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Mathematical Tools for Physical Sciences and Systems Biology

This leaflet is a summary of common mathematical definitions and properties used in Physical Sciences and Systems Biology, including matrix algebra, ordinary and partial differential equations, random processes & some numerical methods for integrating ODEs.

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Matrices and vectors become useful in multi-dimensional problems, e.g. systems of equations or differential equations; hence it is important to know their properties.

Linear independence

The span of a set of vectors $S = \{\tilde{v_1}, \tilde{v_2}, \cdots \tilde{v_n}\}$ is the set of all linear combinations of vectors $\tilde{v_1}, \tilde{v_2}, \cdots \tilde{v_n}$, i.e. the set of all the vectors written in the form:

$$c_1\tilde{v_1} + c_2\tilde{v_2} + \cdots + c_n\tilde{v_n} \text{ with } (c_i)_{1\leq i\leq n} \text{ real numbers}$$

Linear independence: a set of vectors $\{\tilde{v_1}, \tilde{v_2}, \cdots \tilde{v_n}\}$ is linearly dependent if and only if:

- either one of the vectors can be written as a linear combination of the other vectors;
- or: the equation $c_1\tilde{v_1} + c_2\tilde{v_2} + \cdots + c_n\tilde{v_n} = 0$ has one non-trivial solution (other than $c_i = 0$ for all i);
- or: the linear system with augmented matrix $A|\tilde{0}$, where A is the matrix $\left(\vec{v_1}, \vec{v_2} \cdots, \vec{v_n}\right)$, has a non-trivial solution.

Matrix algebra

Definition of a matrix: A matrix of order $m \times n$ is a block of elements arranged in m rows and n columns:

$$A_{m,n} = \begin{pmatrix} a_{1,1} & a_{1,2} & \cdots & a_{1,n} \\ a_{2,1} & a_{2,2} & \cdots & a_{2,n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{m,1} & a_{m,2} & \cdots & a_{m,n} \end{pmatrix}$$

A **square matrix** is a matrix which has the same number of rows and columns, and a **diagonal matrix** has non-zero coefficients on the diagonal only. Column vectors and row vectors are particular matrices of order $(m, 1)$ and $(1, n)$ respectively.

Scalar product: this is the product of a row vector and a column vector which both have the same number of elements. Given a row vector $r = \left(a_1, a_2, \cdots a_n\right)$ and a column vector $c = \left(b_1, b_2, \cdots b_n\right)$, then the scalar product of r and c is:

$$r \cdot c = \sum_{i=1}^{n} a_i b_i$$

Multiplication of matrices: you can only multiply a matrix A (l,**m**) with a matrix B (**m**,n) and you get a matrix of order (l,n). Then the matrix $C = A \cdot B$ has coefficients:

$$c_{i,j} = \sum_{k=1}^{m} a_{i,k} b_{k,j}$$

Trace of a square matrix A: this is the sum of all elements on the diagonal of A.

Determinant of a square matrix A: this is written $|A|$ or $\det A$. The determinant of a matrix $A_{2,2}$ is

$$\det A = a_{1,1}a_{2,2} - a_{1,2}a_{2,1}$$

For matrices $A_{n,n}$ of higher order:

$$\det A = \sum_{j=1}^{n} (-1)^{i+j} M_{i,j} a_{i,j}$$

where $M_{i,j}$ is the minor, i.e. the determinant of the matrix obtained by removing row i and column j from A. The term $(-1)^{i+j}M_{i,j}$ is called **the cofactor** of $a_{i,j}$.

Transpose of a square matrix A: this is written A^T or A' and it is obtained by flipping the rows and columns of the matrix. The transpose of a row vector becomes a column vector. Given 2 matrices A and B and a scalar k, we have the following properties:

$$\begin{aligned} (A^T)^T &= A \\ (kA)^T &= kA^T \\ (A+B)^T &= A^T + B^T \\ (AB)^T &= B^T A^T \end{aligned}$$

Inverse of a square matrix A (n,n): is a matrix, written A^{-1}, such that $AA^{-1} = A^{-1}A = I_n$ where I_n is the identity matrix: $\begin{pmatrix} 1 & 0 & \cdots & 0 \\ 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 1 \end{pmatrix}$. Not all matrices have an inverse.

The inverse A^{-1} of a matrix A, if it exists, can be calculated with the following formulae: $A^{-1} = \frac{1}{\det A} C^T$ where C is the matrix of cofactors of A. Therefore, if the determinant of a matrix is 0, then it is not invertible. The following properties hold:

$$\begin{aligned}(A^{-1})^{-1} &= A\\ (kA)^{-1} &= \frac{1}{k}A^{-1}\\ (AB)^{-1} &= B^{-1}A^{-1}\\ (A^T)^{-1} &= (A^{-1})^T\end{aligned}$$

Rank of a matrix: this is the order of the largest square sub-matrix with non-zero determinant. Alternatively, this is the number of rows (equivalently columns) which are linearly independent.

Elementary row operations: these are used in the Gaussian elimination method to solve systems of equations. There are:

- Interchanging rows;
- Multiplying the elements of a row by a scalar;
- Adding or subtracting to the elements of a row the corresponding elements of another row.

Eigenvalues and eigenvectors: the eigenvalues λ_i and eigenvectors X_i are such that $AX_i = \lambda_i X_i$. The eigenvalues are found by solving the polynomial: $\det(A - \lambda_i I_n) = 0$. The eigenvectors may then be found by solving $AX_i = \lambda_i X_i$.

Differential Equations

First order ODEs of the form $\frac{dy}{dt} = f(y)g(t)$ can be solved by the **method of separation of variables**:

$\int \frac{dy}{f(y)} = \int g(t)dt$ so $H(y) = G(t) + C$ where C is a constant of integration. It may be possible to rearrange and get an explicit expression for y. A classic example is the ODE $\frac{dy}{dt} = ay$ which has solution $y = Ce^{at}$.

First order ODEs of the form $\frac{dy}{dt} + P(t)y = Q(t)$ can be solved by the **method of integrating factor**.

Define the integrating factor $IF(t) = e^{\int P(u)du}$ then $y(t) = e^{-\int P(u)du}\left(\int Q(u)IF(u)du + C\right)$ where C is a constant of integration.

Homogeneous second order ODEs are of the form: $a\frac{d^2y}{dt^2} + b\frac{dy}{dt} + cy = 0$.

Solutions of these ODEs are: $y(t) = c_1e^{r_1t} + c_2e^{r_2t}$ where (c_1, c_2) are constants of integration and (r_1, r_2) are the solutions of the **characteristic equation** $ar^2 + br + c = 0$.

If the two roots are equal $r_1 = r_2 = r$ then the solutions of the ODEs are $y(t) = c_1e^{rt} + c_2te^{rt}$.

Second order ODEs with right hand side are of the form $a\frac{d^2y}{dt^2} + b\frac{dy}{dt} + cy = f(t)$. The solutions of these ODEs are of the form $y(t) = y_H(t) + y_P(t)$ where $y_H(t)$ is the solution of the corresponding homogeneous ODE found as above and $y_P(t)$ is a particular integral of the ODE. The form of the particular integral will be found using guidelines on Table 1.

Table 1: Finding a particular integral to a second order ODE with right hand side. The constants C and D are found by 'plugging' the particular integral in the ODE, which will lead to conditions that define C and D.

For f(x) of the form:	Try a particular integral of the form:
k	C
kx	Cx + D
kx^2	$Cx^2 + Dx + E$
$k\sin x$ or $k\cos x$	$C\cos x + D\sin x$
$k\sinh x$ or $k\cosh x$	$C\cosh x + D\sinh x$
e^{kx}	Ce^{kx}
e^{rx}, where r is a root of the characteristic equation	Cxe^{rx} or Cx^2e^{rx}

Solving systems of two linear first order differential equations : we will only consider systems of 2 equations in this leaflet.

$$\begin{cases}\frac{dx}{dt} = & a_{11}x + a_{12}y\\ \frac{dy}{dt} = & a_{21}x + a_{22}y\end{cases}$$

We write $X = \begin{pmatrix}x\\y\end{pmatrix}$ and $A = \begin{pmatrix}a_{11} & a_{12}\\ a_{21} & a_{22}\end{pmatrix}$. Then the system of ODEs is equivalent to $\frac{dX}{dt} = AX$ and the solutions are: $X = c_1V_1e^{\lambda_1t} + c_2V_2e^{\lambda_2t}$, where (λ_1, λ_2) are the eigenvalues and (V_1, V_2) are the eigenvectors of the matrix A. The eigenvalues can be found using the following formulae: $\lambda_{1,2} = \frac{\beta \pm \sqrt{\beta^2 - 4\gamma}}{2}$ with $\beta = \mathrm{tr}(A)$ and $\gamma = \det A$.

An equilibrium solution is a solution for which $\frac{dy}{dt} = 0$ (for a first order ODE) or $\frac{dX}{dt} = \begin{pmatrix}0\\0\end{pmatrix}$ (for a system of ODEs). In the case of a first order ODE, an equilibrium may be attracting (sink) if nearby solutions (i.e. solutions with initial condition close to the equilibrium) converge to the equilibrium or repelling (source) if nearby solutions diverge from it. For a system of ODEs, the stability of the equilibrium may be classified as follows (see Figure 1):

- If $\beta < 0$ and $\gamma > 0$, the equilibrium is stable (stable node is $\beta^2 > 4\gamma$ and stable spiral is $\beta^2 < 4\gamma$);
- If $\gamma < 0$, the equilibrium is a saddle point;
- If $\beta = 0$ and $\gamma > 0$, the equilibrium is a neutral centre;
- If $\beta > 0$ and $\gamma > 0$, the equilibrium is unstable (unstable node if $\beta^2 > 4\gamma$ and unstable spiral if $\beta^2 < 4\gamma$).

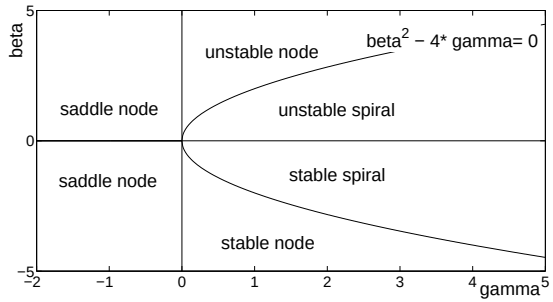

Figure 1: $\beta - \gamma$ parameter plane: change in the nature of an equilibrium with the value of the trace (β) and determinant (γ) of the system matrix.

Systems of non-linear equations are usually not solvable analytically but can be linearised around an equilibrium point. Consider a system with equilibrium $(\mathrm{x}_0, \mathrm{y}_0)$:

$$\begin{cases} \dfrac{\mathrm{dx}}{\mathrm{dt}} = & \mathrm{F}(\mathrm{x},\mathrm{y}) \\ \dfrac{\mathrm{dy}}{\mathrm{dt}} = & \mathrm{G}(\mathrm{x},\mathrm{y}) \end{cases}$$

Then in the neighbourhood of $(\mathrm{x}_0, \mathrm{y}_0)$, the system can be approximated to: $\dfrac{\mathrm{dX}}{\mathrm{dt}} = \mathrm{J}(\mathrm{x}_0,\mathrm{y}_0)\mathrm{X}$ with the Jacobian matrix $\mathrm{J}(\mathrm{x}_0,\mathrm{y}_0) = \begin{pmatrix} \dfrac{\partial \mathrm{F}}{\partial \mathrm{x}}(\mathrm{x}_0,\mathrm{y}_0) & \dfrac{\partial \mathrm{F}}{\partial \mathrm{y}}(\mathrm{x}_0,\mathrm{y}_0) \\ \dfrac{\partial \mathrm{G}}{\partial \mathrm{x}}(\mathrm{x}_0,\mathrm{y}_0) & \dfrac{\partial \mathrm{G}}{\partial \mathrm{y}}(\mathrm{x}_0,\mathrm{y}_0) \end{pmatrix}$

Partial derivatives and Partial Differential Equations

First partial derivatives: consider a function of two variable $\mathrm{f}(\mathrm{x},\mathrm{y})$, then:

- the first derivative of f with respect to x, $\dfrac{\partial \mathrm{f}}{\partial \mathrm{x}}$ or f_x, is obtained by differentiating f **treating y as a constant**;
- the first derivative of f with respect to y, $\dfrac{\partial \mathrm{f}}{\partial \mathrm{y}}$ or f_y, is obtained by differentiating f **treating x as a constant**;

Second partial derivatives: are obtained by differentiating $\dfrac{\partial \mathrm{f}}{\partial \mathrm{x}}$ and $\dfrac{\partial \mathrm{f}}{\partial \mathrm{y}}$. There are therefore 4 second derivatives, i.e.:

- $\dfrac{\partial^2 \mathrm{f}}{\partial \mathrm{x}^2}$ (or f_{xx}) which is obtained by differentiating $\dfrac{\partial \mathrm{f}}{\partial \mathrm{x}}$ with respect to x once more (treating y as a constant again);
- $\dfrac{\partial^2 \mathrm{f}}{\partial \mathrm{y}^2}$ (or f_{yy}) which is obtained by differentiating $\dfrac{\partial \mathrm{f}}{\partial \mathrm{y}}$ with respect to y once more (treating x as a constant again);
- $\dfrac{\partial^2 \mathrm{f}}{\partial \mathrm{y}\partial \mathrm{x}}$ (or f_{xy}) which is obtained by differentiating $\dfrac{\partial \mathrm{f}}{\partial \mathrm{x}}$ with respect to **y** (now treating x as a constant);
- $\dfrac{\partial^2 \mathrm{f}}{\partial \mathrm{x}\partial \mathrm{y}}$ (or f_{yx}) which is obtained by differentiating $\dfrac{\partial \mathrm{f}}{\partial \mathrm{y}}$ with respect to **x** (now treating y as a constant);

For most 'nice' functions, we have $\dfrac{\partial^2 \mathrm{f}}{\partial \mathrm{y}\partial \mathrm{x}} = \dfrac{\partial^2 \mathrm{f}}{\partial \mathrm{x}\partial \mathrm{y}}$

Small increments: given a function f(x,y), it is possible to calculate the increase (or decrease) in f δf if x and y are increased (or decreased) by δx and δy: $\delta \mathrm{f} = \dfrac{\partial \mathrm{f}}{\partial \mathrm{x}}\delta\mathrm{x} + \dfrac{\partial \mathrm{f}}{\partial \mathrm{y}}\delta\mathrm{y}$.

Change of variables:

case 1: if $\mathrm{f} = \mathrm{f}(\mathrm{x},\mathrm{y})$ with $\mathrm{x} = \mathrm{x}(\mathrm{t})$ and $\mathrm{y} = \mathrm{y}(\mathrm{t})$, then $\dfrac{\mathrm{df}}{\mathrm{dt}}$ (also writen as f'(t) or $\dot{\mathrm{f}}(\mathrm{t})$) $= \dfrac{\partial \mathrm{f}}{\partial \mathrm{x}}\dfrac{\mathrm{dx}}{\mathrm{dt}} + \dfrac{\partial \mathrm{f}}{\partial \mathrm{y}}\dfrac{\mathrm{dy}}{\mathrm{dt}}$.

case 2: if $\mathrm{f} = \mathrm{f}(\mathrm{x},\mathrm{y})$ with $\mathrm{y} = \mathrm{y}(\mathrm{x})$ then $\dfrac{\mathrm{df}}{\mathrm{dx}} = \dfrac{\partial \mathrm{f}}{\partial \mathrm{x}} + \dfrac{\partial \mathrm{f}}{\partial \mathrm{y}}\dfrac{\mathrm{dy}}{\mathrm{dx}}$.

case 3: if $\mathrm{f} = \mathrm{f}(\mathrm{x},\mathrm{y})$, $\mathrm{x} = \mathrm{x}(\mathrm{u},\mathrm{v})$ and $\mathrm{y} = \mathrm{y}(\mathrm{u},\mathrm{v})$ then:

$$\begin{cases} \dfrac{\partial \mathrm{f}}{\partial \mathrm{u}} = & \dfrac{\partial \mathrm{f}}{\partial \mathrm{x}}\dfrac{\partial \mathrm{x}}{\partial \mathrm{u}} + \dfrac{\partial \mathrm{f}}{\partial \mathrm{y}}\dfrac{\partial \mathrm{y}}{\partial \mathrm{u}} \\ \dfrac{\partial \mathrm{f}}{\partial \mathrm{v}} = & \dfrac{\partial \mathrm{f}}{\partial \mathrm{x}}\dfrac{\partial \mathrm{x}}{\partial \mathrm{v}} + \dfrac{\partial \mathrm{f}}{\partial \mathrm{y}}\dfrac{\partial \mathrm{y}}{\partial \mathrm{v}} \end{cases}$$

Differential: the differential of $\mathrm{f} = \mathrm{f}(\mathrm{x},\mathrm{y})$ is $\mathrm{df} = \dfrac{\partial \mathrm{f}}{\partial \mathrm{x}}\mathrm{dx} + \dfrac{\partial \mathrm{f}}{\partial \mathrm{y}}\mathrm{dy}$. Inversely, the expression $\mathrm{G}(\mathrm{x},\mathrm{y})\mathrm{dx} + \mathrm{H}(\mathrm{x},\mathrm{y})\mathrm{dy}$ is an exact differential, i.e., there exists a function $\mathrm{f}(\mathrm{x},\mathrm{y})$ so that $\dfrac{\partial \mathrm{f}}{\partial \mathrm{x}} = \mathrm{G}(\mathrm{x},\mathrm{y})$ and $\dfrac{\partial \mathrm{f}}{\partial \mathrm{y}} = \mathrm{H}(\mathrm{x},\mathrm{y})$ if $\dfrac{\partial \mathrm{G}}{\partial \mathrm{y}} = \dfrac{\partial \mathrm{H}}{\partial \mathrm{x}}$.

Partial differential equations (PDE)

Direct integration: if $\dfrac{\partial \mathrm{f}}{\partial \mathrm{x}} = \mathrm{u}(\mathrm{x},\mathrm{y})$ then $\mathrm{f}(\mathrm{x},\mathrm{y}) = \int \mathrm{u}(\mathrm{x},\mathrm{y})\mathrm{dx} + \mathrm{v}(\mathrm{y})$ where $\mathrm{v}(\mathrm{y})$ is a function of y only which can be determined by the initial conditions.

Separation of variables: this method is used to solve 3 classes of PDEs:

- The heat equation: $\dfrac{\partial \mathrm{u}}{\partial \mathrm{t}} = \mathrm{k}^2\dfrac{\partial^2 \mathrm{u}}{\partial \mathrm{x}^2}$;
- The wave equation: $\dfrac{\partial^2 \mathrm{u}}{\partial \mathrm{t}^2} = \mathrm{k}^2\dfrac{\partial^2 \mathrm{u}}{\partial \mathrm{x}^2}$;
- Laplace equation: $\dfrac{\partial^2 \mathrm{u}}{\partial \mathrm{x}^2} + \dfrac{\partial^2 \mathrm{u}}{\partial \mathrm{y}^2} = 0$;

The method consists of:

- Assuming that the solution has the form $\mathrm{u}(\mathrm{x},\mathrm{t}) = \varphi(\mathrm{x})\psi(\mathrm{t})$ (or $\mathrm{u}(\mathrm{x},\mathrm{y}) = \varphi(\mathrm{x})\psi(\mathrm{y})$ in the case of Laplace equation);
- Putting this into the PDE leads to two independent ODEs which can be solved using ODEs techniques;
- Using the initial ($\mathrm{t} = 0$) and boundary ($\mathrm{x} = 0$ or $\mathrm{x} =$ some number) conditions to determine the constants of integration.

Note that if sine and cosine functions are involved, the initial conditions will often lead to a condition like: $\mathrm{f}(\mathrm{x}) = \sum_\mathrm{n} \mathrm{A}_\mathrm{n}\cos(\mathrm{n}\pi\lambda\mathrm{x})$, where f is some function and λ some scalar. Then it is handy to recognise that the coefficients A_n are the coefficients of the Fourier series of the function f. Most often, a family a function $(\varphi_\mathrm{n}, \psi_\mathrm{n})$ will be solution (usually sine, cosine, sinh or cosh functions), and the principle of superposition states that any linear combination of all the solutions is a solution. The general solution will then be $\mathrm{u}(\mathrm{x},\mathrm{t}) = \sum_\mathrm{n} \varphi_\mathrm{n}(\mathrm{x})\psi_\mathrm{n}(\mathrm{t})$.

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Random Processes

Statistical definitions: The **mean** of a random variable X which has realisations x_i with probability $p(x_i)$ is $< X >= \sum_i x_i p(x_i)$. The moment of order n of X is $< X^n >= \sum_i x_i^n p(x_i)$. It is custom to denote the mean by the Greek letter μ.

The **variance** of X is the moment of order 2 about its mean: $\mathrm{var}(X) =< (X- < X >)^2 >=< X^2 > - < X >^2$. The variance describes the variability of X from its mean. The **standard deviation** of X is the square root of its variance: $\mathrm{std}(X) = \sqrt{\mathrm{var}(X)}$. It is custom to denote the variance and standard deviation respectively by σ^2 and σ.

Mean sum theorem: Given a set of random variables (X_i), $< \sum_i X_i >= \sum_i < X_i >$.

Covariance: For 2 random variables X and Y, the covariance is: $\mathrm{cov}(X,Y) =< XY > - < X >< Y >$. The **correlation coefficient** is defined as:

$$\mathrm{cor}(X,Y) = \frac{\mathrm{cov}(X,Y)}{\sqrt{\mathrm{var}(X)\mathrm{var}(Y)}}.$$

If X and Y are **completely correlated**, then $\mathrm{cor}(X,Y) = 1$, if X and Y are **anti-correlated** then $\mathrm{cor}(X,Y) = -1$ and if X and Y are independent then $\mathrm{cor}(X,Y) = 0$. For 2 independent random variables X and Y: $< XY >=< X >< Y >$.

Variance sum theorem: Given 2 random variables X and Y: $\mathrm{var}(X+Y) = \mathrm{var}(X) + \mathrm{var}(Y) + 2\mathrm{cov}(X,Y)$. If X and Y are independent: $\mathrm{var}(X+Y) = \mathrm{var}(X) + \mathrm{var}(Y)$, and for a set of independent random variables (X_i), $\mathrm{var}(\sum_i X_i) = \sum_i \mathrm{var}(X_i)$.

Combining measurements: If n independent measurements (X_i) are made for a particular quantity, then the average measurement is $\bar{X} = \frac{\sum_i X_i}{n}$ and the variance of the average is $\mathrm{var}(\bar{X}) = \frac{\sum_i \mathrm{var}(X_i)}{n^2}$. If the variance is the same for all measurements, i.e., $\mathrm{var}(X_i) = \mathrm{var}(X)$ then $\mathrm{var}(\bar{X}) = \frac{\mathrm{var}(X)}{n}$. The coefficient of variation is defined as $\frac{\mathrm{std}(\bar{X})}{< \bar{X} >}$ and quantifies the precision of the measurement.

Poisson process: is a sequence of discrete events taking place at rate λ which is such that the number of observations $N(t)$ in an interval of length t is Poisson distributed, i.e.

$$P(N(t) = n) = \frac{(\lambda t)^n}{n!} e^{-\lambda t}$$

and the number of events in disjoint time intervals are independent of each other. Then, the time to the next event, T (which is a continuous random variable), is exponentially distributed, i.e.:

$$P(T \le t) = 1 - e^{-\lambda t}$$

This process is memoryless, i.e.: $P(T > (t+s)|T > t) = P(T > s)$.

The Poisson process is very important and widely used to model statistical processes in Physics, Chemistry and Biology.

Decay rate and half-life: the half-life $T_{1/2}$ is the time at which the population is halved: $N(T_{1/2}) = \frac{N(0)}{2}$ and is related to the rate of decay λ of the process by the relationship: $T_{1/2} = \frac{\ln 2}{\lambda}$.

Numerical methods

Given the ODE $\frac{dy}{dx} = f(x,y)$ and the initial condition $y(x_0) = y_0$, we look at methods of integrating the ODE numerically.

Euler scheme: we know from Taylor series that:

$$\begin{aligned} y(x+h) &= y(x) + h\frac{dy}{dx}(x) + \frac{h^2}{2}\frac{d^2y}{dx^2}(x) + \cdots \\ y(x+h) &\approx y(x) + hf(x,y) \end{aligned}$$

Therefore we get the recurrence relationship which is the Euler scheme:

$$\begin{aligned} y(x_0) &= y_0 \\ y_{n+1} &= y(x_{n+1}) = y_n + hf(x_n, y_n) \end{aligned}$$

The error will depend on the value of h chosen, so the smaller the value of h, the smaller the error.

Runge-Kutta scheme: The idea is the same as for the Euler scheme (approximation using Taylor polynomials), but the approximation is usually more accurate than with the Euler scheme.

The formulae for the second-order Runge-Kutta method are:

$$\begin{aligned} k_1 &= hf(x_n, y_n) \\ k_2 &= hf(x_n + \frac{1}{2}h, y_n + \frac{1}{2}k_1) \\ y_{n+1} &= y_n + k_2 \end{aligned}$$

The formulae for the fourth-order Runge-Kutta method (which is used most widely) are:

$$\begin{aligned} k_1 &= hf(x_n, y_n) \\ k_2 &= hf(x_n + \frac{1}{2}h, y_n + \frac{1}{2}k_1) \\ k_3 &= hf(x_n + \frac{1}{2}h, y_n + \frac{1}{2}k_2) \\ k_4 &= hf(x_n + h, y_n + k_3) \\ y_{n+1} &= y_n + \frac{k_1}{6} + \frac{k_2}{3} + \frac{k_3}{3} + \frac{k_4}{6} \end{aligned}$$