EXPONENTIATED EXPONENTIAL MODEL (GOMPERTZ KINETICS) OF NA$^+$ AND K$^+$ CONDUCTANCE CHANGES IN SQUID GIANT AXON

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ABSTRACT The conductance changes, $g_K(t)$ and $g_{Na}(t)$, of squid giant axon under voltage clamp (Hodgkin and Huxley, 1952) may be modeled by exponentiated exponential functions (Gompertz kinetics) from any holding potential V_0 to any membrane clamp potential V. The equation constants are set by the membrane potential V, and include, for any voltage step in the case of g_K, the initial conductance, g_0, the asymptote conductance $\mathring{g}$, and rate constant k: $g_k = \mathring{g}\exp(-be^{-kt})$ where $b = \ln \mathring{g}/g_0$. Equations of similar form relate $\mathring{g}$ and k to the voltage V, and govern the corresponding parameters of the g_{Na} system. For the g_{Na}, the fast phase $y = \mathring{y} \exp(-\mathbf{b}e^{-\mathbf{k}t})$ is cut down in proportion to a slow process $p = (1 - \mathring{p})e^{-\mathbf{k}'t} + \mathring{p}$, and thus $g_{Na} = py$. The expo-exponential functions involve fewer constants than the Hodgkin-Huxley model. In particular, the role of the n, m, h parameters appears to be filled largely by $\ln(\mathring{g}/g_0)$ in the case of g_K and by $\ln(\mathring{y}/y_0)$ in the case of g_{Na}. Membrane action potentials during current clamp may be computed from the conductances generated by use of the appropriate differential forms of the equations; diverse other membrane behaviors may be predicted.

INTRODUCTION

A most elegant and general model for many physical and biological exponential growth or die-off processes is that of Gompertz (1825), who devised an expression for the survivorship curve that provides the basis for actuarial tables. The Gompertz equation is a particular example of an exponentiated exponential, exemplified in differential form by Maxwell's well-known law of distribution of molecular velocities. The Gompertz equation $Y = \mathring{Y} \exp[\ln(\mathring{Y}/Y_0) \exp - (kt)]$ describes a simple exponential process in terms of a rate constant and an initial and an asymptotic value of the independent variable. The equation, illustrated in Fig. 1, is derived from the assumption that in a population of N members, the susceptibility of the individuals to destruction increases exponentially with time. By a change in sign of an exponent, the equation describes the time-course of growth instead of decay. In either case, it delineates a sigmoid curve that is asymmetric, unlike, for example the logistic $N = \mathring{N}/(1 + B\exp - kt)$, to which it may otherwise be compared (Winsor, 1932). The equation is discussed in various texts (Batschelet, 1971; Defares and Sneddon, 1961; Thrall et al., 1967).

The independent variable need not be time (Easton et al., 1976). For example, pressure, temperature, or the concentration of reactants acting in a properly circumscribed system may show Gompertzian kinetics in relation to the dependent variable, such as amount of product in a chemical reaction or frequency of impulses in a nerve.

The emphasis in this paper is on Gompertzian processes in nerve. In particular, I show that the Hodgkin-Huxley (H-H) (1952*c*) ionic conductance curves found in the voltage clamp experiment on squid axon can be well fitted by expo-exponentials. In this treatment, the rate of rise and the maximum conductance are set by the membrane potential, V, while the initial condition is specified by the holding potential, V_0. The equations describe, as do the original H-H equations, the time-course of the conductance change as it depends on the voltage step, and they allow the prediction of g_K and g_{NA} in relation to any arbitrary step or continuous change in membrane potential, including the action potential.

Among the many schemes put forth as alternatives to the original H-H formulation, the Gompertz method described here may be unique. Apparently all other schemes are in one way or another built upon ordinary simple exponential functions or polynomials, and require more constants to describe the events than the expo-exponential equations.

By means of three independent constants—an initial value y_0, an asymptote value $\mathring{y}$, and a rate constant k—the Gompertz formulation describes rate processes that require four constants in ordinary kinetics. In particular, the n, m, h terms in the H-H equations can be dispensed with, thus making unnecessary the processes postulated as required by those terms.

Preliminary notes concerning this material have appeared in abstract form (Easton, 1975, 1976).

GROWTH CURVES DESCRIBE K^+ AND Na^+ CONDUCTANCE OF AXON MEMBRANE

When the membrane potential of an impaled axon is clamped to a depolarizing level, the membrane conductance to K^+ (the g_K) increases along a sigmoid time-course. Hodgkin and Huxley (1952*c*) were able to fit the data for $g_K(t)$ by raising to a power ($n = 4$) the simple exponential decay of the difference between the initial conductance g_0 and the final conductance $\mathring{g}$.

If, instead of a simple exponential decay, an exponentiated exponential is used, the same data can be fitted at least as well, with only the specification of g_0 and $\mathring{g}$, and the required rate constant. The necessity for n has been eliminated and in a sense its role appears to be filled by the logarithm of the ratio $\ln \mathring{g}/g_0$, an intermediary parameter designated b. Sodium conductance (g_{Na}) can be computed by use of similar equations, with the work of m and h also being done essentially by b.

The expo-exponential equation describing the conductance change is derived from the assumption that the voltage step sets in motion an exponential increase in the conductance, and that the proportionality coefficient governing that growth does not remain constant, but decreases exponentially with time, as the "distance" to the maximum declines (see Discussion for derivation). Similarly, the expo-exponential rate (time) constants and the maximum level of conductance reached for each voltage step both show similar expo-exponential relations to the voltage. In sum, the conductance change is expo-exponentially related both to time and to membrane voltage.

In the equations to follow, lower case symbols are used for functions of t, upper case for functions of V. **Boldface** symbols specify the Na system, as does the symbol y. Subscripts Na and K refer to the respective sodium and potassium ions. Thus: k for $g_{K}(t)$, $\mathbf{k}$ for $g_{Na}(t)$, K for $\mathring{g}_{K}(V)$, $\mathbf{K}$ for $\mathring{g}_{Na}(V)$. The symbols are further clarified in Fig. 1.

The data used to demonstrate the Gompertz relations of g_K and g_{Na} are taken from H-H, 1952*c*. Records from their figures were projected and traced, and $g_K(t)$ and $g_{Na}(t)$ for the experimental points were tabulated. Estimates of the Gompertz constants were made from the projected curves, and these estimates, together with the tabulated values, were utilized by a statistical curve-fitting program to find more exact values of the constants (see Appendix).

TABLE I

SYMBOLS DESCRIBING CONDUCTANCE IN K^+ AND Na^+ SYSTEMS

K^+	Na^+	
g	$\mathbf{g}$	Membrane conductance at any time t, during voltage step, V.
$\mathring{g}$	$\mathring{y}$	Maximum conductance ($\mathring{y}$ in absence of g_{Na} inactivation) for any particular voltage step.
b	$\mathbf{b}$	Sets g_K or Y values at zero time. $b = \ln(\mathring{g}/g)$, $\mathbf{b} = (\ln \mathring{y}/y)$.
k	$\mathbf{k}$	For any voltage step, the proportionality ("rate") constant relating conductance increase and time.
	$\mathbf{k}'$	For any voltage step, the rate constant of the g_{Na} inactivation process.

The parameters above are established by the elemental constants following:

	N	Coefficient setting ratio between rate constants for inactivation and activation processes in $g_{Na}(t)$ (same for all voltage steps).
$\bar{g}$	$\bar{y}$	Maximum conductance ($\bar{y}$, in absence of g_{Na} inactivation) that the system approaches for large voltage step.
B	$\mathbf{B}$	Sets g or Y value at holding potential.
K	$\mathbf{K}$	Proportionality ("rate") constant relating $\mathring{g}_K$ (or $\mathring{y}$) to the voltage.
$\bar{k}$	$\bar{\mathbf{k}}$	Specifies maximum value of rate constants k and $\mathbf{k}$.
B'	$\mathbf{B}'$	Sets k (or $\mathbf{k}$) value at V_0, permitting $k(V)$ computation.
K'	$\mathbf{K}'$	Proportionality ("rate") constant relating k_K (or k_{Na}) to the voltage.

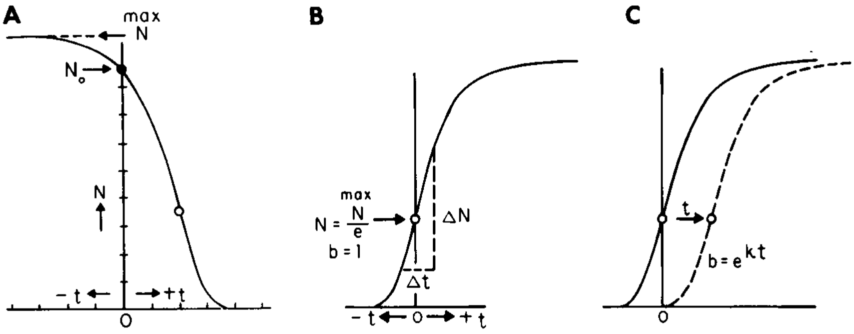

FIGURE 1 Gompertz equations describe die-off and growth processes. N, number of individuals in population at time t. $\mathring{N}$, asymptotic value toward which the population trends (B) or from which it starts (A). Circle indicates inflection point in each curve. A. Survivorship or die-off curve. The time $t = 0$ is placed so b is less than 1. B. Estimation of k value of Gompertz growth curve, from slope at inflection point. C. Estimation of b value from displacement of curve along horizontal axis necessary to bring inflection point to $t = 0$. Estimates of Gompertz constants made as shown in B and C are used to generate more accurate values by means of the curve-fitting program.

POTASSIUM CONDUCTANCE, $g_K(t)$

Hodgkin and Huxley (1952*c*), drew curves of $g_K(t)$ from $I_K(t)$ measurements on the basis of the definition $g_K = I_K/(V - V_K)$, and were then able to predict those same conductance curves from the assumption "that g_K is proportional to the fourth power of a variable which obeys a first-order equation", i.e. $g_K = \bar{g}_K n^4$; $dn/dt = \alpha_n(1 - n) - \beta_n n$. In this formulation, α and β are fixed by the voltage step, V, and generate n which yields g_K.

A Gompertz function with parameters set directly by V gives at least as good a fit as the H-H model. In Fig. 2 A, the data points from Fig. 3 of H-H 1952*c* are fitted by the equation:

$$g_K = \mathring{g} \exp(-be^{-kt}). \tag{1}$$

In this equation k is specific for any particular $g_K(t)$ curve. It specifies the "slope" of the curve and is determined directly by the magnitude of the voltage step. The maximum conductance $\mathring{g}$ is the asymptotic value which g_K approaches at $t = \infty$, while b sets the curve on the time axis.

$$\text{i.e., } b = \ln(\mathring{g}/g_0). \tag{2}$$

The best fit parameters for the set of $g_K(t)$ curves were plotted: $\mathring{g}_K(V)$ and $k_K(V)$. These relations could be expressed as Gompertz growth curves. The best-fit values for these curves were then found by the curve-fitting program.

Figs. 2B and C show that the members of the family of $g_K(t)$ curves are tied together by expressions in which the equation parameters $\mathring{g}$ and k are set by a Gompertz relation

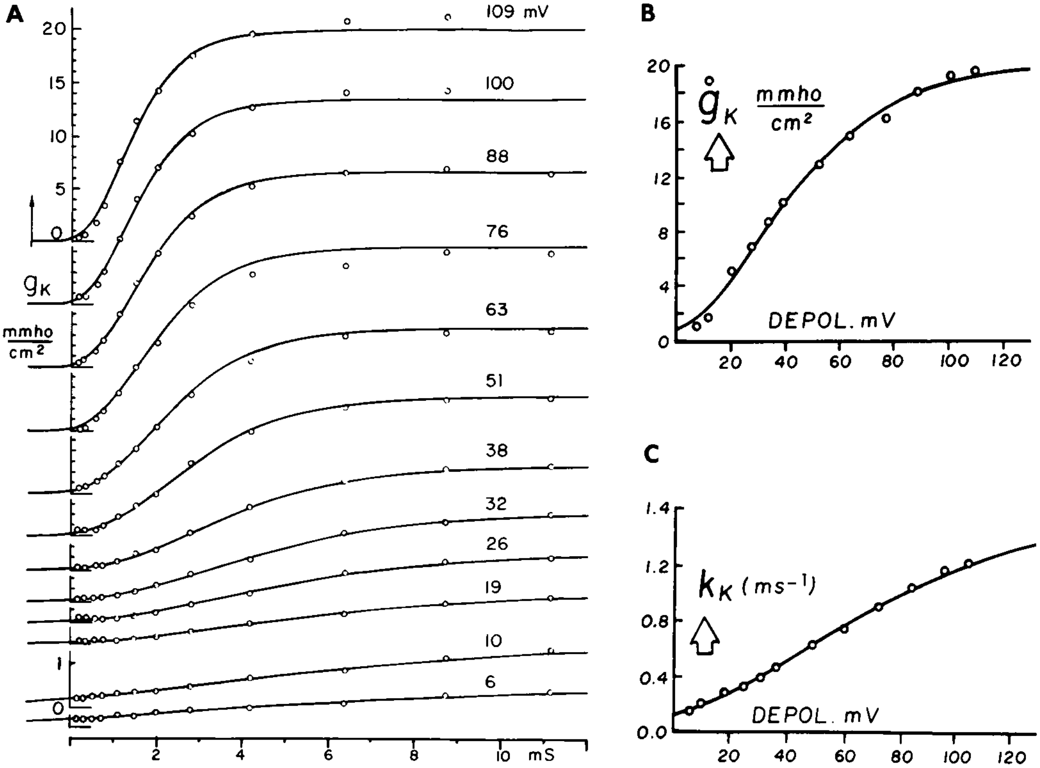

FIGURE 2 A. Gompertz growth curves describe K^+ conductance $g_K(t)$ resulting from voltage clamp step. Points are experimentally determined conductance changes for K^+, according to Hodgkin and Huxley, 1952*c*, Fig. 3. Voltage steps in millivolts at right. For each set of points, a line is drawn that is the best-fit Gompertz growth curve for Eq. 1 (Table II). B. Gompertz maxima are set by voltage steps (Eq. 3). Ordinate, asymptotic value of conductance (mmho/cm^2), Points for $\overset{\circ}{g}_K$, found to be best fit for each curve in Fig. 2 A. Abscissa, voltage steps, as in A, above. Line, from best fit Gompertz equation $\overset{\circ}{g}_K(V)$. See Table I for equations and constants. C. "Gompertz slope" rate constants are set by voltage steps. (Eq. 4). Ordinate, k_K (ms^{-1}) found to be best fit for each curve in Fig. 2 A. Abscissa, depolarization step in millivolts, considered positive (as in 2 A).

to the voltage step V. For $\overset{\circ}{g}_K$ the equation is: (Fig. 2B):

$$\overset{\circ}{g} = \bar{g}e \exp(-Be^{-KV}). \tag{3}$$

Here, $\bar{g}$ is the maximum conductance for K^+ that the system can show to the largest depolarization, under the given conditions and in the given state of the axon. The constant B sets the conductance at the holding potential V_0, while K is the proportionality ("rate") constant relating K^+ conductance to the membrane potential. For the time rate constant k, (lower case, see Eq. 1) the equation is (Fig 2 *c*):

$$k = \bar{k}e \exp(-B'e^{-K'V}), \tag{4}$$

where $\bar{k}$ is the maximum value of the time rate constant, B' is the shift factor, and K' is the rate constant for the rate at which the time rate constant changes with voltage. Thus, in place of α and β determining the conductance $g_K(t)$ indirectly through n, we have $\mathring{g}_K$, k_K generating $g_K(t)$ directly for a specific voltage step (see Table II for values).

SODIUM CONDUCTANCE, $g_{Na}(t)$

Hodgkin and Huxley (1952*c*) accounted for the time-course of sodium conductance during a step in V_M by two independent processes with different rate constants: first, Na^+ activation, described by a first-order, third-degree differential equation for m, determined by rate constants α_m and β_m; and second, Na^+ inactivation, h, controlled by rate constants α_h and β_h.

The transient rise in sodium conductance associated with a depolarizing pulse is of the form described by the first derivative of a Gompertzian growth curve, the product of two terms; the original Gompertz growth curve and a simple exponential decay curve:

$$g_{Na} \approx dY/dt = \mathring{Y} \exp(-\mathbf{b}e^{-\mathbf{k}t})\mathbf{kb}\, e^{-\mathbf{k}t}. \tag{5}$$

The apparently good fit obtained with Eq. 5 includes a predicted initial g_{Na} an order of magnitude or more too large. If the rate constant is adjusted to obtain a rapid rise and a lower initial value, then the subsequent fall is too rapid. To take care of both the rapid rise from a small initial level and the slow return to that same level, the equation was modified to give a finite level for the decay process to approach, and was supplied

TABLE II

GOMPERTZ EQUATIONS AND CONSTANTS FOR $g(t)$, DIFFERENTIAL EQUATIONS FOR $V(t)$

K^+ system	
(1) $g_K = \mathring{g}e^{-be^{-kt}}$	(2) $b = \ln(\mathring{g}/g)$
(18) $dg_K/dt = gk \ln(\mathring{g}/g)$	
(3) $\mathring{g} = \bar{g}^{-Be^{-KV}}$	(4) $k = \bar{k}e^{-B'e^{-K'V}}$
$\bar{g} = 20.2$ mmho/cm^2	$\bar{k} = 1.68$ mS^{-1}
$B = 3.20$	$B' = 2.78$
$K = 0.040$ mV^{-1}	$K' = 0.020$ mV^{-1}
Na system	
(6) $g_{Na} = yp$	$b = \ln(\mathring{y}/y)$
(7) $y = \mathring{y}e^{-\mathbf{b}e^{-\mathbf{k}t}}$	(8) $p = (p_0 - \mathring{p})e^{-\mathbf{k}'t} + \mathring{p}$
(22) $dy/dt = y\mathbf{k} \ln(\mathring{y}/y)$	(20) $dp/dt = -\mathbf{k}'(p - \mathring{p})$
$p_0 = 1$	(21) $\mathring{p} = G_0/\mathring{y}$
(12) $\mathbf{k}' = N\mathbf{k}$	
(13) $\mathring{y} = \bar{y}e^{-\mathbf{B}e^{-\mathbf{K}V}}$	(14) $\mathbf{k} = \bar{\mathbf{k}}e^{-\mathbf{B}'e^{-\mathbf{k}'t}}$
$\bar{y} = 44.8$ mmho/cm^2	$\bar{\mathbf{k}} = 15.5$ ms^{-1}
$\mathbf{B} = 6.39$	$\mathbf{B}' = 2.50$
$\mathbf{K} = 0.046$ mV^{-1}	$\mathbf{K}' = 0.0180$ mV^{-1}
$N = 0.146$	

with two different rate constants, **k** and **k**′, for the growth and for the decay processes, respectively. Consistent with comments above, we define

$$g_{\mathrm{Na}} = py, \tag{6}$$

where y is a standard Gompertz growth equation,

$$y = \mathring{y} \exp(-\mathrm{b}e^{-kt}), \tag{7}$$

and p is a coefficient that describes the proportion that y reaches of its otherwise expected value. The coefficient p is described by a simple exponential decay from p_0 to $\mathring{p}$: or

$$p = (p_0 - \mathring{p})e^{-\mathbf{k}'t} + \mathring{p}. \tag{8}$$

Symbolizing the initial value of g_{Na} as G_0, we find, from Eq. 6.

$$p = g_{\mathrm{Na}}/y, \qquad p_0 = G_0/y_0, \qquad \mathring{p} = \mathring{g}/\mathring{y}. \tag{9, A, B, C}$$

During a voltage step, it appears that g_{Na} approaches a final value $\mathring{\mathbf{g}}$, equal to its initial value G_0. Therefore:

$$\mathring{\mathbf{g}} = G_0 = p_0 y_0 = \mathring{p}\mathring{y}. \tag{10 A}$$

The initial value $p_0 = 1$, by definition. Therefore,

$$\mathring{p} = y_0/\mathring{y} \text{ and } G_0 = y_0. \tag{10 B}$$

Thus

$$g_{\mathrm{Na}} = \mathring{y} - \mathbf{b}e^{-\mathbf{k}t}[(1 - G_0/\mathring{y})e^{-\mathbf{k}'t} + G_0/\mathring{y}]. \tag{11}$$

Further, assume

$$\mathbf{k}' = N\mathbf{k}, \tag{12}$$

i.e. that the decay (inactivation) process occurs at a rate that is the same fraction of the growth (activation) process at all depolarizations. This is the simplest relation that can be postulated to exist between the two rates, and it was approximately verified when the equation was fit individually to the g_{Na} data sets.

The $\mathring{y}(V)$ and $\mathbf{k}(V)$ relations are clearer when the fitting program includes the specification that G_0 shall be a common value for all voltage steps. This is a reasonable stipulation, since the voltage step cannot influence the value of G_0. The program further includes the command to estimate a common value of N for the entire set of curves.

The $g(t)$ data points resulting from a particular voltage step were used to generate constants for the line of best fit through those points. Each such individual fit is shown as a solid line in Fig. 3A. When the fit was made collectively, that is, a common value of G_0 and a common value of N for all the data sets were called for, discrepancies accumulated at the smallest depolarizations, as shown by the dashed lines.

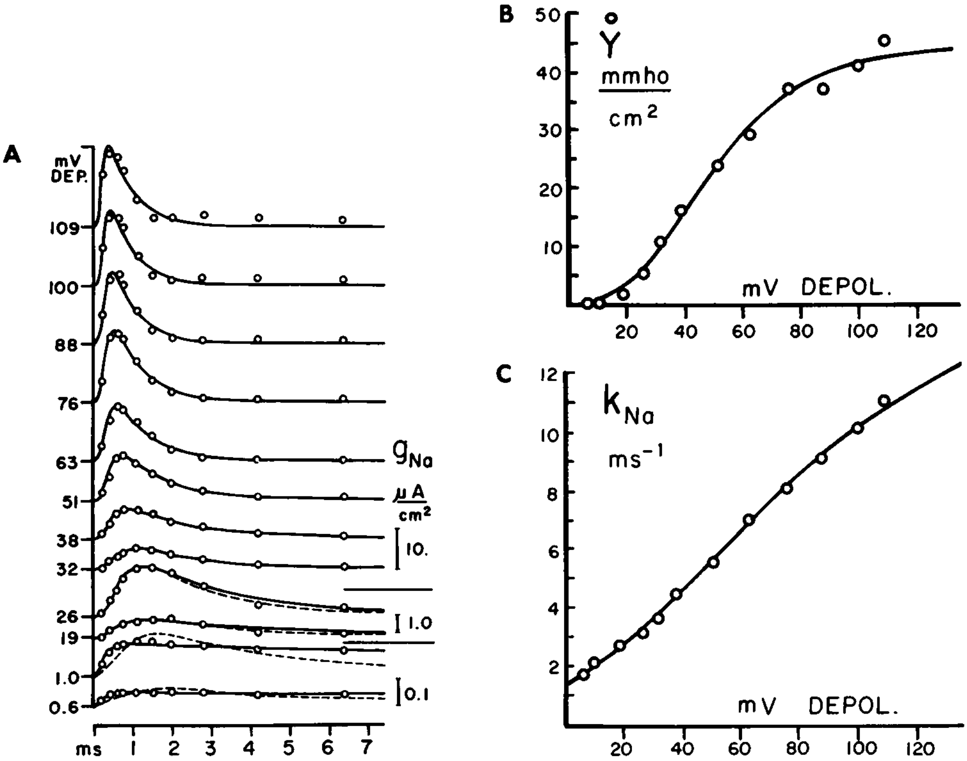

FIGURE 3 A. Gompertz kinetics-fit $g_{Na}(t)$ curves. Experimental points were taken from Hodgkin and Huxley (1952*c*, Fig. 6) show time-courses of g_{Na} for each voltage step noted at left. Scales for g_{Na} in three ranges shown at right. Lines: Best-fit curves generated from product of a Gompertz growth curve and a modified exponential decay curve (Eq. 11). Solid lines from individual fit for each curve. Dashed lines show fit adjustment when g_{Na0} and N of Eq. 12 are common for all curves (see text). B. Gompertz maxima are set by voltage steps (Eq. 2). Ordinate, Asymptote value of conductance (mmho/cm^2) (points) for $\mathring{y}$, found to be best fit for each curve in Fig. 3 A. Abscissa, voltage steps, as in A, above. Line from best fit "Gompertz" equation $\mathring{y}(V)$. See Table II for equations and constants. C. Gompertz slope rate constants are set by voltage steps. (Eq. 14). Ordinate, k (ms^{-1}) found to be best fit for each curve in Fig. 2 A. Abscissa, depolarization step in millivolts, considered positive (as in 2 A).

The parameters of the conductance curves change systematically with the voltage step, as shown in Figs. 3 B–C; equations relating those parameters to the membrane potential were devised with values of the constants appropriate to the given holding potential, $V_0 = 0$. The equations take the same form as those used for g_K:

$$\mathring{y} = \bar{y}\exp(-\mathbf{B}\mathbf{e}^{-\mathbf{K}\mathbf{V}}), \tag{13}$$

$$\mathbf{k} = \mathbf{k}\exp(-\mathbf{B}'e^{-\mathbf{K}'\mathbf{V}}). \tag{14}$$

Thus the constants, **k**, **k**$'$ (= N**k**), $\mathring{y}$, are set by the voltage and thereby allow, for any voltage step, the calculation of $g_{Na}(t)$.

The real test for these equations as a model for the excitable membrane is the generation of an action potential. The rules governing the Gompertz parameters during continuous change in V can be inferred from the response to step changes in V.

Hodgkin and Huxley showed that the membrane action potential could be found from the solution of the equation:

$$\mathrm{d}V/\mathrm{d}t = I_M - g_{\mathrm{K}}(V - V_{\mathrm{K}}) - g_{\mathrm{Na}}(V - V_{\mathrm{Na}}) - g_L(V - V_L). \qquad (15)$$

It is only necessary therefore, to find g_{K} and g_{Na} in terms of expo-exponentials.

The proper form of differential equation for $g_{\mathrm{K}}(t)$ is derived as follows: Using g for K^+ conductance, take logs of Eq. 1:

$$\ln\,(g/\mathring{g}) = -\,be^{-kt}. \qquad (16)$$

Differentiate Eq. 1 with respect to t and substitute into Eq. 16, inverting the ln ratio

$$\mathrm{d}g/\mathrm{d}t = gkbe^{-kt}, \qquad (17)$$

$$= gk\,\ln\,(\mathring{g}/g). \qquad (18)$$

The parameters k and $\mathring{g}$ are obtained from Eqs. 2 and 3.

The differential equation for $g_{\mathrm{Na}}(t)$ may be obtained directly from Eq. 6:

$$\mathrm{d}g_{\mathrm{Na}}/\mathrm{d}t = y(\mathrm{d}p/\mathrm{d}t) + p(\mathrm{d}y/\mathrm{d}t), \qquad (19)$$

noting from Eq. 8 that $\exp - (kt) = (p - \mathring{p})/(p_0 - \mathring{p})$, we see that the differential equation that gives rise to p (Eq. 8) is:

$$\mathrm{d}p/\mathrm{d}t = -\,\mathbf{k}'(p - \mathring{p}), \qquad (20)$$

where

$$p = g/y,\ \mathring{p} = G_0/Y. \qquad (21)$$

The differential equation for y may be derived in the same way as that for g (Eqs. 17-18), but starting with Eq. 7:

$$\mathrm{d}y/\mathrm{d}t = y\mathbf{k}\,\ln\,(\mathring{y}/y). \qquad (22)$$

Substitute Eqs. 20 and 22 into Eq. 19, and solve for $g_{\mathrm{Na}}(t)$. The parameters k_{Na} and $\mathring{y}$ are obtained from Eqs. 13 and 14. Thus the conductances necessary for computing the action potential are obtained directly by use of a single rate constant for the K^+ system and two additional rate constants for the Na^+ system, plus constants that define the range of the conductance changes available for each system.

The action potentials were then computed according to the following plan: For the initial condition, $V = 0$, and $t = 0$, the sum of I_{Na} and I_{K} was computed. Therefrom, the leakage current was determined; assuming $V_{\mathrm{L}} = 10.613$ mV (H-H 1952*c*), g_{L} was

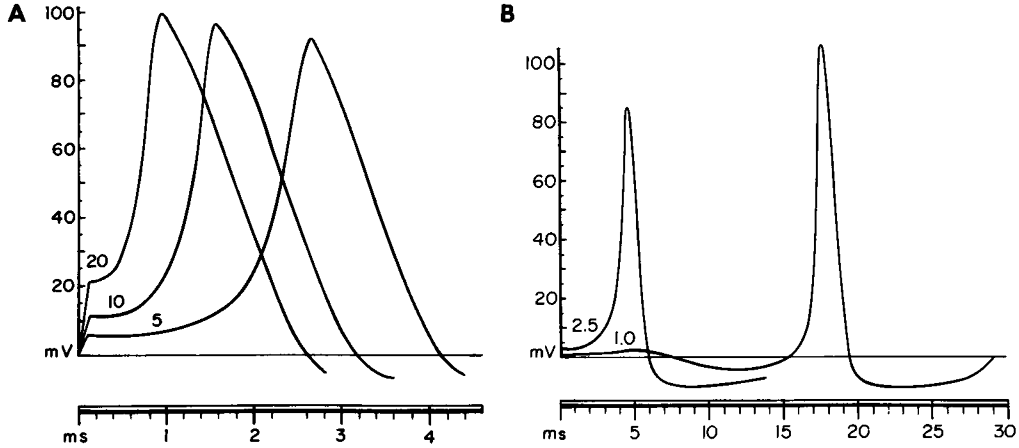

FIGURE 4 Action potentials computed from bounded exponential expression for conductance. Lines are solutions of H-H action potential equation (Eq. 15), when g_K is computed from Eq. 18 with parameters set by Eqs. 2 and 3, and g_{Na} is computed from Eqs. 19–22, with parameters set by Eqs. 13 and 14. A. Effect of different stimulus intensities: 5, 10, and 20 μA. B. Computed response to 10 μA and to 2.5 μA, same as corresponding response in Fig. 4 A, except the time scale was changed to show after-hyperpolarization and repetition. Small stimulus produces a subthreshold response, followed by after-hyperpolarization and a spike.

then computed so that the net current was 0 at $V = 0$. When a stimulus was given, the resulting voltage change generated changes in the Gompertz parameters, Y, $\mathring{g}_K$, k_K, and k_{Na}, so that new levels of g_K and g_{Na} were produced. Numerical integration of the action potential equation was carried out according to standard procedures. The equations used for the calculation are those in Table II, together with Eq. 15.

The differential equations were solved numerically by use of a Runge-Kutta subroutine program. Typical solutions are shown in Fig. 4.

MECHANISM OF GOMPERTZ KINETICS OF CONDUCTANCE CHANGES

The expo-exponential equations do not identity a specific mechanism responsible for the conductance change, but suggestions can be made in terms of the assumptions of Gompertz kinetics. The change in g_K may be understood as follows. The conductance g is defined as the ratio of the rate of movement of charge to driving force. For a particular voltage step, the effectiveness of that driving force in moving the charges diminishes according to the number of charges moved, for the accumulating charges set up a counter-force. When in fact they exert a force equal to the applied driving force, then there will be no further movement of charge, i.e. the conductance has reached its ceiling.

Assume that the conductance increases exponentially with time, i.e.,

$$dg/dt = rg, \tag{23A}$$

where r is the specific rate coefficient describing the fractional increment of conductance for small equal intervals of time. Assume that this rate coefficient decreases exponentially with time. Then:

$$dg/g dt = r = r_0 e^{-kt} \tag{23 B}$$

To obtain the time-course of the conductance change, integrate g with respect to t, from g to $\mathring{g}$.

$$\int dg/g = \int r_0 e^{-kt}\, dt, \tag{24}$$

$$\ln g]_{g}^{\mathring{g}} = -\, r_0 e^{-kt}/k]_{t}^{t=\infty}. \tag{25}$$

at $\mathring{g}$, $r_0 e^{-kt} = 0$; therefore

$$\ln \mathring{g} - \ln g = r_0 e^{-kt}/k, \tag{26}$$

$$g = \mathring{g} \exp\left(-(r_0/k)e^{-kt}\right). \tag{27}$$

Define $r_0/k = b$, to obtain the classical Gompertz equation, corresponding to Eq. 1. Note that at $t = 0, g = g_0$, and $b = \ln(\mathring{g}/g_0)$.

If the independent variable is something other than time, the derivation is similar. The asymptote $\bar{g}$ associated with a voltage step reflects the total conductance that can be mobilized by the particular voltage step. Assume that in the Gompertz relation of conductance to voltage step, the specific growth rate of $\bar{g}$ with respect to V occurs at a rate R that decreases exponentially with voltage. Therefore we have the relation

$$d\mathring{g}/\mathring{g} dt = R = R_0 e^{-KV}, \tag{28}$$

which, integrated with respect to V from $\mathring{g}$ to $\bar{g}$, yields Eq. 3.

The $k(V)$ relation may be adduced from similar assumptions. At high V, there is an upper limit to k set by the density of the particles moved and the impediments they encounter in their movement. The fractional change in k brought about by equal increments of V decreases exponentially as V increases and the theoretical maximum k is approached; thus;

$$dk/k dV = R' = R_0' e^{-K'V}, \tag{29}$$

which, integrated, yields Eq. 4. The elemental relations of the g_{Na} system can be derived similarly, with the provision that the inactivation (p) system be added (Eq. 8).

PREDICTIONS FROM THE EQUATIONS

These equations allow the prediction of membrane behaviors such as are described in Hodgkin and Huxley's original papers, (H-H 1952*a*, *b*, *c*), in addition to those here detailed. As an example, consider the description of $g_{Na}(t)$ from any holding potential V_0 to any clamp voltage step V.

An initial conductance g_0 and the asymptote value $\mathring{g}$ of the conductance generated by the step are calculated from Eq. 2 by use of the value of V_0 and V, respectively. The value of the parameter **b** then follows from ln $(\mathring{y}/y_0)$ and **k** is computed from

Eq. 3, with $V = V$, the voltage step. The conductance $g_{Na}(t)$ can then be computed for any point up to time t, by use of Eq. 1. For hyperpolarization, if $\mathring{y}$ is the value of y at the voltage to which the step is returned, then y_0' is the value of y at the voltage from which the step is taken. The rate constant **k** is computed for the voltage to which the membrane is stepped ($V = 0$, for example).

The parameter **b** is a positive quantity in the growth equation, associated with depolarization, when $\mathring{y} > y_0$, but it becomes a negative quantity for hyperpolarization when $\mathring{y} < y_0$ and the equation is then a simple exponentiated exponential decay. Thus the same equation, with only change in sign of **b**, describes the conductance at pulse-off as well as at pulse-on. By use of these rules, the time-course of g_{Na} after pulse termination can be predicted to any time, as in Hodgkin and Huxley (1952*a*, Figs. 4 and 10).

Cole and Moore (1960) showed that prehyperpolarization delayed the onset of outward currents during voltage clamp. This effect is readily predicted from the present equations. Prehyperpolarization resets the zero reference level from which the conductance change proceeds consequent to the depolarization. In the equations relating $\mathring{g}_K$ and k_K to V, this means that the initial g_{K_0} from which the conductance rises will become less (Fig. 2 A). Note that the curve in Fig. 2 A showing the conductance achieved for any clamp voltage, i.e. $\mathring{g}(V)$, also describes the steady conductance for any holding potential, i.e. $g_0(V_0)$. Thus the quantity $b = \ln(\mathring{g}/g_0)$ for each voltage step will increase according to the extent of prehyperpolarization. The effect of an increase in b is to shift a Gompertz growth curve to the right, and that is in fact what happens to the g_K (and to the I_K) curve then generated by a reset to a particular depolarizing step.

The effect of prehyperpolarization will be less dramatic on g_{Na} than on g_K, since the slope of the latter curve at $-V$ is much greater than the slope of the former, and b will consequently be less changed after the prehyperpolarization.

RELATION TO *m, n, h*

Although the new equations do not exclude the presence of molecular gates in the sense of n, m, and h processes, neither do they seem to require them. In the H-H scheme, α_n, α_m, α_h, β_n, β_m, and β_h instantly take up new values when a voltage step is applied, and allow the generation of n, m, and h, which gives rise to g_K and g_{Na}. When expo-exponentials are used, on the other hand, k_K and k_{Na} instantly take up new values and generate g_K and g_{Na} directly when a voltage step is applied. The Gompertz model suggests that if there is an underlying process, which as it occurs, generates the conductance change, then the rate constant of that process is identical to the rate constant of the conductance change itself.

Coupling between activation (m) and inactivation (h) of conductance of the membrane to Na^+, suggested by Hoyt (1968), was demonstrated by Hoyt and Adelman (1970) (see also Goldman and Schauf, 1972; Armstrong, 1975). In this regard, the present scheme is particularly satisfactory because the rate constants bear a constant ratio to one another.

CONCLUSION

The Gompertz form of expo-exponential affords a new way of predicting squid axon voltage clamp conductance data. With one rate constant, generating a sigmoid curve, a Gompertz equation describes a simple exponential process, and the information about mechanism that it may convey ought therefore to be about the same as may be implicit in an ordinary simple exponential. The difference is that the Gompertz formulation can describe the full course of a process, $y(x)$, from exponential start to exponential conclusion, and it permits extrapolation of y, in positive or negative direction of x, when alteration of some parameter may make such extrapolation appropriate. This flexibility is created when the assumption is made that the rate of exponentiation of an exponential process changes exponentially with the independent variable. The Gompertz formulations give a simplicity of expression that allows easy description of processes that may otherwise require formidable complexities of ordinary kinetics. In sum, they appear to have as good or better predictive capabilities than ordinary kinetics, and with less trouble.

A crucial item in this versatility is the **b** term, an intermediate constant, a fact that has apparently escaped previous attention. It is specified by the ratio of the initial to the final state of the system, or by the rate of the initial rate of change of the independent variable (in respect to the dependent) to the rate at which that rate changes. It is a "shift factor," establishing the position on the horizontal axis of the curve it governs. However, it has no independent existence, and the conductance changes are predicted only on the basis of initial and final values of the conductance and the rate constant(s).

Asymmetric sigmoid curves such as $k(V)$ and $\mathring{g}(V)$ described by the Gompertz equation are particular instances of a general form appropriate to what are often described as cooperative processes. Gompertz kinetics, or more explicitly, the mathematics of expo-exponentials as here exemplified, may be the simplest way to handle those otherwise often intractable asymmetric sigmoid relationships.

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APPENDIX

Curve-Fitting

The curve constants were first estimated by hand, and were then evaluated more exactly by means of a statistical curve-fitting program provided by Dr. J. J. Louviere. The program was run on a CDC Cyber 73 Computer (Control Data Corp., Minneapolis, Minn.). The following is taken from the program description:

"The program function maximization is set up as a FORTRAN IV subroutine named MAX. The algorithm comes from a paper by Hooke and Jeeves (1961). They proposed a method for obtaining the extremum of a function by using a direct search computer subroutine. Unlike most classical methods of solution, the Hooke and Jeeves procedure does not demand knowledge of the first or second partial derivatives of the function. Two types of moves are performed in MAX. Exploratory moves increase or decrease the value of each variable by a fixed step size and thus establish the direction of future search. After a set of successful exploratory moves, a pattern move is performed. The pattern move duplicates all of those changes that were successful on the exploratory moves. In addition, exploratory moves are also performed to modify the pattern. If the pattern move is a success, another is performed. When all exploratory pattern moves fail, the exploratory move step size is reduced until the criterion for maximization is achieved."

Up to 50 parameters may be estimated by means of this program. The user must state the number of parameters, provide initial estimates, set the step size, and specify the number of iterations, and may hold constant any of the parameters.

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