

Appendix

Mathematical Concepts and the Trapezoidal Method

1 Algebra, variables and equations

Algebra is a way of describing relationships in general terms, usually as equations. For example, Wilhelm Beer observed that the optical absorbance, A , of a dilute solution was directly proportional to the concentration, C , of the solute:

$$A \propto C \quad (\text{A1})$$

To write the relationship as an equation we need a constant of proportionality, k :

$$A = kC \quad (\text{A2})$$

If C is in mol L^{-1} , and the path length is 1 cm, then $k = \epsilon$, the molar absorptivity of the solute. If the solvent also absorbs light, the background absorption, b can be added to the equation:

$$A = kC + b \quad (\text{A3})$$

A is known as the *dependent* variable because it changes as a result of changes in C , the *independent* variable. Equation A3 can be represented graphically by plotting A against C . The independent variable is plotted along the bottom (x -axis) and the dependent variable along the y -axis (Figure A1).

When $C = 0$, $y = b$, so the value of b can be obtained from the intercept of the line with the y -axis. The value of k is obtained from the slope of the line. Estimates of the intercept and slope are best derived from least squares regression analysis which can be done on many hand-held calculators, an Excel spreadsheet, as well as specifically designed regression software programs. If the line is a calibration line then it is usual to rearrange Equation A3, so that concentrations can be calculated from measured absorbance values. Subtracting b from both sides and dividing both sides by k gives:

$$C = \frac{A-b}{k} \quad (\text{A4})$$

2 Indices and powers

When a number, a , is multiplied by itself a number of times, n , the product can be written a^n . For example:

$$a \times a = a^2 \quad (\text{A5})$$

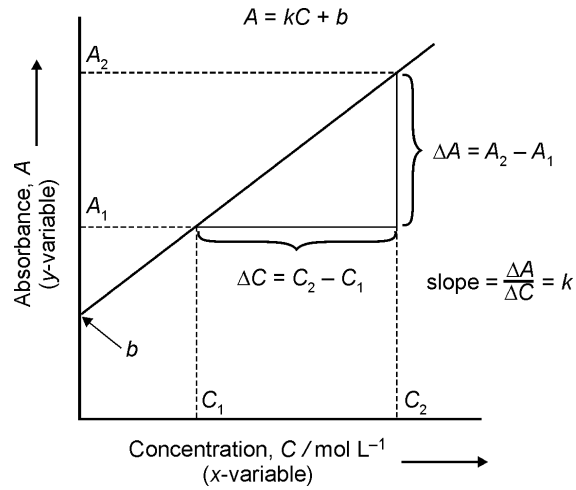


Figure A1 Straight line representation of $A = kC + b$.

and, in this case, a is said to be 'squared'. Similarly,

$$a \times a \times a = a^3 \quad (\text{A6})$$

the result is 'a cubed' or 'a to the 3'. Multiplying a^2 and a^3 :

$$a \times a \times a \times a \times a = a^5 \quad (\text{A7})$$

Note that the result is $a^{(2+3)}$ and a general rule can be written:

$$a^n \times a^m = a^{(n+m)} \quad (\text{A8})$$

Using similar logic it can be shown that:

$$\frac{a^n}{a^m} = a^{(n-m)} \quad (\text{A9})$$

Thus:

$$\frac{1}{a^n} = a^{-n} \quad (\text{A10})$$

and:

$$(a^n)^m = a^{nm} \quad (\text{A11})$$

A fractional index indicates that a root should be taken:

$$a^{\frac{1}{n}} = \sqrt[n]{a} \quad (\text{A12})$$

3 Logarithms

Tables of logarithms and antilogarithms are used to simplify multiplication and division of complex numbers using only addition and subtraction. In common logarithms, (base 10) each number is expressed as 10 raised to the appropriate power. Logarithms have additional importance in pharmacology for contracting the range of numbers and in the linear transformation of data. The base of the logarithm can be indicated e.g. 'log₁₀' but generally common logarithms are written 'log'. Logarithms to the base e ($e \approx 2.718 \dots$) are referred to as natural logarithms, and can be written log_e or more commonly, simply, ln. A word of warning, in many computer languages, and in engineering parlance, 'log' means 'log_e'. To convert a logarithm to a number the base of the logarithm is raised to the logarithm. For example,

$$\log 2 = 10^2 = 100$$

and if:

$$x = \ln y, \quad \text{then } y = e^x \quad (\text{A13})$$

Negative numbers cannot have logarithms, but note that

$$\log \frac{1}{x} = -\log x \quad (\text{A14})$$

Furthermore, it should be noted that although logarithms are dimensionless, it is necessary, to indicate the units of the original number. So for a concentration of $C \text{ mg L}^{-1}$, the logarithm should be written: $\log (C/\text{mg L}^{-1})$.

4 Calculus

4.1 Differentiation

Calculus was invented to deal with slopes of curves and areas under them. When the rate of change of a measurement (e.g. y as a function of x) is changing, we may wish to determine the average rate of change of y with respect to x . This is done by differentiation. Suppose δy represents a small increase in y which occurs while x increases by δx , then $\delta y/\delta x$ is the mean gradient of the graph over the small range examined. If we reduce the values of δy and δx towards zero, then the line showing the gradient tends towards a tangent. The limiting value of $\delta y/\delta x$ is called dy/dx or the differential coefficient of y with respect to x . The process of finding the limit of dy/dx is *differentiation*, and dy/dx is a measure of the slope of the tangent at a given value of x [Figure A2(a)]. If the y -variable is time, t , and the x -variable is concentration, C , then dC/dt is the instantaneous rate of change in concentration at that time.

For equations of the type: $y = ax^n + b$

$$\frac{dy}{dx} = anx^{(n-1)} \quad (\text{A15})$$

Thus for a straight line, $y = ax + b$, $n = 1$, so

$$y = ax^1 + b$$

$$\frac{dy}{dx} = ax^{(1-1)} = ax^0 = a \quad (\text{A16})$$

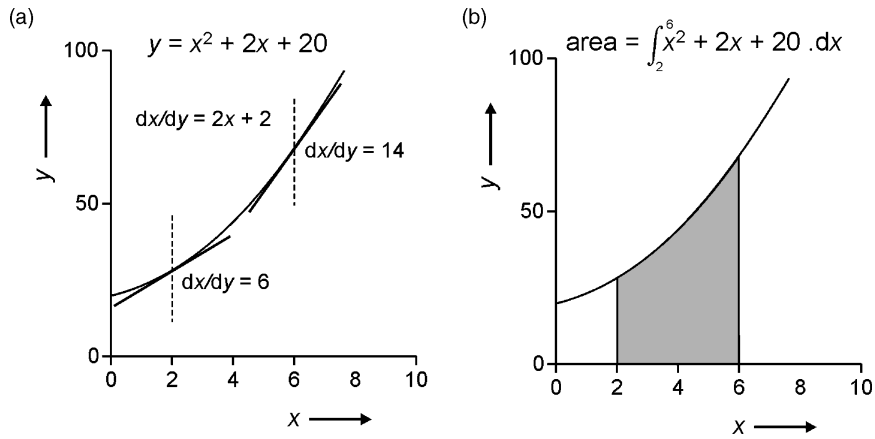


Figure A2 (a) Differentiation allows the slope at any value of x to be calculated. (b) Integration between $x = 2$ and $x = 6$ allows the area depicted by the shading to be calculated (see text for details).

i.e. the slope of the straight line is a . Reciprocals of x are treated the same way:

$$y = \frac{1}{x^n} = x^{-n} \quad (\text{A17})$$

$$\frac{dy}{dx} = -nx^{-n-1} = -nx^{-(n+1)}$$

However the differential of $\ln x$ is a special case:

$$y = \ln x \quad (\text{A18})$$

$$\frac{dy}{dx} = \frac{1}{x}$$

4.2 Integration

The reverse of differentiation is integration. If dy/dx is known we may wish to find y in terms of x . Thus, if dy/dx is some function of x , written as $f(x)$, then y is the integral of $f(x)$ with respect to x :

$$y = \int f(x) \cdot dx \quad (\text{A19})$$

If $y = ax^n$, then:

$$y = \int ax^n \cdot dx = a \int x^n \cdot dx = \frac{ax^{(n+1)}}{n+1} + c \quad (\text{A20})$$

Note the appearance of c , sometimes referred to as a constant of integration, which is necessary because constants are 'lost' on differentiation, see Equation A16. The value is found by substituting $x = 0$, when $y = c$.

The integral of $1/x$ is of particular importance because of the form of the rate equation of first-order reactions:

$$y = \int \frac{1}{x} \cdot dx = \ln x + c = ce^x \quad (\text{A21})$$

A quantity written as a power of e is an exponential function, and the above may be written $c \exp(x)$. The quantity increases more and more rapidly as the power increases – *exponential growth*. If the power is negative, e.g. $y = e^{-x}$, then this represents *exponential decay* and y becomes ever nearer to 0 as x increases, but only reaches 0 when x is infinite; y is said to *asymptote* to 0.

4.2.1 Areas under curves

Integration is important for calculating areas under curves. Using the equation of Figure A2 as an example, the area under the curve (AUC) from 2 and 6 is obtained by integrating between the limits:

$$AUC_{(2-6)} = \int_2^6 x^2 + 2x + 20 \cdot dx = \left[\frac{x^3}{3} + x^2 + 20x \right]_2^6 \quad (\text{A22})$$

$AUC_{(2-6)}$ is the difference between the value obtained by substituting $x = 6$ and $x = 2$.

$$AUC_{(2-6)} = \left[\frac{6^3}{3} + 6^2 + 20(6) \right] - \left[\frac{2^3}{3} + 2^2 + 20(2) \right]$$

$$AUC_{(2-6)} = 228 - 46.7$$

$$AUC_{(2-6)} = 181.3$$

Note that because we are using the difference, the constant of integration cancels and need not be included. In this example, the numbers were dimensionless and so AUC has no units. However, in most practical instances the x - and y -values will represent variables with units and so anything derived from them should have the appropriate units. The slope of a $\ln(\text{concentration})$ against time plot has units of time to the minus 1 (T^{-1}). The area under the curve of a plasma concentration (mg L^{-1}) against time (h) plot has units of mg h L^{-1} , for example.

4.2.2 Calculating AUC values: the trapezoidal method

Probably the simplest way to obtain the area under a curve is the *trapezoidal method*. The plasma concentration–time curve is plotted and each segment between adjacent collection time points treated as a trapezium [Figure A3(a)]. The area of the trapezium is the average length of two sides multiplied by the width between them, so for the n^{th} trapezium the area, A_n , is:

$$A_n = \frac{C_n + C_{(n+1)}}{2} (t_{(n+1)} - t_n) \quad (\text{A23})$$

The area from $t = 0$ to the time of last plasma sample, $AUC_{(0-t)}$ is obtained by adding the areas of all the trapeziums. The remaining area, from the time of the last collected sample to infinity is extrapolated using

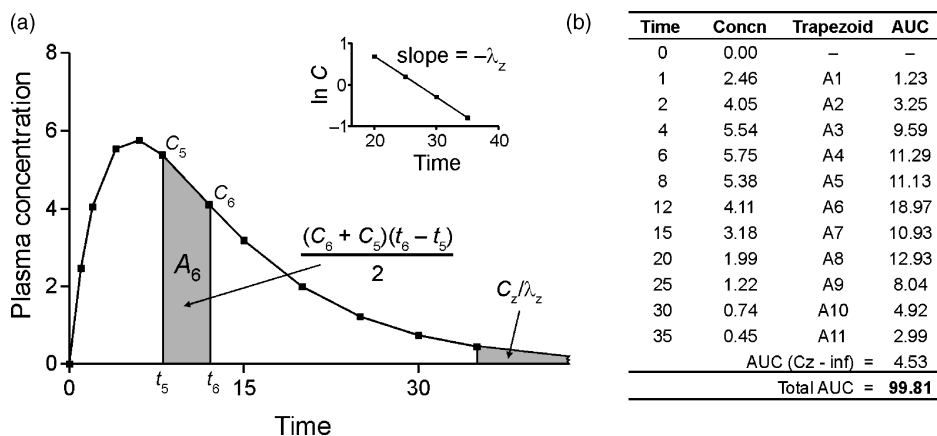


Figure A3 (a) Example of the trapezoidal method of calculating the area under a concentration versus time curve. The rate constant is calculated from the slope of the terminal points of $\ln C$ versus time plot (inset). (b) Printout from an Excel spreadsheet showing the areas of individual trapeziums and the total which is in good agreement with the theoretical value of 100 for this example.

C_z/λ_z , where λ_z is the rate constant of the terminal decay phase. This can be estimated from a $\ln(\text{concentration})$ versus time plot of the terminal data [Figure A3(a) inset]. The areas are conveniently calculated from the concentration–time data using a spreadsheet [Figure A3(b)].

Points to note are:

- It is the area under the concentration–time plot, NOT the $\ln(\text{concentration})$ –time plot that must be used.
- Although the first segment on the oral plot is a triangle the formula for a trapezium gives the correct area because length of one side is 0.
- The greater the number of trapeziums the greater will be the accuracy of the calculation.
- Ideally the extrapolated area should be <5% of the total.
- The units of AUC are concentration \times time e.g. mg h L^{-1} .

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