

The critical role of logarithmic transformation in Nernstian equilibrium potential calculations

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Sawyer JE, Hennebry JE, Revill A, Brown AM. The critical role of logarithmic transformation in Nernstian equilibrium potential calculations. *Adv Physiol Educ* 41: 231–238, 2017; doi:10.1152/advan.00166.2016.—The membrane potential, arising from uneven distribution of ions across cell membranes containing selectively permeable ion channels, is of fundamental importance to cell signaling. The necessity of maintaining the membrane potential may be appreciated by expressing Ohm's law as current = voltage/resistance and recognizing that no current flows when voltage = 0, i.e., transmembrane voltage gradients, created by uneven transmembrane ion concentrations, are an absolute requirement for the generation of currents that precipitate the action and synaptic potentials that consume >80% of the brain's energy budget and underlie the electrical activity that defines brain function. The concept of the equilibrium potential is vital to understanding the origins of the membrane potential. The equilibrium potential defines a potential at which there is no net transmembrane ion flux, where the work created by the concentration gradient is balanced by the transmembrane voltage difference, and derives from a relationship describing the work done by the diffusion of ions down a concentration gradient. The Nernst equation predicts the equilibrium potential and, as such, is fundamental to understanding the interplay between transmembrane ion concentrations and equilibrium potentials. Logarithmic transformation of the ratio of internal and external ion concentrations lies at the heart of the Nernst equation, but most undergraduate neuroscience students have little understanding of the logarithmic function. To compound this, no current undergraduate neuroscience textbooks describe the effect of logarithmic transformation in appreciable detail, leaving the majority of students with little insight into how ion concentrations determine, or how ion perturbations alter, the membrane potential.

equilibrium potential; logarithms; Nernst equation; potassium

THE CONCEPT of equilibrium potential, also called reversal potential, and the role that it plays in determining the membrane potential are of fundamental importance to understanding neural excitability (in this report, E_m denotes membrane potential, E_{rev} denotes a general description of the equilibrium/reversal potential, and E_K, etc. denotes the equilibrium potential for a particular ion). The Nernst equation, which determines E_{rev}, can estimate E_m in astrocytes, a glial cell subtype whose cell membrane is exclusively permeable to K^+ (23). The Goldman-Hodgkin-Katz voltage equation, an expansion of the Nernst equation that was developed to estimate the permeability changes that underlie the action potential (14), also functions to estimate the E_m of cells permeable to more than one ion (12).

Students who fail to grasp the Nernst equation are at a disadvantage, as they are inclined to learn rather than understand. The limitations of such a strategy may be readily appreciated by realizing that E_m is not a static property but varies in response to such processes as synaptic input and action potential generation. For example, students should intuitively be able to deduce the effects of altering the transmembrane concentrations of Na^+, K^+, or Cl^- on E_{rev} or E_m, and appreciate that in circumstances where $E_m \neq E_K$, that K^+ moves across the membrane in the direction that restores E_m toward E_K. However, students struggle to master the concept of how selectively permeable ion channels in the cell membrane combined with transmembrane ion gradients lead to a transmembrane potential difference, an issue that has been recognized (27) and repeatedly addressed (7, 17, 26, 33).

The Nernst equation may be regarded as comprising a conceptual component and a practical component. The conceptual component was addressed in a recent article (6) where models were proposed that described in an elegant and accessible manner movement of K^+ down a transmembrane concentration gradient via K^+-permeable ion channels, when intracellular K^+ (K_i^+) > extracellular K^+ (K_o^+). The work done or energy associated with such diffusion of ions (W_{diff}) can be quantified as follows: $W_{diff} = RT \ln K_o/K_i$ [where R is the gas constant (8.315 $V \cdot C \cdot K^{-1} \cdot mol^{-1}$) and T is temperature (in K)], implying that the steeper the transmembrane concentration gradient, the greater the energy generated. However, this diffusion creates a potential difference across the cell membrane, which drives K^+ from the outside to the inside of the cell; the resulting electrical work (W_{elec}) can be quantified as follows: $W_{elec} = E_K Fz$ [where F is Faraday's constant (96,480 C/mol) and z is the valence of the ion (unitless)]. Equilibrium occurs where the diffusional and electrical forces balance and there is no net movement of K^+. This can be expressed as $W_{diff} = W_{elec}$, which can be expanded into the following Nernst equation thus:

$$R\mathrm{T}\ln\frac{K_o}{K_i} = E_K Fz \quad (1)$$

$$E_K = \frac{R\mathrm{T}}{zF}\ln\frac{K_o}{K_i} \quad (2)$$

An accessible derivation of the Nernst equation can be found in Bertil Hille's classic textbook (12).

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This paper deals with the practical component, the mathematical operations required to solve the Nernst equation, and may be viewed as a companion piece to the conceptual description (6).

In describing E_{rev}, most neuroscience textbooks deliver contrived scenarios based on even concentrations of ions dispersed across a membrane that suddenly becomes selectively permeable to a particular ion (3) or describe existing uneven ion distributions (15) with no explanation as to how such a situation arose. These artificial descriptions deprive the student of the fascinating origins of the membrane potential, which date back >3.7 billion years to the emergence of the first life on earth. Although some aspects of the origins of life on earth remain contentious (18), a consensus opinion may be summarized as follows. The first single-celled prokaryotic organisms originated in a sea high in salt content with a Na^+-to-K^+ ratio of 5:1. A key definition of life is a cellular entity capable of reproduction; thus, life consisted of lipid membrane-bound sacks of cytoplasm containing RNA (1). An impermeant lipid membrane would have retained the intracellular macromolecules but would not have permitted the entry of nutrients or expulsion of waste products; thus, a permeable membrane favored cellular survival. The negatively charged intracellular proteins created an ion gradient favoring the entry of positively charged ions into the cell. However, the stability of RNA is compromised in high-Na^+ environments (8); thus, to balance the negative charge, the membranes evolved a selective permeability to K^+ while remaining relatively impermeable to Na^+ (12). The K^+ accumulation in the cell in excess of its extracellular concentration was sustained by Na^+-K^+-ATPase, which maintained a low intracellular Na^+ concentration and high intracellular K^+ concentration ($[K^+]_i$) (28). Thus, maintenance of a steep transmembrane K^+ gradient has been a feature of cells for billions of years and is fundamental in generating the negatively charged cell membrane potential. The negative membrane potential and high extracellular Na^+ concentration was exploited in the evolution of the action potential, the primary mode of cell-to-cell communication in the nervous system.

The Equilibrium Potential

Complex relationships exist between ion concentrations, fluxes of ions across selectively permeable cell membranes, and the resulting voltage differences across cell membranes. However, if certain basic assumptions are accepted, namely, if one assumes the flow of ions across a cell membrane is one-dimensional and that the voltage gradient is perpendicular to the membrane, then the relationship between ion fluxes and voltage gradients can be described by the transport equation (32). This equation can be further simplified to the Nernst equation by assuming that the membrane is permeable to only one ion and that net flux of all ions is zero. The Nernst equation introduces the concept of the equilibrium potential of an ion that is distributed across a semipermeable membrane and is defined as the electrical potential at which there is no net ion movement across the membrane, due to transmembrane concentration gradients being balanced by uneven electric charges across the membrane. The relationship is derived ultimately for an individual ion, such as a representative cation (A^+), as follows:

$$E_{rev} = \frac{RT}{zF} \ln \frac{[A^+]_o}{[A^+]_i} \quad (3)$$

where E_{rev}, the point of zero current flow, is the reversal potential for A^+ (in V) (12). In the context of ions distributed across a cell membrane, $[A^+]_o$ and $[A^+]_i$ are the extracellular and intracellular concentrations of cation A^+, respectively. As mammals maintain a constant body temperature and laboratory experiments tend to be carried out at fixed temperatures, the Nernstian relationship may be simplified, since RT/F can be expressed as a single number relative to a fixed temperature, e.g., 26.7 mV at 37°C. This value is unaffected when the value of z, the number of elementary charges per ion, is +1, as is the case with Na^+ and K^+. In addition, the constant for converting from the natural logarithm (ln) to $\log_{10}$ is 2.303. Thus, the Nernst equation at 37°C simplifies to the following:

$$E_{rev} = 61.5 \log_{10} \frac{[A^+]_o}{[A^+]_i} \quad (4)$$

For anions, e.g., Cl^-, where $z = -1$, RT/zF at 37°C is −26.7; thus, E_{Cl} is expressed as follows:

$$E_{Cl} = -61.5 \log_{10} \frac{[Cl^-]_o}{[Cl^-]_i} \text{ or } E_{Cl} = 61.5 \log_{10} \frac{[Cl^-]_i}{[Cl^-]_o} \quad (5)$$

The second expression is a result of $\log(a/b) = -\log(b/a)$ (see below). However, this is as far as elementary undergraduate textbooks proceed with the equation (3, 21), leading to students learning the equation rather than understanding how each of its constituent parts contributes to E_{rev}. According to *Eq. 3*, E_{rev} varies linearly with temperature and logarithmically with the ion concentration ratio, but no information is given regarding how logarithmic transformation affects the ion concentration ratio. This is not a trivial point as the ion concentration ratio can be positive, negative, or equal to 1, with each condition responding differently to logarithmic transformation. Thus, to understand how ion concentrations affect E_{rev}, we must first describe the effects of logarithmic transformation.

Description of the Logarithmic Function

Detailed accounts of the development and implementation of the logarithmic function by Napier in 1614 can be found in the following reviews: Refs. 4, 5, 13, 19, and 31.

For our purposes, the following definitions will suffice:

$$\text{If } c^x = a, \text{ then } \log_c a = x \quad (6)$$

That is, the logarithm, to the base c (where $c \neq 1$), of a, is x.

The First Law of Logarithms (2) may be expressed as follows:

$$\log_c ab = \log_c a + \log_c b \quad (7)$$

In addition, the Second Law of Logarithms, whose derivation can be found elsewhere (2), is also fundamental in helping us to understand the effect of logarithmic transformation in Nernstian calculations, where

$$\log_c (a/b) = \log_c a - \log_c b \quad (8)$$

Logarithm to the Base 10

The logarithm to the base 10 ($\log_{10}$) is a convenient form by which to express numbers since it simplifies calculations based

on the decimal numbering system and clarifies the relationships between numbers separated by orders of magnitude, e.g., 3.14 and 31.4. Logarithms, such as 2.871, are composed of the characteristic and the mantissa, with the characteristic being the integral part (2) and the mantissa being the fractional or decimal part (0.871). As shown in Fig. 1*A*, it can be reasonably deduced that the characteristic of 743.2 is 2, since 743.2 lies between 100 and 1,000. Expressing a number in scientific notation (30), i.e., in the form $a \times 10^b$, where $1 < a > 10$ and b is the appropriate exponent or power, clarifies the conversion of a number to $\log_{10}$ since the characteristic can be deduced from Fig. 1*A* as the power or exponent required to express the number in scientific notation, i.e., 7.432×10^2. This is comparable to considering $\log_{10}743.2$ as being equivalent to $\log_{10}7.432 + \log_{10}100$ (*Eq. 7*), using the First Law of Logarithms. The mantissa of any number expressed in scientific notation is between 0 and 1 since the number, by definition, must lie between 1 and 10 (Fig. 1*A*). In this case, the mantissa is 0.871; thus, $\log_{10}743.2$ is equal to 2.871 (0.871 + 2). It should be readily apparent that one of the great advantages of the $\log_{10}$ system is that it relates numbers such as 743.2 and 7432, with the characteristic increasing by 1 for each order of magnitude increase in the number, the mantissa unchanged.

Figure 1*A* shows that $\log_{10}(<1)$ is a positive number, that $\log_{10}1 = 0$, and that $\log_{10}(>1)$ is a negative number. Although not immediately apparent, such simple relationships govern the association between E_{rev}, E_m, and transmembrane ion concentrations. Since $\log_{10}$ of any number >1 is negative, the polarity of E_{rev} can be deduced by a simple rule of thumb: if the extra- and intracellular concentrations of the ion are known, for cations, if the extracellular concentration is greater than the intracellular concentration, E_{rev} is positive, but if the reverse is the case, then E_{rev} is negative. Similar reasoning can be applied to anions. For example, under normal conditions, $[K^+]_o$ in the brain is ~5 mM, with $[K^+]_i$ = 150 mM (3). Since the ratio of $[K^+]_o$ to $[K^+]_i$ is >1, E_{rev} for K^+ is negative. Similarly, for Na^+, where the extracellular concentration is 150 mM and the intracellular concentration is 15 mM, E_{rev} for Na^+ is positive (3).

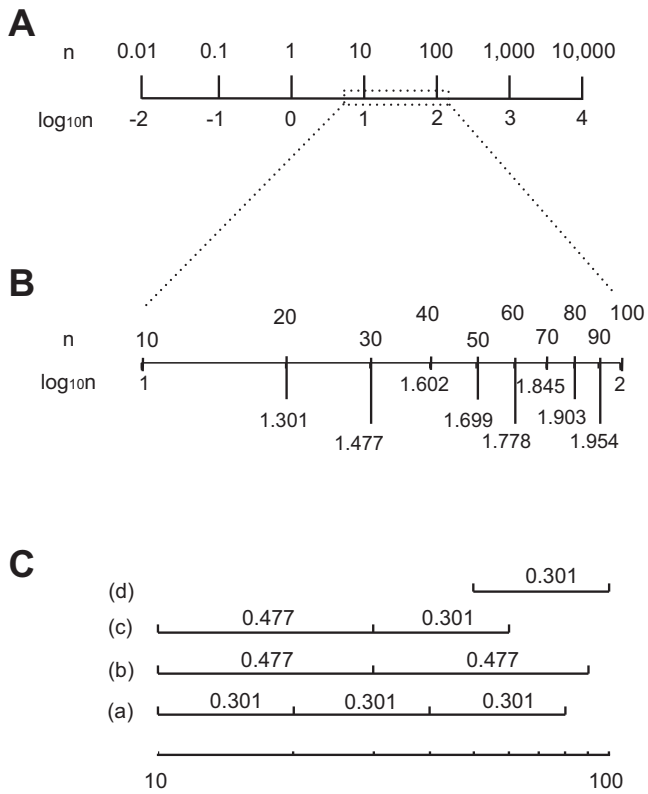

Fig. 1. Representation of data on a logarithmic scale. *A*: linear representation of the relationship between geometrical progression (*top*) of numbers (n) and the arithmetic progression (*bottom*) of the corresponding logarithms to the base 10 of the numbers ($\log_{10}n$). *B*: a logarithmic scale between 10 and 100 displays uneven intervals between numbers. *C*: the underlying concept that multiplication by a fixed amount moves data along the axis by a fixed distance on a logarithmic scale.

Logarithmic Graphing

In disciplines related to neuroscience, such as physiology and pharmacology, students will frequently encounter data plotted on logarithmic scales, with an understanding of such plotting required to comprehend the underlying scientific principles (22). This is especially true of plots of E_m versus $[K^+]_o$, where $[K^+]_o$ is conventionally plotted on a $\log_{10}$ scale (14). Plotting data on a $\log_{10}$ scale clarifies the logarithmic relationship, since on a linear scale moving a fixed distance along the axis moves the data along the axis by adding that fixed amount, whereas on a logarithmic scale moving a fixed distance involves multiplication by a fixed factor. Thus, the major ticks on a log scale increase by orders of magnitude when base 10 is used, such that the major ticks progress in the following sequence: 1, 10, 100, 1,000, i.e., each major increment is 10 times larger that the previous value, and the distances between 1 and 10, and 10 and 100, are equal. This can be shown in Fig. 1*B*, which shows the logarithmic scale from 10 to 100. It is apparent that the positions of the minor tick intervals are unevenly spaced, due to the scale being based on the $\log_{10}$ of the number rather than the number itself as occurs on a linear scale. The simple way to understand logarithmic scaling is to realize that the distance between 10 and 20, i.e., 0.301, is the distance gained along the x-axis by multiplying by 2. This is shown in Fig. 1*C*,*a*, which shows that the product of multiplying 10 by 2 (i.e., 20) results in a movement of 0.301 along the x-axis. Similarly, the product of 20 and 2 (40) gains 0.301 along the axis, as does the product of 40 and 2 (80) (i.e., $\log_{10}40 = \log_{10}20 + \log_{10}2 = 1.301 + 0.301 = 1.602$). Thus, the distances between 10 and 20, 20 and 40, and 40 and 80 are equal, the product of each calculation being the result of multiplication by 2. In a similar fashion, the distance from 10 to 30 and from 30 to 90 (0.477) represents multiplication by 3 (Fig. 1*C*,*b*). The value of 60 can be calculated by adding the distance between 10 to 30 (i.e., multiplication by 3) and 30 to 60 (multiplication by 2; Fig. 1*C*,*c*), and, finally, the position of 50 on the axis can be deduced by dividing 100 by 2, i.e., expressing $\log_{10}50$ as $\log_{10}(100/2)$ and using the Second Law of Logarithms to expand the expression, ultimately subtracting the distance between 10 to 20 from 100 (i.e., $2 - 0.301 = 1.699$; Fig. 1*C*,*d*). The conversion of multiplication into the movement of fixed distances along an axis is the basis of slide rule operation (29).

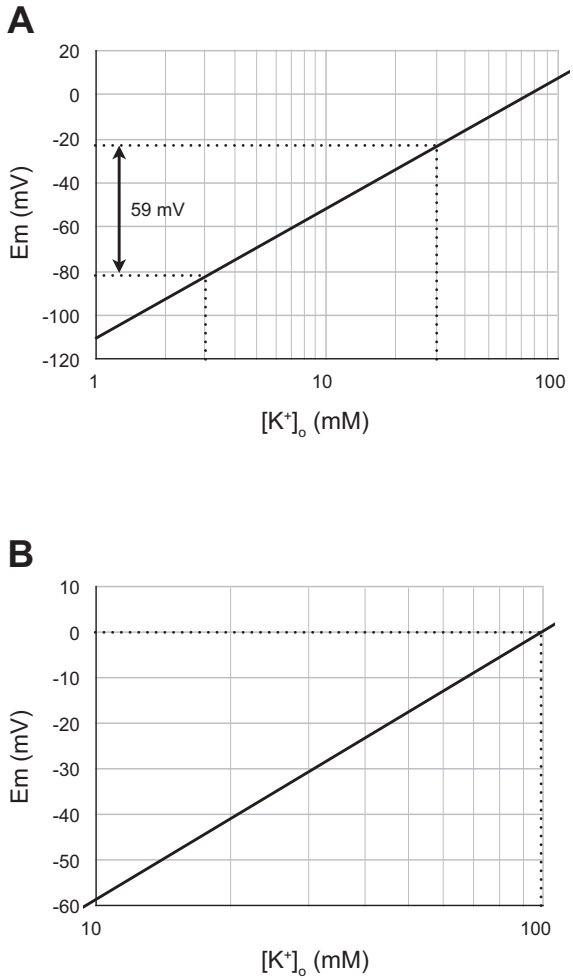

Fig. 2. Nernstian relationship between membrane potential (E_m) and extracellular K^+ concentration ($[K^+]_o$). *A*: a hypothetical cell permeable only to K^+, with a constant intracellular K^+ concentration ($[K^+]_i$) of 75 mM, shows a linear relationship (diagonal solid line) with $[K^+]_o$ plotted on a $\log_{10}$ scale. E_m depolarized 59 mV for each order of magnitude increase in $[K^+]_o$, e.g., raising $[K^+]_o$ from 3 to 30 mM depolarized E_m from −82 to −23 mV, a 59-mV shift (horizontal dotted lines). *B*: $[K^+]_i$ can be estimated by extrapolating from 0 mV (dotted horizontal line; see text).

Membrane Potential and $[K^+]_o$

The Nernst equation was applied in two classic papers from 1966, published by the American Physiological Society, in which Steven Kuffler and coworkers described the response of E_m of glial cells (equivalent to mammalian astrocytes) in the optic nerve of the mud puppy *Necturus* to alterations in $[K^+]_o$ (16) and to an electrical stimulus (20). These two experimental paradigms offer an ideal opportunity with which to illuminate how logarithmic transformation of transmembrane ion ratios determine E_m and how stimulus-induced, identical increases in $[K^+]_o$ result in attenuating E_m depolarizations. These were landmark studies as they showed, for the first time, using an equation based on logarithms, that the glial cell membrane was exclusively permeable to K^+. Appreciation of these papers can be enhanced by calculating how the E_m of a hypothetical cell, exclusively permeable to K^+, would respond to changes in $[K^+]_o$ by applying the appropriate values to the Nernst equation. Note that Kuffler et al.'s experiments were carried out at 23°C (thus, RT/F is 59 mV), and since the cell is exclusively permeable to K^+, it follows that E_m is equal to E_K:

$$E_m = E_K = 59\log_{10}\frac{[K^+]_o}{[K^+]_i} \quad (9)$$

The first step is to assume a reasonable estimate of $[K^+]_i$ of 75 mM (12) and that this value remains constant. E_m for a range of $[K^+]_o$ from 1 to 100 mM is shown in Fig. 2*A*, where plotting $[K^+]_o$ on a $\log_{10}$ scale reveals a linear relationship between $[K^+]_o$ and E_m, with the slope increasing by 59 mV for each order of magnitude increase in $[K^+]_o$. How can we explain this 59-mV shift in E_m in a simple, logical, and easy to understand manner?

We start by calculating E_m where $[K^+]_o$ is either 3 or 30 mM, with a constant $[K^+]_i$ of 75 mM, and using the First and Second Laws of Logarithms (see *Eqs. 10–14* in Table 1).

Note that the only difference occurs in *Eq. 12*, where the First Law of Logarithms is used to expand $\log_{10}30$ into $\log_{10}10 + \log_{10}3$. The subsequent multiplication by 59 of the logarithmically transformed fragments reveals why E_m increases by 59 mV for each decade increase in $[K^+]_o$.

In the experiments carried out by Kuffler et al., the *Necturus* optic nerve was placed in a perfusion chamber; the composition of the artificial cerebrospinal fluid perfusing the tissue could be altered as desired. Glial cells were impaled with a sharp microelectrode, and E_m was continuously recorded. Kuffler et al. found that the glial cell E_m of *Necturus* behaved in the same way as the hypothetical cell, with a 59-mV shift in E_m for a decade increase in $[K^+]_o$ (see Fig. 8 in Ref. 16), which we have reproduced in Fig. 2*B*. These data strongly indicated that K_o^+ controlled the E_m of the glial cell to the extent that increases in $[K^+]_o$ depolarized E_m in a manner predicted by the Nernst relationship, validating the assumption that in *Necturus* optic nerve glial cells, E_m was equal to E_K.

Table 1. *Calculation of E_m where $[K^+]_o$ is either 3 mM or 30 mM, with a constant intracellular K^+ concentration of 75 mM, and using the First and Second Laws of Logarithms*

3 mM $[K^+]_o$	30 mM $[K^+]_o$	Equation
$E_m = 59\ \log_{10}(3/75)$	$E_m = 59\ \log_{10}(30/75)$	*10*
$E_m = 59 \times (\log_{10}3 - \log_{10}75)$	$E_m = 59 \times (\log_{10}30 - \log_{10}75)$	*11*
	$E_m = 59 \times (\log_{10}10 + \log_{10}3 - \log_{10}75)$	*12*
$E_m = 59 \times (0.477 - 1.875)$	$E_m = 59 \times (1 + 0.477 - 1.875)$	*13*
$E_m = 28.1 - 110.6 = -82.5$ mV	$E_m = 59 + 28.1 - 110.6 = -23.5$ mV	*14*

E_m, membrane potential; $[K^+]_o$, extracellular K^+ concentration.

Estimating the Value for $[K^+]_i$

Kuffler et al. then used the Nernst equation to estimate the value of $[K^+]_i$ in the following way. As shown in Fig. 1*A*, $\log_{10}1 = 0$; thus, where the concentrations of $[K^+]_o$ and $[K^+]_i$ are equal, $\log_{10}[K^+]_o/[K^+]_i = 0$ and, therefore, $E_m = 0$ (Fig. 2*B*). Kuffler et al. showed experimentally that where $E_m = 0$ mV, $[K^+]_o = 99$ mM and, thus, $[K^+]_i = 99$ mM also, illustrating how understanding the Nernst equation allows estimates of intracellular concentrations of ions, measurements that were beyond the technical capabilities of the day.

Stimulus-Induced Changes in E_m

Individual stimuli. The effect of axon impulses on the E_m of glial cells was investigated by stimulating the intact nerve with 10 pulses at a frequency of 10 Hz while the E_m of glial cells was recorded with sharp electrodes (see Fig. 4 in Ref. 20; redrawn in Fig. 3*A*). Frankenhauser and Hodgkin provided clear evidence of K^+ efflux during the repolarising phase of an action potential (9), data since confirmed with K^+-sensitive microelectrodes (25). Given the low resting $[K^+]_o$, long duration of K^+ channel opening, and small interstitial space, there is a measurable rise in $[K^+]_o$ resulting from action potential conduction, with repetitive firing resulting in significant and prolonged $[K^+]_o$ elevations (25). The stimulus-induced transient glial depolarizations are shown when nerves were bathed in $[K^+]_o$ of 3, 4.5, and 1.5 mM. As previously calculated (*Eq. 9*), E_m of a *Necturus* glial cell perfused with 3 mM $[K^+]_o$ and 99 mM $[K^+]_i$ is -89 mV. The increase in $[K^+]_o$ that underlies the stimulus-induced transient 12-mV depolarization (Fig. 3*A*, *left* trace) can be calculated as follows:

$$(-89 - 12) = 59\log_{10}\frac{[K^+]_o + 3}{99} \quad (15)$$

$$-1.305 = \log_{10}\frac{[K^+]_o + 3}{99} \quad (16)$$

which can be rearranged according to *Eq. 6* as follows:

$$10^{-1.305} = \frac{[K^+]_o + 3}{99} \quad (17)$$

$$[K^+]_o = 1.9 \text{ mM} \quad (18)$$

Thus, the stimulus causes release of sufficient K^+ from the axons into the interstitial space to increase $[K^+]_o$ by 1.9 mM. Similar reasoning was used by Hodgkin and Katz to calculate the attenuation in action potential amplitude when $[Na^+]_o$ was decreased in squid giant axons (see Fig. 6 in Ref. 14).

In *Necturus* nerves bathed in 4.5 mM $[K^+]_o$, E_m can be calculated, as previously demonstrated in *Eq. 9*, as follows:

$$E_m = 59\log_{10}\frac{4.5}{99} = -79 \text{ mV} \quad (19)$$

At a baseline value of 4.5 mM $[K^+]_o$ stimulus will augment this to (4.5 + 1.9 mM) 6.4 mM, and hence the stimulus-induced transient depolarisation can be calculated as follows:

$$E_m = 59\log_{10}\frac{6.4}{99} = -70 \text{ mV} \quad (20)$$

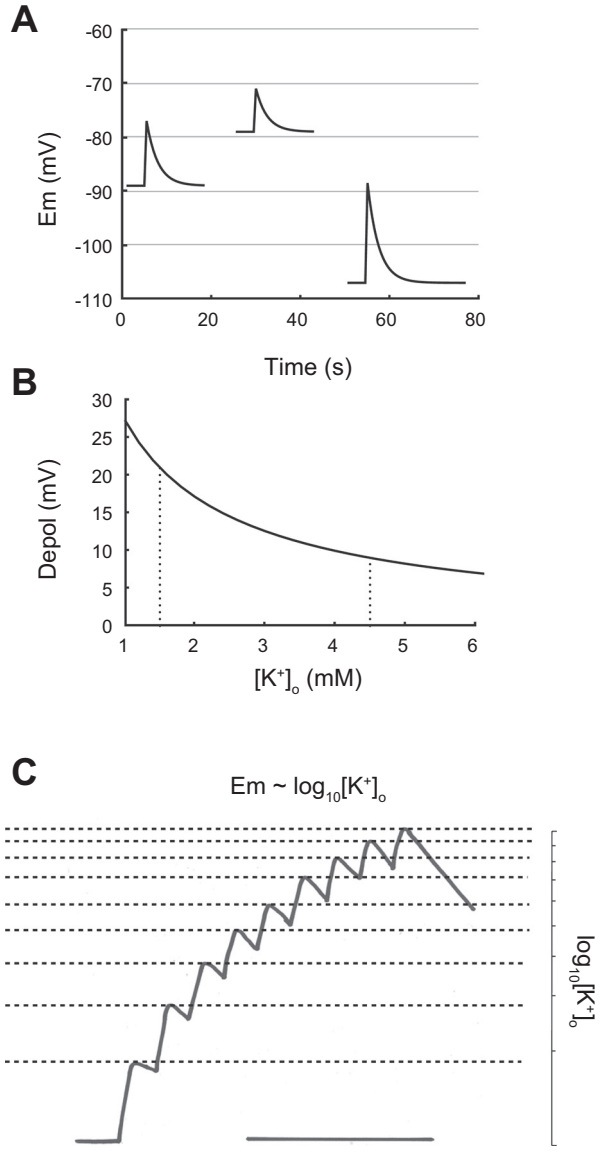

Fig. 3. Stimulus-induced changes in glial E_m. *A*: redrawn Fig. 4 from Ref. 20 demonstrating the stimulus-evoked transient depolarization of the glial cell membrane in *Necturus* optic nerves bathed in 3 mM (*left* trace), 4.5 mM (*middle* trace), and 1.5 mM (*right* trace) $[K^+]_o$. *B*: calculated stimulus-evoked depolarization that would occur in glial cells bathed in $[K^+]_o$ over the range of 1-6 mM. The dotted lines border the $[K^+]_o$ used experimentally (20). Note that this relationship is what one would obtain by subtracting the open circle data points from the corresponding resting E_m in Fig. 5 of Ref. 20. *C*: diminished amplitude of *Necturus* glial E_m depolarization in response to sequential stimuli. The vertical $\log_{10}$ scale shows the attenuation of fixed increases in $[K^+]_o$. The experimental trace was redrawn from Fig. 6 of Ref. 20 to show the attenuation of E_m depolarization in response to nine sequential stimuli. The horizontal scale bar is 5 s; the vertical axis (in mV) was omitted due to the qualitative nature of our description.

Similarly, for 1.5 mM baseline $[K^+]_o$, E_m is -107 mV, and the stimulus causes a depolarization to -86 mV.

The depolarization induced by identical stimuli to those imposed during the experiment (i.e., stimuli that will release sufficient K^+ from axons to increase $[K^+]_o$ by 1.9 mM) over a range of $[K^+]_o$ from 1.5 to 4.5 mM can be calculated by subtracting the E_m calculated with an additional 1.9 mM $[K^+]$ in the interstitial fluid from the E_m calculated as previously described (*Eq. 9*):

$$\text{Depolarization (in mV)} = 59\log_{10}\frac{[K^+]_o + 1.9}{99} - 59\log_{10}\frac{[K^+]_o}{99} \quad (21)$$

Note that the lower the $[K^+]_o$, and hence the more hyperpolarised the E_m, the greater the amplitude of the stimulus-induced depolarization (Fig. 3*B*).

Sequential stimuli. In subsequent experiments, Kuffler et al. measured E_m of *Necturus* optic nerve glial cells in response to a train of nine stimuli at a frequency of 10 Hz, 1 s apart. The response recorded offers an ideal opportunity to relate the effect of altering $[K^+]_o$ on E_m/E_K. If we adhere to the principal that identical stimuli increase $[K^+]_o$ by identical amounts, then we can assume that each of the nine stimuli increases $[K^+]_o$ by identical amounts. Under such circumstances, a simple way to understand the effects of $[K^+]_o$ on E_m is to visually relate the two properties. This can be done by plotting the $\log_{10}[K^+]_o$ versus the recording of E_m. The Nernst relationship in these conditions can be reduced to $E_m \sim \log_{10}[K^+]_o$ since RT/zF and $[K^+]_i$ remain constant (*Eq. 9*). For the purposes of clarity, we assume that each stimulus increases $[K^+]_o$ by one minor tick (Fig. 3*C*, *right* axis). By plotting $\log_{10}[K^+]_o$ on a vertical axis and aligning with E_m, it can readily be seen that, although not a perfect match, the increases in $[K^+]_o$ result in successive glial E_m depolarizations of diminishing amplitude. Such a relationship is succinctly expressed by the authors of similar experimental results, when they stated the following (24):

According to the K^+ theory each depolarizing step in the response to one of these equal K^+ increments and the diminishing amplitude of successive steps is simply a consequence of the logarithmic relationship between $[K]_o$ and membrane potential (i.e. the efficacy of a given K^+ increment in producing depolarization decreases as the ambient $[K]_o$ increases).

Workshops

In our interactions with students entering the first-year Neuroscience undergraduate course at the University of Nottingham, it has become apparent that they are unprepared for the rigors of the types of calculations using logarithmic transformation illustrated in this paper, despite the fact that many of these students possess A-level passes in Maths. This is particularly concerning as the A-level syllabus has the following goals regarding logarithms (10).

1. Understand the relationship between logarithms and indexes and use the laws of logarithms (excluding change of base),
2. Understand the definition and properties of e^x and $\ln x$, including their relationship as inverse functions and their graphs,
3. Use logarithms to solve equations of the form $a^x = b$ and similar inequalities, and
4. Use logarithms to transform a given relationship to linear form and, hence, determine unknown constants by considering the slope and/or *y*-intercept.

The most likely explanation for students' deficits in understanding logarithms is the perceived redundancy of the subject in the age of desktop computers/calculators/smartphones, which can easily carry out logarithmic transformation without the need to understand or navigate log tables, which only a generation ago was an absolute requirement for all students. In informal conversations with students, logarithms were viewed as antiquated and irrelevant, reinforcing the impression that most students regarded Maths as a difficult and inaccessible subject.

To reacquaint second-year Neuroscience students with the logarithmic function, we carried out revision workshops designed to identify deficiencies in students' knowledge followed by a 2-h workshop that covered the content of this paper, with a postworkshop assessment to determine any improvements in performance. At this stage of the course, students have had a 1-h introductory lecture on membrane potentials and the Nernst equation. In the first part of the workshop, students were given an exercise (APPENDIX A: *ASSESSMENT 1*) that was designed to test their knowledge of multiple areas related to logarithms (nomenclature, laws of logarithms, simple calculations, Nernst equation-related calculations, and complex calculations). Students were required to complete the test in 30 min; no calculators were allowed, and students were not forewarned about the test. The test was carried out anonymously to protect student privacy. Students were asked to write on the front of the test paper their mathematical qualifications and grade (e.g., B grade at A level). Sixty-five students contributed, and of those students, 21 students had passes at A-level Maths, whereas the other 44 students had achieved a General Certificate of Secondary Education in Maths, a lower qualification (for a description of the A-level system in England, see Ref. 11). Figure 4*A* shows the performance of students either possessing or lacking A-level Maths. The results are dismal, as of the 1,040 questions, only 75 were answered correctly (7.2%). There was no significant difference in the performance of those students possessing or lacking A-level Maths ($P = 0.47$ by Fisher's exact test). Within a week of carrying out the test, students were given a workshop covering the contents of this paper. Students were then reassessed within a few days with a new exercise (see APPENDIX B: *ASSESSMENT 2*), which was similar in structure and content to the initial test, to allow quantitative comparison of any improvement in performance. Postworkshop performance (Fig. 4*B*) showed a considerable improvement ($P < 0.0001$ by Wilcoxon's matched pairs single-ranked test). The data collected in the first workshop determined the extent of the problem that confronts students. Academic staff who were taught logarithms expect present-day students to possess an equivalent degree of understanding, but this is not the case. In circumstances such as these, students are reluctant to admit to such gaps in knowledge, and, thus, these deficits are not remedied. The workshop described in this paper, or equivalent variations, appears to be an effective means by which to address this issue.

The objective of this workshop was to determine if students understood the logarithmic transformation by applying the rules described in this paper. These results strongly suggest that no assumption of competency in logarithms can be made in incoming undergraduate Life Sciences students in the United Kingdom; the possession of A-level Maths no indicator of understanding in the subject. Students clearly benefit from remedial workshops that reinforce basic logarithmic descriptions and calculations. This is likely due to the fact that in the workshop we reinforced the role of the logarithm as integral to key processes (logarithmic transformation underlies the graphing of dose-response relationships that are ubiquitous in phar-

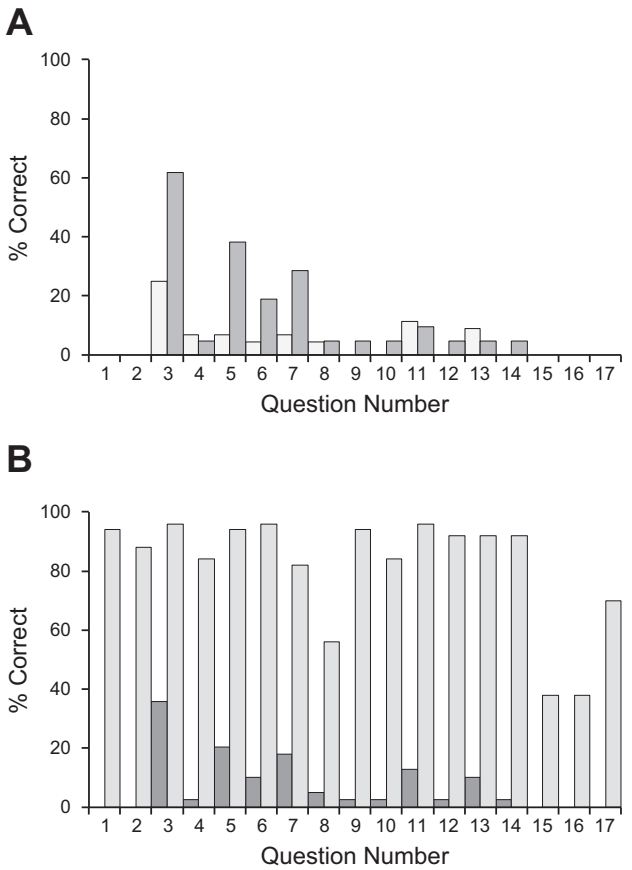

Fig. 4. Summary of student performance pre- and postworkshop. *A*: comparison of performance in the 16 questions of *assessment 1*. The results are normalized based on 65 student responses, and the students were categorized as lacking (light shaded bars) or possessing (dark shaded bars) A-level Maths. There was no significant difference between the two groups. *B*: postworkshop analysis showed a significant improvement in student performance postworkshop (light shaded bars) compared with preworkshop performance (dark shaded bars) based on the 16 questions of *assessment 2*.

macology, pH and Nernst equation calculations relating to membrane potentials) that must be mastered by students wishing to prosper in a Life Sciences degree. We would thus recommend a revision session is given to all incoming undergraduate Life Sciences students entering United Kingdom universities on the topics contained in this paper to bring all students to an equivalent level of understanding.

Discussion

Examination of classic physiology textbooks shows an attention to detail with regard to elementary physicochemical relationships that has not survived into the 21st century. It could reasonably be argued that the 45 pages devoted by J. Walter Woodbury (32) to the genesis of the membrane potential is excessive, but in his defense, all the information that an undergraduate is ever likely to need on the subject is present and can be skipped by the disinterested student, whereas to omit such information leaves the student in a state of ignorance. The general level of knowledge assumed by authors of previous generations with regard to the reversal/membrane potential can be appreciated when considering statements such as "the reversed potential difference which could be obtained by a mechanism of this kind might be as great as 60 mV, in a nerve with an internal sodium concentration equal to one tenth that of the outside" (14) and "As would be expected . . . equilibrium potentials change sign if the charge of the ion is reversed or if the direction of the gradient is reversed, and they fall to zero when there is no gradient" (12).

The omission of the rules of physics and physical chemistry that govern physiological processes in current textbooks is compounded by recent advances in technology that have rendered the requirements to understand the logarithmic function obsolete for everyday purposes. However, these technical advances have come at a cost, namely, an ill-conceived acceptance of redundancy of aspects of mathematics that are vital to students' understanding of fundamental physiological principles. In this paper, we have identified deficits in student understanding of the logarithmic function, which were remedied with a revision workshop, covering the contents of this paper. We sought to impress upon students the benefits of mastering the logarithmic function and reference two classic papers whose conclusions can only be fully appreciated if the application of the logarithmic function in the Nernst equation to membrane potential calculations is fully understood.

APPENDIX A: ***ASSESSMENT 1***

Answers to the questions are in parentheses.

Nomenclature of the Logarithm

1. What is the characteristic of 2.4? (2)
2. What is the mantissa of 3.6? (0.6)

Laws

3. How else can logab be expressed? (log$a$ + log$b$)
4. How else can log(a/b) be expressed? −[log(b/a)]

Simple Calculations

5. $\log_{10}100$ = _____ (2)
6. $\log_{10}0.1$ = _____ (−1)
7. $\log_{10}10{,}000$ = ____ (5)

Understanding the Logarithmic Scale

8. On a $\log_{10}$ scale, what is the ratio between the distance from 10 and 20 and from 20 and 80? (0.5)
9. If $\log_{10}30 = 1.477$, what is $\log_{10}900$? (2.954)
10. If $\log_{10}2 = 0.301$, what is $\log_{10}5$? (0.699)

Nernst Type Calculations

11. For anion A, if $[A]_o$ = 100 mM and $[A]_i$ = 10 mM, what is polarity of E_A? (−ve)
12. For cation B, if $[B]_o = [B]_i$, what is the value of E_B? (0 mV)
13. For cation A, if $[A]_o$ = 100 mM and $[A]_i$ = 10 mM, and for cation B, if $[B]_o$ = 1 M and $[B]_i$ = 1 mM, what is the ratio of E_A to E_B? (0.33)

Complex Calculations

14. What $[H^+]$ equates to pH 2.301? (0.005)
15. $\log_{10}0.0003$ = ____ (−3.523)
16. $\log_{10}0.3 + \log_{10}30$ = ____ (0.954)

APPENDIX B: ***ASSESSMENT 2***

Nomenclature of the Logarithm

1. What is the characteristic of 1.0? (1)
2. What is the mantissa of 4.9? (0.9)

Laws

3. How else can $\log_a b$ be expressed? ($\log b/\log a$)
4. How else can $-\log(a/b)$ be expressed? $\log(b/a)$

Simple Calculations

5. $\log_{10}1 =$ ____ (0)
6. $\log_{10}1{,}000 =$ ____ (3)
7. $\log_{10}0.01 =$ ____ (-2)

Understanding the Logarithmic Scale

8. On a $\log_{10}$ scale, what is the ratio of the distance from 10 and 30 and from 30 and 90? (1)
9. If $\log_{10}2 = 0.301$, what is $\log_{10}400$? (2.602)
10. If $\log_{10}50 = 1.699$, roughly what is $\log_{10}7$? (0.85)

Nernst Type Calculations

11. For anion A, if $[A]_i = 100$ mM and $[A]_o = 10$ mM, what is polarity of E_A? ($-$ve)
12. For cation B, if $[B]_o = 10[B]_i$, what is the polarity of E_B? ($+$ve)
13. For monovalent cation A, the value of $E_A = +60$ mV. What would the value of E_A be for a divalent cation if the value of $[A]_o$ was doubled and $[A]_i$ was unchanged? ($+40$ mV)

Complex Calculations

14. What $[H^+]$ equates to pH 3.301? (0.0005)
15. $\log_{10}0.02 =$ ____ (-1.699)
16. If $\log_{10}2 = 0.301$, what is $\ln_e 2$? (0.693)

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

J.E.R.S., J.E.H., A.R., and A.M.B. analyzed data; J.E.R.S., J.E.H., A.R., and A.M.B. drafted manuscript; J.E.R.S., J.E.H., A.R., and A.M.B. edited and revised manuscript; J.E.R.S., J.E.H., A.R., and A.M.B. approved final version of manuscript; A.M.B. conceived and designed research; A.M.B. prepared figures.

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