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SCIENCE

Biological Response Curves

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Many growth and biological response curves have a sigmoid shape or can be considered to be portions of S-shaped curves. Such curves are similar to the graphic representations of electron and proton transfers (when all are plotted in an analogous way), and such curves can be described mathematically by using a general equation that is based on the mathematical expressions governing electron and proton exchanges. The purpose of this article is to identify the existing analogies and to show how certain growth and biological response curves conform to this relationship.

The general equation for the sigmoid curves under consideration is

$$X = K + f \log (A/B) \qquad (1)$$

where X is one of the variables in the system; K is a constant characteristic of the mid-point of the curve; f is a constant characteristic of the "spread" of the curve; and A/B is the ratio of two components of the system that act as a "buffer" pair.

In proton transfers, the titration curve is described within certain limitations by the familar Henderson-Hasselbalch equation:

$$pH = pK + \log \frac{[A^-]}{[HA]} \qquad (2)$$

For electron transfers, the voltage of an oxidation-reduction system is described by the equation:

$$E_h = E_0 + \frac{0.06}{n} \log \frac{[\text{oxid.}]}{[\text{red.}]} \qquad (3)$$

Both of these curves have been plotted in Fig. 1, the first for an acid whose pK is 5, the second for an oxidation-reduction system whose $E_0 = +0.2$ v and $n = 1$ and 2 (other systems would give identical curves). When the two equations are spread over the same distance on the abscissa, the curve for electron transfers coincides with the curve for proton transfers.

The f components of different S-shaped curves will obviously have no comparative value unless all such curves are considered on the same basis by making each $K = 1.0$. The f of the original curve divided by the original K will then give the F that corresponds to $K = 1$. Whereas the values for f in the original curves for electron and proton transfers are constant irrespective of the absolute value for K, the values for F corresponding to a K of 1.0 vary with the E_0 or pK at which the F is calculated.

An S-shaped curve conforming to the general equation will yield a straight line when log (A/B) is plotted as the ordinate against $X - K$ as the abscissa, and the slope of the line will equal $1/f$.

Normal Distribution

The Henderson-Hasselbalch equation is derived from the mass action formulation for the ionization of a weak acid:

$$\frac{[H^+] \times [A^-]}{[HA]} = K \qquad (4)$$

When the Henderson-Hasselbalch equation (Eq. 2) is differentiated in order to obtain the rate of change of the titration curve (*1*), the following equation for the buffer value is obtained.

$$\beta = \frac{\Delta B}{\Delta pH} = \frac{2.3\, K \times C \times H}{(K + H)^2} \qquad (5)$$

As is noted earlier, the usual way of plotting Eq. 2 in the form of $[A^-]/[HA]$ against pH yields a symmetrical S-shaped curve. Plotting Eq. 5 as buffer value against pH gives a normal frequency-distribution curve. Figure 2 shows the essential identity of such a buffer value curve with a normal distribution curve whose standard deviation is 1.

Thus the normal frequency-distribution curve is related to the symmetrical S-shaped curves that are characteristic of electron and proton exchanges. Thompson (*2*) has pointed out that "the bell-shaped and the S-shaped curves form a reciprocal pair, the integral and the differential of one another." So far as proton transfers are concerned, both types of curve are derived from the same fundamental mass-action relationship. The mean of a normal distribution curve corresponds to the K of an S-shaped curve, and the asymptotic "limits" of a distribution curve coincide with the practical "limits" of the S-shaped curves for proton and electron transfers. Hence, the mean of a normal distribution curve corresponds to the value obtained with an equal mixture of the two forms making up the "buffer" pair, while the practical limits ($\pm 3\sigma$) correspond to the values obtained when essentially only one of the two possible forms is present.

Response Curves

Many growth curves are symmetrical and identical with the curve for proton and electron transfers. Figure 3 shows the close parallelism between a number of unrelated growth curves and the S-shaped curve for electron and proton transfers shown in Fig. 1 when the abscissas and ordinates for all of these curves are made to coincide.

Some bioassay curves are S-shaped and conform to the same equation when it is expressed as follows.

$$\text{Dose} = K + f \log \frac{(\text{percentage responding})}{(\text{percentage not responding})} \qquad (6)$$

Plotting the percentage response as the ordinate is analogous to the usual plot of the ratio of $[A^-]/[HA]$ in a titration curve or the ratios of oxidized/reduced forms in electron transfers; the latter plots could equally well be considered to represent the percentage of acid neutralized or the percentage of a given substance oxidized.

Figure 4 shows the dose-response curves

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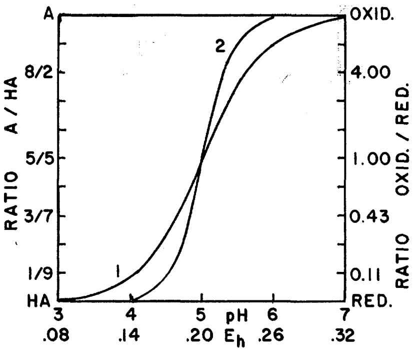

Fig. 1. Curves representing electron and proton transfers. (Curve 1) Titration curve for an acid, $pK = 5$, according to Eq. 2. The same curve results from the oxidation-reduction equation, Eq. 3, when $n = 1$. (Curve 2) Oxidation-reduction reaction when $n = 2$. Curve 2 would coincide with curve 1 if it were spread over the same distance on the x-axis. Note that the ordinate is not a linear plot of the ratio but is a regular progression that corresponds to a percentage of the maximum.

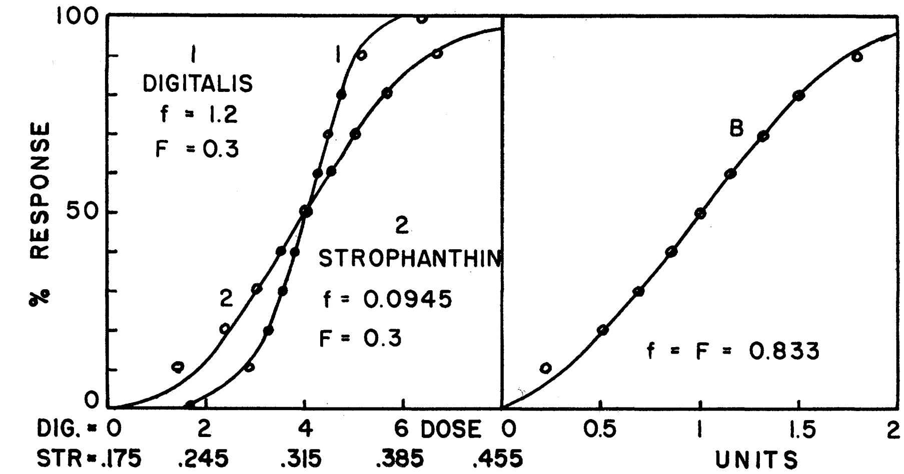

Fig. 4. The solid lines are dose-response curves for the assay of digitalis (curve 1), strophanthin (curve 2), and estrogen (curve B), according to Burn (*3, 4*). The values for f are calculated by substituting experimental data in Eq. 6. $F = f/K$. The circles represent points calculated for the given values of f.

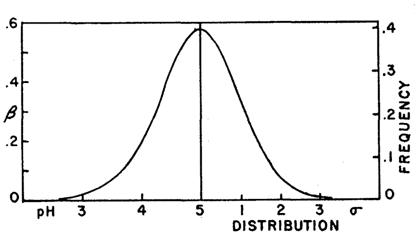

Fig. 2. Comparison of the buffer value and normal distribution curves. The left-hand portion of the curve is a plot of buffer value versus pH for a 1M acid, $pK = 5$, according to Eq. 5. The right-hand portion is a frequency-distribution curve where $N = 1$ and $\sigma = 1$.

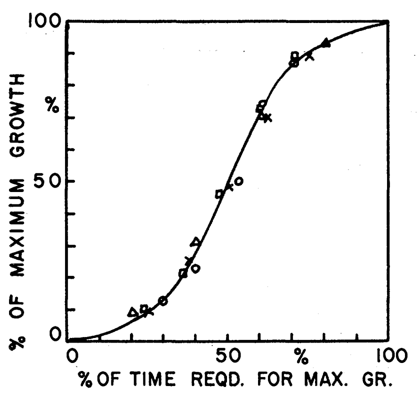

Fig. 3. Growth curves. The solid line is the theoretical S-shaped curve for proton or electron transfers as given in Fig. 1, while the symbols represent points on the actual growth curves published by Thompson (*2*). ×, Growth of beanstalk to 80 centimeters in 8 days; □, growth of lupine to 160 millimeters in 21 days; △, prenatal growth of child to 490 millimeters in 10 months; ○, growth of maize to 80 centimeters in 100 days.

for the assay of digitalis, strophanthin, and estrogen as given by Burn (*3, 4*). Calculating the f values to a K of 1.0 yields an $F = 0.3$ for both the digitalis and strophanthin curves, and an $F = 0.833$ for the estrogen assay. Since the digitalis and strophanthin curves have the same value for F, the two curves are identical and will coincide when they are plotted on the same basis by graphing the dosage as a plus or minus percentage of the dose giving a 50-percent response (*4*), thereby making $K = 1$. When the dose required to produce a 100-percent response is twice the dose that gives a 50-percent response, the resulting S-shaped curve has an $F = 0.5$. When the assay range is greater or less than this, the F is correspondingly greater or less than 0.5.

Skewed curves. A skewed distribution corresponds to an unsymmetrical S-shaped curve, as is shown in Fig. 5. The S-shaped curve can be derived from the frequency distribution by calculating the percentage of values that fall below or above any given value. In this "summation curve," the distance between the two quartiles (the 25- and 75-percent points) very nearly coincides with the standard deviation of the normal curve (*2*). For a skewed frequency curve, the geometric mean is more probable than the arithmetic mean. Since the logarithm of the geometric mean of a series of numbers is the arithmetic mean of their logarithms, the logarithms of the variants and not the variants themselves will tend to obey the Gaussian law and follow the normal curve of frequency (*2*).

Figure 6A shows the skewed type of dose-response curve that is obtained in determining the toxicity of cocaine in mice (*4*). Plotting the logarithm of the dose, instead of the dose itself, as abscissa yields a symmetrical curve (Fig. 6B) that follows the general equation. This is similar to a plot of the Henderson-Hasselbalch equation in which the negative logarithm of the hydrogen-ion concentration, rather than the hydrogen-ion concentration itself, is plotted as the abscissa.

Hemisigmoid Curves

If a biological effect starts at the midpoint of a sigmoid curve, only the upper half of the latter will be revealed in a dose-response curve. Such hemisigmoid curves follow the general equation for S-shaped curves when it is recognized that only half of a typical sigmoid curve is under consideration. When they are plotted in the usual way (A/B versus X), these hemisigmoid curves have the shapes illustrated in Fig. 7A. A plot of log X against A/B yields the curves shown in Fig. 7B. Such a log relationship is obviously not linear, but the central portion of each curve approaches linearity.

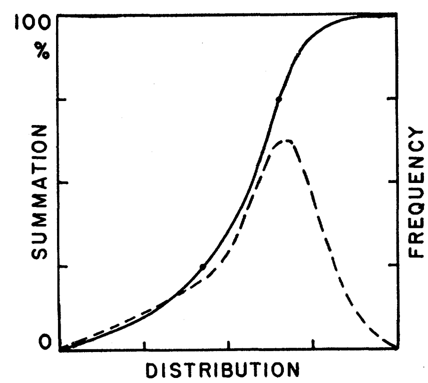

Fig. 5. A skewed distribution curve (dotted line) and its corresponding unsymmetrical S-shaped summation curve.

The ratio A/B is equivalent to the percentage of B converted to A, and it is analogous to the percentage response in a bioassay procedure. In analyzing a hemisigmoid bioassay curve, its origin or zero-dose response is equated to an equal mixture of A and B (corresponding to the mid-point of a sigmoid curve), while the maximum response corresponds to 100 percent of A. The assay range therefore extends from 50 percent of the maximum response (at zero dosage) to a 100-percent response at its asymptotic limit, and the distance in between is apportioned equally. Since the dosage at the beginning of the assay curve is inevitably zero, the K of the general equation for sigmoid curves is also zero and can be dropped from the equation, leaving

$$\text{Dosage} = f \log \frac{\text{percentage of maximum response}}{100 - \text{percentage of maximum response}} \qquad (7)$$

when the percentage response is equated to a scale of 50 to 100 percent rather than 0 to 100 percent.

Figure 8 shows the dose-response curves for the bioassay of androsterone and insulin (*4*). From the experimental curves, the recorded values for f can be calculated. The circles show the close correspondence between the actual assay curves and the theoretical curves calculated with these appropriate values for f. The log dose-response curves show the "linear" central portion that has been used extensively for comparative assay purposes. Assay curves that conform to Eq. 7 will yield a true straight line throughout the assay range when log [(percentage of maximum response)/ (− 100 percentage of maximum response)] is plotted on a scale of 50- to 100-percent response as the ordinate against the dose as the abscissa, and the slope of the line will be 1/f.

All growth and dose-response curves cannot be represented by the simple relationships described, and similar sigmoid curves can often be represented by very different types of differential equations. However, the examples cited emphasize a fundamental unity of many chemical and biological relationships. Since biological phenomena are dependent on chemical reactions, and since the latter are concerned with electron and proton exchanges, there is a fundamental basis for the analogies and correlations that have been made.

References

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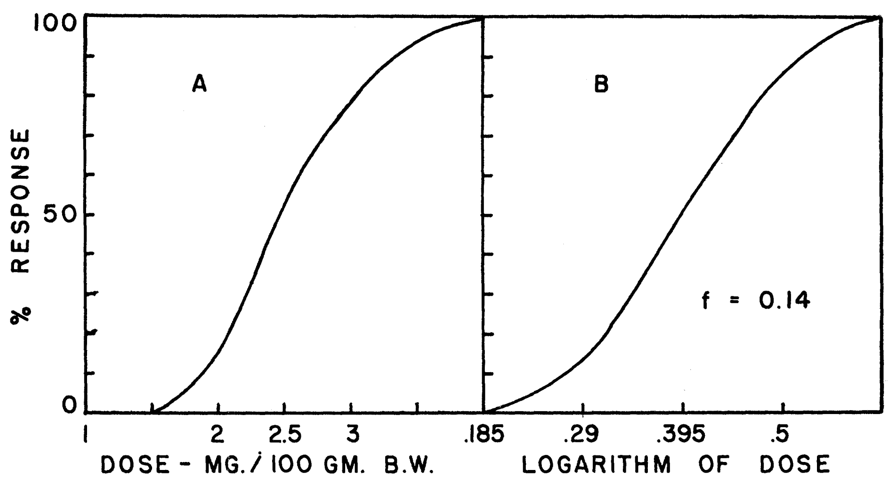

Fig. 6. (*A*) The unsymmetrical dose-response curve for the toxicity of cocaine in mice (*4*). (*B*) The same data plotted as log dose versus response to yield a symmetrical curve that follows the equation: log dose = 0.395 + 0.14 log [(percentage responding)/(percentage not responding)].

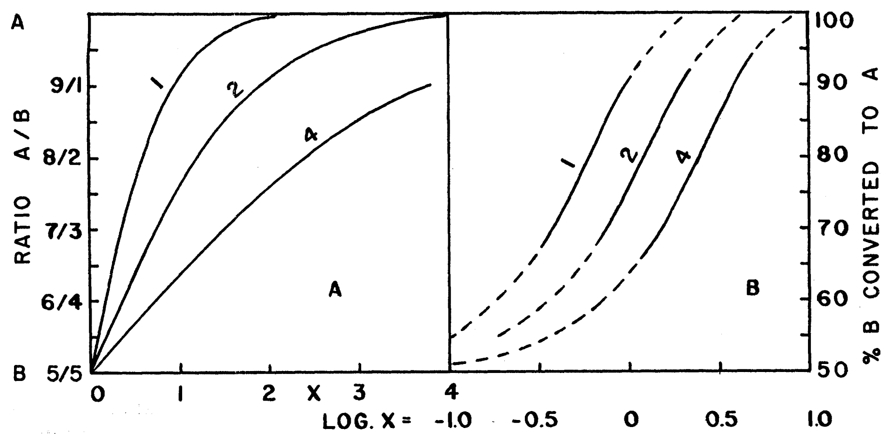

Fig. 7. (*A*) Hemisigmoid curves according to the equation: $X = K + f \log (A/B)$, when $K = 0$ and only the upper half of the total curve is plotted; $f = 1$, 2, or 4 as indicated. (*B*) A corresponding plot of log X (instead of X) against the ratio of A/B.

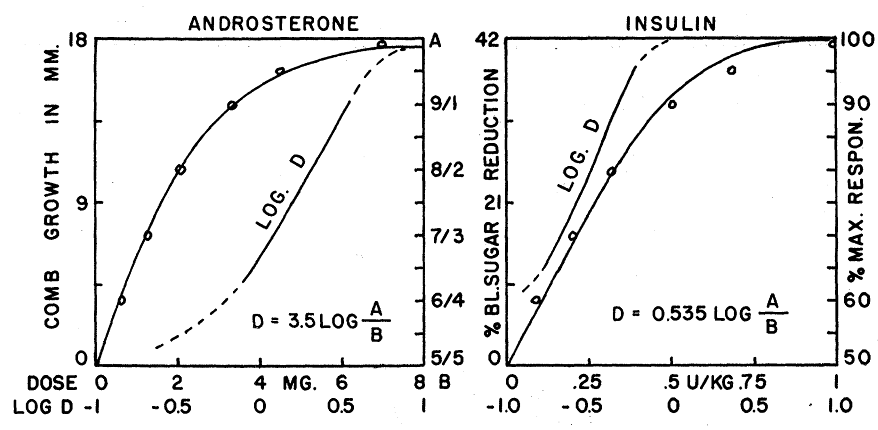

Fig. 8. The solid lines are the experimental bioassay curves for androsterone and insulin (*4*). The circles are theoretical points calculated from the equation: dose = $K + f$ log (A/B), when $K = 0$ and $f = 3.5$ for androsterone and $f = 0.535$ for insulin. The ratio A/B is equivalent to (percentage maximum response)/(100 − percentage maximum response), with the assay curve starting at the mid-point of a sigmoid curve, that is, at the 50-percent response level. The log dose-response curves are also shown.