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CHAPTER

1

Mathematical Toolkit

Learning Objectives

1.1 Calculus Essentials

1.2 Linear Algebra

1.3 Ordinary Differential Equations

1.4 Numerical Methods Essentials

1.5 Engineering Math Tools

Mathematics is the working language of bioprocess engineering. Every concept that follows in this book — growth kinetics, mass transfer, reactor design, chromatography — is expressed in equations. A student who is comfortable with calculus, basic linear algebra, and ordinary differential equations can read those equations like a story; a student who is not will struggle even with very simple problems. This chapter is a quick refresher, not a full course in mathematics. The goal is to bring back the few results you must keep in active memory, with biology-flavoured examples wherever possible.

1.1 Calculus Essentials

Calculus deals with two main questions. First, how does one quantity change with another? Second, what is the total accumulated effect of a continuous change? In bioprocess engineering, the first question shows up every time we ask how fast biomass is growing or how fast a substrate is being consumed. The second question shows up every time we ask how much product has been made over the full duration of a fermentation. The first leads to differentiation; the second leads to integration.

1.1.1 Limits, Continuity and Differentiability

A limit tells you the value a function approaches as the input approaches some target. We write this as the limit of $f(x)$ as x approaches a , written $\lim_{x \rightarrow a} f(x)$. The function need not actually take that value at $x = a$ — the limit only describes the behaviour very close to a . For example, the function $(x^2 - 1)/(x - 1)$ is not defined at $x = 1$ because the denominator is zero, but as x approaches 1, the function approaches 2.

A function is **continuous** at a point if its limit at that point equals its value at that point. Continuity simply means the graph of the function has no breaks or jumps at that point. A function is **differentiable** at a point if a unique tangent line exists there — that is, the curve is smooth at that point. Every differentiable function is continuous, but the reverse is not always true. For example, the function $|x|$ is continuous everywhere but not differentiable at $x = 0$, because the curve has a sharp corner there.

1.1.2 The Derivative

The **derivative** of a function $f(x)$ at the point x measures how fast f is changing at that point. Its formal definition uses a limit:

$$f'(x) = \lim_{h \rightarrow 0} \frac{f(x+h) - f(x)}{h} \quad (1.1)$$

In simple terms, the derivative is the slope of the tangent to the curve at the point x . It is written in three common ways: $f'(x)$, df/dx , and Df . All three mean the same thing. When the function describes a quantity that depends on time, the derivative gives the **rate** at which the quantity is changing — for example, dX/dt is the rate at which biomass concentration X is changing with time.

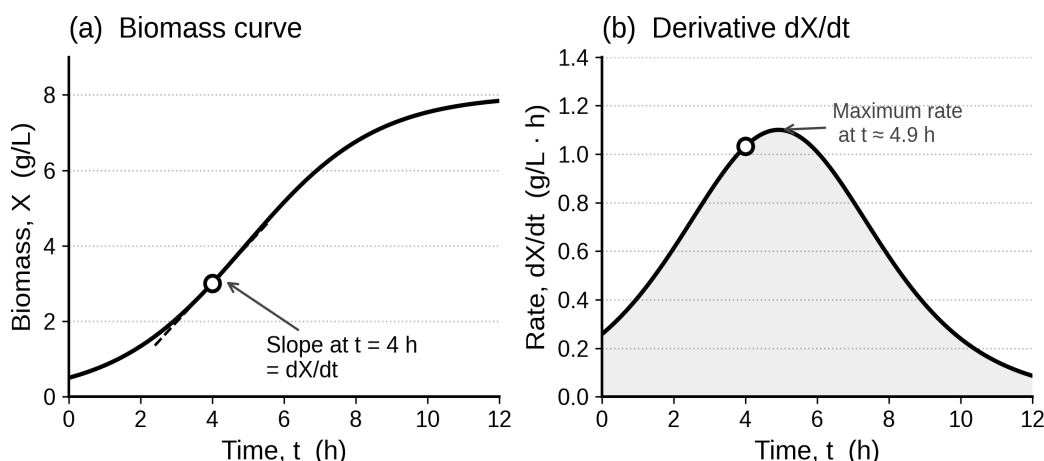


Figure 1.1 (a) Biomass concentration X plotted against time for a typical batch culture. The dashed line shows the tangent at $t = 4$ h; its slope is the derivative dX/dt at that point. (b) The derivative dX/dt plotted against time. The maximum rate of growth happens near $t \approx 5$ h, after which the rate falls because the substrate is running out and the cells are slowing down.

The most useful differentiation rules are the power rule (the derivative of x^n is $n \cdot x^{n-1}$), the product rule (the derivative of $u \cdot v$ is $u' \cdot v + u \cdot v'$), the quotient rule (the derivative of u/v is $(u' \cdot v - u \cdot v')/v^2$), and the chain rule (the derivative of $f(g(x))$ is $f'(g(x)) \cdot g'(x)$). These four rules together cover almost every derivative you will need to take in this book.

KEY POINT

In a batch fermentation, the simplest growth model assumes that the rate of biomass production is proportional to the biomass already present. The kinetic equation is $dX/dt = \mu X$. This is a first-order ordinary differential equation. Its solution is the exponential growth curve $X(t) = X_0 e^{\mu t}$. The derivative on the left side of the equation is exactly the slope of the curve in Figure 1.1(a). The connection between calculus and microbial growth begins right here.

$$\frac{dX}{dt} = \mu X \quad (1.2)$$

In equation (1.2), μ is the specific growth rate (units h^{-1}) and X is the biomass concentration (units g/L). The same first-order form appears in Chapter 8 for thermal death of microbial cells during sterilization, and in Chapter 9 for first-order decay of an enzyme. The mathematics behind these very different bioprocess problems is identical.

INTERESTING FACT

Calculus was invented independently by Isaac Newton in England (around 1666) and Gottfried Wilhelm Leibniz in Germany (around 1675). They quarrelled bitterly about who deserved credit for it. The notation dx/dt that we still use today is from Leibniz; the dot notation $\dot{X}$ used in classical mechanics is from Newton. Bioprocess engineers use Leibniz's notation almost exclusively, because dx/dt makes the units of the derivative obvious (g/L per h).

1.1.3 Partial Derivatives, Maxima and Minima

When a quantity depends on more than one variable, we need the partial derivative. Suppose enzyme activity E depends on both temperature T and pH. The **partial derivative** $\partial E/\partial T$ tells you how E changes when T changes while pH is held fixed. Similarly, $\partial E/\partial(\text{pH})$ tells you how E changes with pH while T is held fixed. The two together tell the complete picture.

To find the maximum or minimum of a function, set its derivative equal to zero. Points where $f'(x) = 0$ are called critical points. The second derivative test distinguishes between them — if $f''(x)$ is negative at a critical point, the point is a local maximum; if positive, a local minimum; if zero, the test is inconclusive.

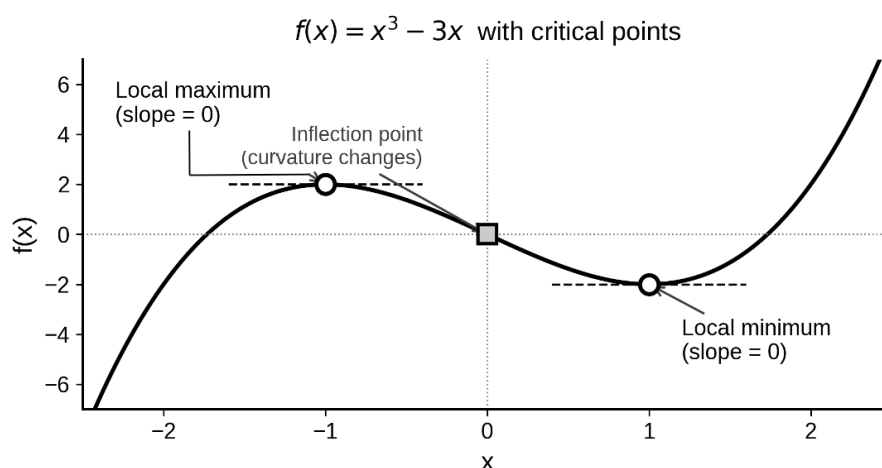


Figure 1.2 Critical points of $f(x) = x^3 - 3x$. The derivative $f'(x) = 3x^2 - 3$ is zero at $x = -1$ and $x = +1$. The second derivative $f''(x) = 6x$ is negative at $x = -1$ (local maximum) and positive at $x = +1$ (local minimum). At $x = 0$ the curvature changes sign — this is an inflection point.

1.1.4 Integration

Integration is the reverse of differentiation. The integral of a function over an interval gives the area under the curve. In bioprocess problems, we use integrals to find the total amount of something accumulated over time. The basic rules: the integral of x^n is $x^{n+1}/(n+1)$ for $n \neq -1$; the integral of $1/x$ is $\ln|x|$; the integral of e^{ax} is $\frac{e^{ax}}{a}$; and the integral of $\cos(x)$ is $\sin(x)$. Two important techniques are integration by substitution and integration by parts.

WORKED EXAMPLE 1.1

Problem. In a batch fermentation, the rate of ethanol production is $r_p = 0.5 \cdot t$ g/L · h, where t is the time in hours. Find the total ethanol produced between $t = 0$ and $t = 4$ h.

Solution. Total ethanol (P) = $\int_{t_1}^{t_2} r_p dt = \int_0^4 0.5 \cdot dt = 0.5 \cdot (t^2/2)$ evaluated from 0 to 4 = $0.5 \cdot 8 = 4$ g/L.

Comment. Whenever a rate is given as a function of time, the total accumulated quantity is found by integrating the rate. This is how we estimate batch yield from a measured rate-time profile.

1.2 Linear Algebra

Linear algebra is the mathematics of arrays of numbers. In bioprocess engineering it appears most prominently in metabolic engineering, where the stoichiometry of a metabolic network is captured by a matrix and the steady-state condition is just a system of linear equations.

1.2.1 Matrices and Determinants

A **matrix** is a rectangular array of numbers arranged in rows and columns. A matrix with m rows and n columns is called an $m \times n$ matrix. To multiply two matrices A (size $m \times n$) and B (size $n \times p$), the column count of A must match the row count of B ; the result is an $m \times p$ matrix in which entry (i, j) is the dot product of row i of A with column j of B . The **determinant** of a square matrix is a single number that captures whether the matrix is invertible. A 2×2 determinant is calculated as:

$$\det [a \ b ; c \ d] = a d - b c \quad (1.3)$$

If the determinant is zero, the matrix is singular — its rows (or columns) are linearly dependent and it cannot be inverted. Three useful properties of determinants: swapping two rows changes the sign; multiplying a row by a constant k multiplies the determinant by k ; adding a multiple of one row to another row leaves the determinant unchanged. These three operations are exactly what Gaussian elimination uses to solve linear systems.

1.2.2 Systems of Linear Equations

A system of linear equations like $2x + y = 5$ and $x - y = 1$ can be written compactly as a matrix equation $A \cdot x = b$, where A is the matrix of coefficients, x is the column of unknowns, and b is the column of right-hand-side values. The system has a unique solution exactly when $\det(A) \neq 0$. The standard solution method is Gaussian elimination — apply row operations until the matrix is reduced to upper-triangular form, then back-substitute.

In metabolic flux analysis, the stoichiometric matrix S has one row for each metabolite and one column for each reaction. The condition for steady state — that no metabolite accumulates inside the cell — is the matrix equation $S \cdot v = 0$, where v is the column of reaction fluxes. This is a homogeneous system of linear equations. Cells are doing linear algebra without knowing it.

1.2.3 Eigenvalues and Eigenvectors

An **eigenvector** of a square matrix A is a non-zero vector v such that $A \cdot v$ points in the same direction as v itself, only stretched (or compressed) by some scalar factor λ called the **eigenvalue**. The defining equation is:

$$A v = \lambda v \quad (1.4)$$

Eigenvalues are found by solving the characteristic equation $\det(A - \lambda I) = 0$, which gives a polynomial in λ whose roots are the eigenvalues. Eigenvalues describe the natural modes of a linear system. They appear in the analysis of coupled reaction networks, in the stability analysis of bioreactor operation, and in metabolic control analysis.

REVISION POINT

The stoichiometric matrix **S** of a metabolic network has m rows (one per metabolite) and n columns (one per reaction). Each entry S_{ij} is the stoichiometric coefficient of metabolite i in reaction j (positive for products, negative for substrates). At steady state, **S**·**v** = **0**, where v is the vector of reaction fluxes. This single matrix equation is the foundation of flux balance analysis — every metabolic-engineering paper of the last twenty years started from it.

WORKED EXAMPLE 1.2

Problem. Find the eigenvalues of the matrix

$$A = \begin{bmatrix} 3 & 1 \\ 0 & 2 \end{bmatrix}$$

Solution. To find the eigenvalues of a matrix, we must solve the **characteristic equation**, defined as:

$$\det(A - \lambda I) = 0$$

Where I is the identity matrix.

1. Set up the characteristic matrix:

Subtract λ from the diagonal elements of A : $A - \lambda I = \begin{bmatrix} 3 - \lambda & 1 \\ 0 & 2 - \lambda \end{bmatrix}$

2. Calculate the determinant:

For a 2×2 matrix, the determinant is calculated as $(ad - bc)$: $\det(A - \lambda I) = (3 - \lambda)(2 - \lambda) - (1)(0)$

$$\det(A - \lambda I) = (3 - \lambda)(2 - \lambda)$$

3. Solve for λ : Set the characteristic polynomial to zero:

$$(3 - \lambda)(2 - \lambda) = 0$$

This gives two solutions:

- $3 - \lambda = 0 \Rightarrow \lambda_1 = 3$
- $2 - \lambda = 0 \Rightarrow \lambda_2 = 2$

Comment. For an upper-triangular or lower-triangular matrix, the eigenvalues are simply the diagonal entries. This shortcut saves time on exam problems.

1.3 Ordinary Differential Equations

An **ordinary differential equation** (ODE) is an equation that relates a function and its derivatives. Almost every kinetic model in this book is an ODE. The order of an ODE is the order of the highest derivative it contains. An ODE is **linear** if it can be written so that the unknown function and its derivatives appear only to the first power and are not multiplied by each other; otherwise it is non-linear.

1.3.1 Variable-Separable ODEs

A first-order ODE is variable-separable if it can be re-arranged into the form $g(y) dy = f(x) dx$. Once the variables are separated, both sides can be integrated independently to give the solution. The ODE that describes exponential growth, $dX/dt = \mu X$, is the simplest variable-separable equation in biology. Worked Example 1.3 below shows the standard solution procedure step by step.

1.3.2 First-Order Linear ODEs

A first-order linear ODE has the standard form:

$$\frac{dy}{dx} + P(x)y = Q(x) \quad (1.5)$$

where $P(x)$ and $Q(x)$ are known functions of x . The standard trick is to multiply both sides by an integrating factor $\mu(x) = e^{\int P(x) dx}$. After this multiplication the left side becomes the derivative of the product $\mu \cdot y$; the equation can then be integrated directly. This trick covers a surprising number of bioprocess problems — fed-batch cultures, mass-balance equations on transient reactors, and the response of a sterilization vessel during heat-up are all first-order linear ODEs.

WORKED EXAMPLE 1.3

Problem. A batch culture of *Saccharomyces cerevisiae* is inoculated at $X_0 = 0.5$ g/L into a flask of rich medium. The specific growth rate is $\mu = 0.4$ h⁻¹. Find the biomass concentration X after 6 hours, assuming exponential growth applies throughout.

Solution. Start with the kinetic equation $dX/dt = \mu X$. This is variable-separable. Move all X -terms to one side and all t -terms to the other: $dX/X = \mu dt$. Integrate both sides: $\ln(X) = \mu t + C$. Use the initial condition $X = X_0$ at $t = 0$ to fix C : $C = \ln(X_0)$. Substitute and rearrange:

$$X(t) = X_0 e^{\mu t}$$

Numerical answer. Plug in numbers: $\mu t = 0.4 \times 6 = 2.4$. Therefore $X(6) = 0.5 \times e^{2.4} = 0.5 \times 11.02 = 5.51$ g/L.

Comment. The yeast biomass has grown by roughly 11-fold in 6 hours. In real life, this would only continue until the substrate begins to run out — the assumption that μ stays constant is the limitation of this simple model.

1.3.3 Second-Order Linear ODEs with Constant Coefficients

A second-order homogeneous linear ODE with constant coefficients has the standard form:

$$a \frac{d^2 y}{dx^2} + b \frac{dy}{dx} + c y = 0 \quad (1.6)$$

The standard solution method is to assume $y = e^{rx}$, substitute, and obtain the characteristic equation $a r^2 + b r + c = 0$. The two roots r_1 and r_2 are then plugged back into the assumed form. Three cases arise: real distinct roots give $y = C_1 e^{r_1 x} + C_2 e^{r_2 x}$; equal roots give $y = (C_1 + C_2 x) e^{rx}$; complex roots $r = \alpha \pm i\beta$ give $y = e^{\alpha x} [C_1 \cos(\beta x) + C_2 \sin(\beta x)]$ — the last case describes oscillating systems such as the glycolytic oscillations covered in Chapter 5.

INTERESTING FACT

The chemostat — the most important continuous-culture device in microbiology — was invented by Jacques Monod in Paris in 1950 and independently by Aaron Novick and Leo Szilard in Chicago a few months later. The first paper on chemostat theory was just six pages long, but it founded the entire mathematical treatment of continuous fermentation. The chemostat works because, at steady state, the differential equation $dX/dt = (\mu - D) \cdot X$ has the simple solution $\mu = D$ — the growth rate equals the dilution rate. Without ODEs, this elegant result would not even be writable.

1.4 Numerical Methods Essentials

Most ODEs and many algebraic equations in bioprocess engineering have no closed-form solution. In such cases we use numerical methods that approach the answer step by step on a computer.

1.4.1 Finding Roots — Bisection and Newton-Raphson

Both methods solve the equation $f(x) = 0$ for x . The **bisection method** begins with two values a and b that bracket the root (so that $f(a)$ and $f(b)$ have opposite signs) and repeatedly halves the interval. It is slow but always works. The **Newton-Raphson method** is faster — it begins with a single guess x_0 and uses the tangent line at $f(x_0)$ to estimate where the curve crosses zero:

$$x_{n+1} = x_n - \frac{f(x_n)}{f'(x_n)} \quad (1.7)$$

Newton-Raphson typically converges in just 4–5 iterations to many decimal places. It will fail if the initial guess is too far from the root or if $f'(x)$ becomes zero during iteration.

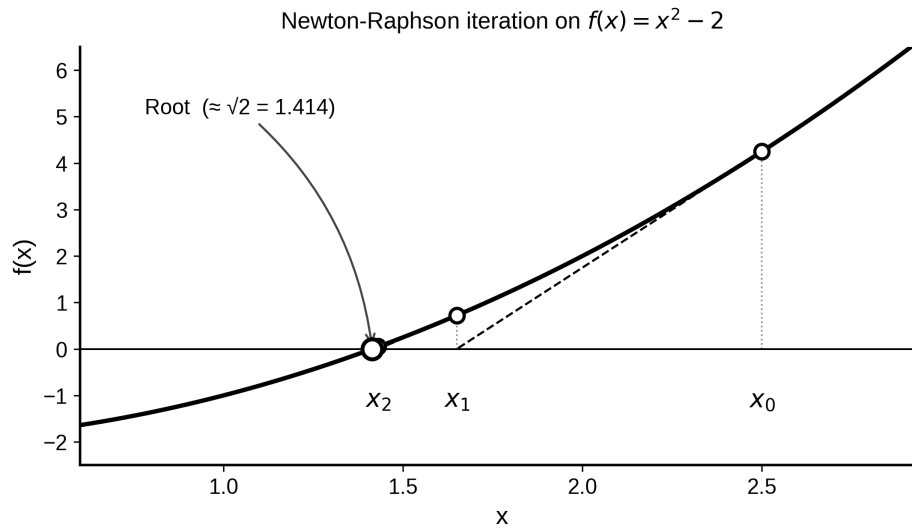


Figure 1.3 Newton-Raphson iteration applied to $f(x) = x^2 - 2$ starting from $x_0 = 2.5$. The dashed line is the tangent at the current point; it crosses the x -axis at the next estimate. After three iterations the value is within 10^{-5} of the true root $\sqrt{2} = 1.4142$. Each step approximately doubles the number of correct digits — this is called quadratic convergence.

WORKED EXAMPLE 1.4

Problem. Estimate $\sqrt{2}$ using Newton-Raphson, starting from $x_0 = 1.5$. Show the first two iterations.

Solution. Take $f(x) = x^2 - 2$ so that $f'(x) = 2x$. Apply equation (1.7):

Iteration 1. $f(x_0) = 1.5^2 - 2 = 0.25$; $f'(x_0) = 3.0$; $x_1 = 1.5 - 0.25/3.0 = 1.4167$.

Iteration 2. $f(x_1) = 1.4167^2 - 2 = 0.0069$; $f'(x_1) = 2.8334$; $x_2 = 1.4167 - 0.0069/2.8334 = 1.4142$.

Comment. After only 2 iterations, the answer is correct to 4 decimal places. The true value $\sqrt{2} = 1.41421$ — quadratic convergence in action.

1.4.2 Numerical Integration

To estimate a definite integral when an analytic solution is not possible, we approximate the area under the curve by simple shapes. The **trapezoidal rule** divides the interval $[a, b]$ into n equal pieces of width $h = (b - a)/n$ and adds up the areas of n trapezoids:

$$\int f(x) dx \approx \frac{h}{2} [f(x_0) + 2f(x_1) + \dots + 2f(x_{n-1}) + f(x_n)] \quad (1.8)$$

Simpson's 1/3 rule is more accurate for smooth curves: it fits a parabola through every three consecutive points instead of a straight line through every two. Simpson requires n to be even. In practice, Simpson with $n = 8$ is accurate enough for almost any GATE or CSIR problem.

1.4.3 ODE Solvers

To integrate an ODE numerically, we step forward in time in small intervals Δt , computing the next value of y from the current one. The simplest method is **Euler's method**: $y_{n+1} = y_n + \Delta t \cdot f(x_n, y_n)$. It is easy to code but loses accuracy if Δt is large. The **Runge-Kutta-4** (RK4) method takes four trial slopes inside each step and averages them in a clever weighted way. RK4 is the standard solver in MATLAB's *ode45*, COBRApy, and most commercial bioprocess simulators.

1.5 Engineering Math Tools

1.5.1 Dimensional Analysis and Unit Conversions

Every physical quantity has a **dimension** (mass M , length L , time T , amount N , temperature Θ) and **units** (kg, m, s, mol, K). An equation must be dimensionally consistent — both sides must reduce to the same combination of base dimensions. Dimensional analysis lets you spot a wrong answer before you compute it. The specific growth rate μ has dimension $1/T$, so an answer of $\mu = 0.4$ g/L would be wrong by inspection. Common bioprocess unit conversions: $1 \text{ L} = 10^{-3} \text{ m}^3$, $1 \text{ atm} = 101\,325 \text{ Pa}$, $1 \text{ kcal} = 4.184 \text{ kJ}$. Always carry units along through every calculation.

1.5.2 Significant Figures and Error Propagation

Every measurement has uncertainty. Significant figures are the digits that are reliably known. When two measured values are added or subtracted, the absolute uncertainty of the result is the sum of the absolute uncertainties of the inputs. When two values are multiplied or divided, the relative uncertainty (Δ/value) of the result is roughly the sum of the relative uncertainties of the inputs. A **least-squares fit** finds the straight line that minimises the sum of squared deviations between data and fit; its slope and intercept come from the standard linear-regression formulas.

WORKED EXAMPLE 1.5

Problem. In a batch culture, biomass concentration was measured at four time points: $t = 0, 2, 4, 6$ h gave $X = 0.5, 1.4, 4.0, 11$ g/L. Plot $\ln(X)$ versus t and find the specific growth rate μ .

Solution. Compute $\ln(X)$ for each point: $\ln(0.5) = -0.693$; $\ln(1.4) = 0.336$; $\ln(4.0) = 1.386$; $\ln(11) = 2.398$. The four points ($t, \ln X$) lie almost on a straight line — exactly what equation (1.2) predicts. The slope of the line gives μ .

Slope estimate. $\mu \approx (2.398 - (-0.693))/(6 - 0) = 3.091/6 = 0.515 \text{ h}^{-1}$.

Comment. Whenever you suspect exponential behaviour, plot the natural log of the dependent variable against the independent variable. A straight line confirms the model and the slope is the rate constant — no algebra needed.

1.5.3 Log-Log and Semi-Log Plots

Different data sets become straight lines on different kinds of axes. An **exponential** relationship $y = a e^{kx}$ becomes a straight line on a **semi-log plot** — $\log y$ vs x — with slope k . A **power law** $y = a x^n$ becomes a straight line on a **log-log plot** — $\log y$ vs $\log x$ — with slope n . Recognising which transformation linearises which form is a high-yield exam skill: it lets you read off rate constants and reaction orders from a graph without doing any algebra.

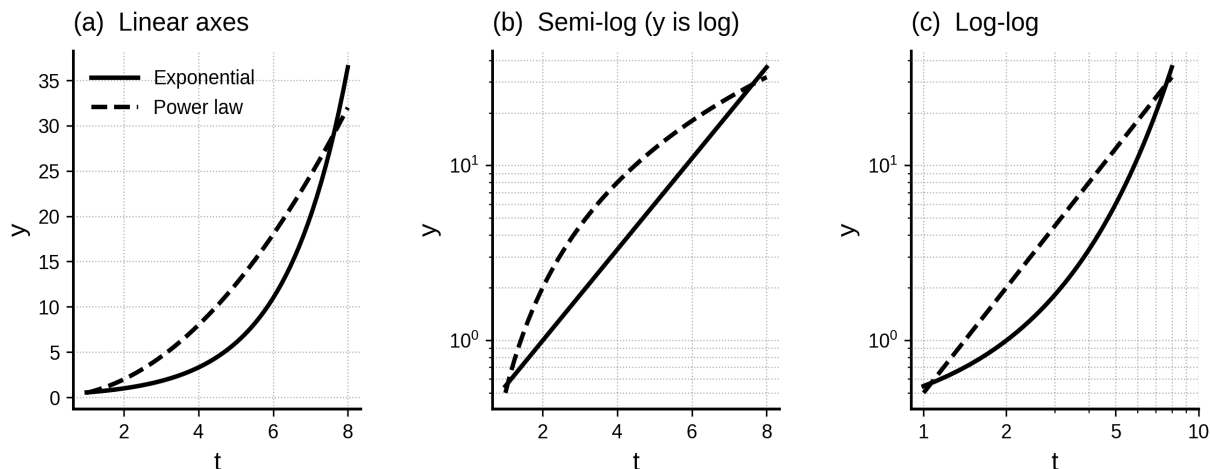


Figure 1.4 The same two data sets — one exponential, one power-law — plotted on three different kinds of axes. (a) Linear axes: both look curved. (b) Semi-log: the exponential becomes a straight line. (c) Log-log: the power-law becomes a straight line. Identifying the correct kind of plot is often the first step in analysing kinetic data.

Important Formula**1. Exponential growth — log linearisation**

$$\ln X_t = \ln X_0 + \mu t$$

When to apply. Plotting $\ln X$ versus t in batch culture gives a straight line in the exponential phase. The slope is the specific growth rate μ ; the intercept is $\ln X_0$. Use to extract μ from biomass-time data.

2. Doubling time

$$t_d = \frac{\ln 2}{\mu}$$

When to apply. Time for biomass to double during exponential growth. Useful for quick comparison of strains and conditions.

3. Arrhenius equation

$$k = A \cdot e^{-E_a / RT}$$

When to apply. Temperature dependence of any rate constant — enzyme reactions, spore inactivation, nutrient degradation. Plot $\ln k$ vs $1/T \rightarrow$ straight line with slope $-E_a/R$.

4. Linear regression — least-squares slope

$$m = \frac{\sum (x_i - \bar{x})(y_i - \bar{y})}{\sum (x_i - \bar{x})^2}$$

When to apply. Best-fit slope of $y = mx + c$. Use for fitting kinetic data, calibration curves, and any linearised relationship.

5. Numerical integration — Forward Euler

$$y_{n+1} = y_n + h \cdot f(y_n)$$

When to apply. Simplest ODE step. Local error $O(h^2)$; fast but inaccurate. Use for quick spreadsheet simulations and back-of-envelope checks.

6. Reynolds number (pipe flow)

$$Re = \frac{\rho v D}{\mu}$$

When to apply. Dimensionless ratio of inertial to viscous forces. < 2100 laminar, > 4000 turbulent in pipes. Used to choose flow correlation.