Contents

Preface to the Second Edition xiii
Preface to the First Edition xv
Symbols and Physical Constants xvii
Acknowledgements xxi

1 Useful Concepts in Molecular Modelling 1
   1.1 Introduction 1
   1.2 Coordinate Systems 2
   1.3 Potential Energy Surfaces 4
   1.4 Molecular Graphics 5
   1.5 Surfaces 6
   1.6 Computer Hardware and Software 8
   1.7 Units of Length and Energy 9
   1.8 The Molecular Modelling Literature 9
   1.9 The Internet 9
   1.10 Mathematical Concepts 10
   Further Reading 24
   References 24

2 An Introduction to Computational Quantum Mechanics 26
   2.1 Introduction 26
   2.2 One-electron Atoms 30
   2.3 Polyelectronic Atoms and Molecules 34
   2.4 Molecular Orbital Calculations 41
   2.5 The Hartree–Fock Equations 51
   2.6 Basis Sets 65
   2.7 Calculating Molecular Properties Using ab initio Quantum Mechanics 74
   2.8 Approximate Molecular Orbital Theories 86
   2.9 Semi-empirical Methods 86
   2.10 Hückel Theory 99
   2.11 Performance of Semi-empirical Methods 102
   Appendix 2.1 Some Common Acronyms Used in Computational Quantum Chemistry 104
   Further Reading 105
   References 105
CHAPTER ONE

Useful Concepts in Molecular Modelling

1.1 Introduction

What is molecular modelling? 'Molecular' clearly implies some connection with molecules. The Oxford English Dictionary defines 'model' as 'a simplified or idealised description of a system or process, often in mathematical terms, devised to facilitate calculations and predictions'. Molecular modelling would therefore appear to be concerned with ways to mimic the behaviour of molecules and molecular systems. Today, molecular modelling is invariably associated with computer modelling, but it is quite feasible to perform some simple molecular modelling studies using mechanical models or a pencil, paper and hand calculator. Nevertheless, computational techniques have revolutionised molecular modelling to the extent that most calculations could not be performed without the use of a computer. This is not to imply that a more sophisticated model is necessarily any better than a simple one, but computers have certainly extended the range of models that can be considered and the systems to which they can be applied.

The 'models' that most chemists first encounter are molecular models such as the 'stick' models devised by Dreiding or the 'space filling' models of Corey, Pauling and Koltun (commonly referred to as CPK models). These models enable three-dimensional representations of the structures of molecules to be constructed. An important advantage of these models is that they are interactive, enabling the user to pose 'what if …' or 'is it possible to …' questions. These structural models continue to play an important role both in teaching and in research, but molecular modelling is also concerned with more abstract models, many of which have a distinguished history. An obvious example is quantum mechanics, the foundations of which were laid many years before the first computers were constructed.

There is a lot of confusion over the meaning of the terms 'theoretical chemistry', 'computational chemistry' and 'molecular modelling'. Indeed, many practitioners use all three labels to describe aspects of their research, as the occasion demands! 'Theoretical chemistry' is often considered synonymous with quantum mechanics, whereas computational chemistry encompasses not only quantum mechanics but also molecular mechanics, minimisation, simulations, conformational analysis and other computer-based methods for understanding and predicting the behaviour of molecular systems. Molecular modellers use all of these methods and so we shall not concern ourselves with semantics but rather shall consider any theoretical or computational technique that provides insight into the behaviour of molecular systems to be an example of molecular modelling. If a distinction has to be
made, it is in the emphasis that molecular modelling places on the representation and
manipulation of the structures of molecules, and properties that are dependent upon
those three-dimensional structures. The prominent part that computer graphics has
played in molecular modelling has led some scientists to consider molecular modelling as
little more than a method for generating 'pretty pictures', but the technique is now firmly
established, widely used and accepted as a discipline in its own right.

A closely related subject is molecular informatics. This is a rather new term, making a precise
definition difficult, but it is usually considered to encompass two disciplines: chemoinfor-
matics and bioinformatics. Of these two areas, chemoinformatics (also written cheminfor-
matics) is the newer name but the older discipline; chemists have been using computers
to store, retrieve and manipulate information about molecules almost since computers
were invented. Both chemoinformatics and bioinformatics have risen to prominence primar-
ily as a consequence of the introduction of new experimental techniques. For the chemist
these experimental techniques are combinatorial library synthesis and high-throughput
screening, which enable very large numbers of molecules to be synthesised and tested; for
the biologist they are the automated sequencing machines that are being used to determine
the human genome. A characteristic feature of molecular informatics is that it is concerned
with information about large numbers of molecules, much larger than is typically the case
for a traditional molecular modelling study. For this reason, informatics was initially
more concerned with less complex representations of molecules that did not fully represent
their three-dimensional properties. However, even this distinction is now being eroded and
there is increasing use made of more traditional molecular modelling techniques within
informatics.

In the rest of this chapter we shall discuss a number of concepts and techniques that
are relevant to many areas of molecular modelling and so do not sit comfortably in any
individual chapter. We will also define some of the terms that will be used throughout
the book.

1.2 Coordinate Systems

It is obviously important to be able to specify the positions of the atoms and/or molecules
in the system to a modelling program*. There are two common ways in which this can be
done. The most straightforward approach is to specify the Cartesian \((x, y, z)\) coordinates of
all the atoms present. The alternative is to use internal coordinates, in which the position
of each atom is described relative to other atoms in the system. Internal coordinates are
usually written as a Z-matrix. The Z-matrix contains one line for each atom in the
system. A sample Z-matrix for the staggered conformation of ethane (see Figure 1.1) is

*For a system containing a large number of independent molecules it is common to use the
term 'configuration' to refer to each arrangement; this use of the word 'configuration' is not to be con-
 fused with its standard chemical meaning as a different bonding arrangement of the atoms in a
molecule
as follows:

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In the first line of the Z-matrix we define atom 1, which is a carbon atom. Atom number 2 is also a carbon atom that is a distance of 1.54 Å from atom 1 (columns 3 and 4). Atom 3 is a hydrogen atom that is bonded to atom 1 with a bond length of 1.0 Å. The angle formed by atoms 2–1–3 is 109.5°, information that is specified in columns 5 and 6. The fourth atom is a hydrogen, a distance of 1.0 Å from atom 2, the angle 4–2–1 is 109.5°, and the torsion angle (defined in Figure 1.2) for atoms 4–2–1–3 is 180°. Thus for all except the first three atoms, each atom has three internal coordinates: the distance of the atom from one of the atoms previously defined, the angle formed by the atom and two of the previous atoms, and the torsion angle defined by the atom and three of the previous atoms. Fewer internal coordinates are required for the first three atoms because the first atom can be placed anywhere in space (and so it has no internal coordinates); for the second atom it is only necessary to specify its distance from the first atom and then for the third atom only a distance and an angle are required.

It is always possible to convert internal to Cartesian coordinates and vice versa. However, one coordinate system is usually preferred for a given application. Internal coordinates can usefully describe the relationship between the atoms in a single molecule, but Cartesian coordinates may be more appropriate when describing a collection of discrete molecules. Internal coordinates are commonly used as input to quantum mechanics programs, whereas calculations using molecular mechanics are usually done in Cartesian coordinates. The total number of coordinates that must be specified in the internal coordinate system is six fewer
A torsion angle $A$-$B$-$C$-$D$ is defined as the angle between the planes $A$, $B$, $C$ and $B$, $C$, $D$. A torsion angle can vary through $360^\circ$ although the range $-180^\circ$ to $+180^\circ$ is most commonly used. We shall adopt the IUPAC definition of a torsion angle in which an eclipsed conformation corresponds to a torsion angle of $0^\circ$ and a trans or anti conformation to a torsion angle of $180^\circ$. The reader should note that this may not correspond to some of the definitions used in the literature, where the trans arrangement is defined as a torsion angle of $0^\circ$. If one looks along the bond $B$-$C$, then the torsion angle is the angle through which it is necessary to rotate the bond $AB$ in a clockwise sense in order to superimpose the two planes, as shown.

than the number of Cartesian coordinates for a non-linear molecule. This is because we are at liberty to arbitrarily translate and rotate the system within Cartesian space without changing the relative positions of the atoms.

1.3 Potential Energy Surfaces

In molecular modelling the Born–Oppenheimer approximation is invariably assumed to operate. This enables the electronic and nuclear motions to be separated; the much smaller mass of the electrons means that they can rapidly adjust to any change in the nuclear positions. Consequently, the energy of a molecule in its ground electronic state can be considered a function of the nuclear coordinates only. If some or all of the nuclei move then the energy will usually change. The new nuclear positions could be the result of a simple process such as a single bond rotation or it could arise from the concerted movement of a large number of atoms. The magnitude of the accompanying rise or fall in the energy will depend upon the type of change involved. For example, about 3 kcal/mol is required to change the covalent carbon–carbon bond length in ethane by 0.1 Å away from its equilibrium value, but only about 0.1 kcal/mol is required to increase the non-covalent separation between two argon atoms by 1 Å from their minimum energy separation. For small isolated molecules, rotation about single bonds usually involves the smallest changes in energy. For example, if we rotate the carbon–carbon bond in ethane, keeping all of the bond lengths and angles fixed in value, then the energy varies in an approximately sinusoidal fashion as shown in Figure 1.3, with minima at the three staggered conformations. The energy in this case can be considered a function of a single coordinate only (i.e. the torsion angle of the carbon–carbon bond), and as such can be displayed graphically, with energy along one axis and the value of the coordinate along the other.
Changes in the energy of a system can be considered as movements on a multidimensional ‘surface’ called the energy surface. We shall be particularly interested in stationary points on the energy surface, where the first derivative of the energy is zero with respect to the internal or Cartesian coordinates. At a stationary point the forces on all the atoms are zero. Minimum points are one type of stationary point; these correspond to stable structures. Methods for locating stationary points will be discussed in more detail in Chapter 5, together with a more detailed consideration of the concept of the energy surface.

1.4 Molecular Graphics

Computer graphics has had a dramatic impact upon molecular modelling. It should always be remembered, however, that there is much more to molecular modelling than computer graphics. It is the interaction between molecular graphics and the underlying theoretical methods that has enhanced the accessibility of molecular modelling methods and assisted the analysis and interpretation of such calculations.

Molecular graphics systems have evolved from delicate and temperamental pieces of equipment that cost hundreds of thousands of pounds and occupied entire rooms, to today’s inexpensive workstations that fit on or under a desk and yet are hundreds of times more powerful. Over the years, two different types of molecular graphics display have been used in molecular modelling. First to be developed were vector devices, which construct pictures using an electron gun to draw lines (or dots) on the screen, in a manner similar to an oscilloscope. Vector devices were the mainstay of molecular modelling for almost two decades but have now been largely superseded by raster devices. These divide the screen into a large number of small ‘dots’, called pixels. Each pixel can be set to any of a large number of colours, and so by setting each pixel to the appropriate colour it is possible to generate the desired image.

Molecules are most commonly represented on a computer graphics screen using ‘stick’ or ‘space-filling’ representations, which are analogous to the Dreiding and Corey-Pauling-Koltun (CPK) mechanical models. Sophisticated variations on these two basic types have
been developed, such as the ability to colour molecules by atomic number and the inclusion of shading and lighting effects, which give 'solid' models a more realistic appearance. Some of the commonly used molecular representations are shown in Figure 1.4 (colour plate section). Computer-generated models do have some advantages when compared with their mechanical counterparts. Of particular importance is the fact that a computer model can be very easily interrogated to provide quantitative information, from simple geometrical measures such as the distance between two atoms to more complex quantities such as the energy or surface area. Quantitative information such as this can be very difficult if not impossible to obtain from a mechanical model. Nevertheless, mechanical models may still be preferred in certain types of situation due to the ease with which they can be manipulated and viewed in three dimensions. A computer screen is inherently two-dimensional, whereas molecules are three-dimensional objects. Nevertheless, some impression of the three-dimensional nature of an object can be represented on a computer screen using techniques such as depth cueing (in which those parts of the object that are further away from the viewer are made less bright) and through the use of perspective. Specialised hardware enables more realistic three-dimensional stereo images to be viewed. In the future 'virtual reality' systems may enable a scientist to interact with a computer-generated molecular model in much the same way that a mechanical model can be manipulated.

Even the most basic computer graphics program provides some standard facilities for the manipulation of models, including the ability to translate, rotate and 'zoom' the model towards and away from the viewer. More sophisticated packages can provide the scientist with quantitative feedback on the effect of altering the structure. For example, as a bond is rotated then the energy of each structure could be calculated and displayed interactively.

For large molecular systems it may not always be desirable to include every single atom in the computer image: the sheer number of atoms can result in a very confusing and cluttered picture. A clearer picture may be achieved by omitting certain atoms (e.g. hydrogen atoms) or by representing groups of atoms as single 'pseudo-atoms'. The techniques that have been developed for displaying protein structures nicely illustrate the range of computer graphics representation possible (the use of computational techniques to investigate the structures of proteins is considered in Chapter 10). Proteins are polymers constructed from amino acids, and even a small protein may contain several thousand atoms. One way to produce a clearer picture is to dispense with the explicit representation of any atoms and to represent the protein using a 'ribbon'. Proteins are also commonly represented using the cartoon drawings developed by J Richardson, an example of which is shown in Figure 1.5 (colour plate section). The cylinders in this figure represent an arrangement of amino acids called an α-helix, and the flat arrows an alternative type of regular structure called a β-strand. The regions between the cylinders and the strands have no such regular structure and are represented as 'tubes'.

1.5 Surfaces

Many of the problems that are studied using molecular modelling involve the non-covalent interaction between two or more molecules. The study of such interactions is often facilitated
Useful Concepts in Molecular Modelling

by examining the van der Waals, molecular or accessible surfaces of the molecule. The *van der Waals* surface is simply constructed from the overlapping van der Waals spheres of the atoms, Figure 1.6. It corresponds to a CPK or space-filling model. Let us now consider the approach of a small 'probe' molecule, represented as a single van der Waals sphere, up to the van der Waals surface of a larger molecule. The finite size of the probe sphere means that there will be regions of 'dead space', crevices that are not accessible to the probe as it rolls about on the larger molecule. This is illustrated in Figure 1.6. The amount of dead space increases with the size of the probe; conversely, a probe of zero size would be able to access all of the crevices. The *molecular surface* [Richards 1977] is traced out by the inward-facing part of the probe sphere as it rolls on the van der Waals surface of the molecule. The molecular surface contains two different types of surface element. The *contact surface* corresponds to those regions where the probe is actually in contact with the van der Waals surface of the 'target'. The *re-entrant* surface regions occur where there are crevices that are too narrow for the probe molecule to penetrate. The molecular surface is usually defined using a water molecule as the probe, represented as a sphere of radius $1.4 \text{Å}$.

The *accessible surface* is also widely used. As originally defined by Lee and Richards [Lee and Richards 1971] this is the surface that is traced by the centre of the probe molecule as it rolls on the van der Waals surface of the molecule (Figure 1.6). The centre of the probe molecule can thus be placed at any point on the accessible surface and not penetrate the van der Waals spheres of any of the atoms in the molecule.

Widely used algorithms for calculating the molecular and accessible surfaces were developed by Connolly [Connolly 1983a,b], and others [e.g. Richmond 1984] have described formulae for the calculation of exact or approximate values of the surface area. There are many ways to represent surfaces, some of which are illustrated in Figure 1.7 (colour plate section). As shown, it may also be possible to endow a surface with a translucent quality, which enables the molecule inside the surface to be displayed. Clipping can also be used.
to cut through the surface to enable the ‘inside’ to be viewed. In addition, properties such as the electrostatic potential can be calculated on the surface and represented using an appropriate colour scheme. Useful though these representations are, it is important to remember that the electronic distribution in a molecule formally extends to infinity. The ‘hard sphere’ representation is often very convenient and has certainly proved very valuable, but it may not be appropriate in all cases [Rouvray 1997, 1999, 2000].

1.6 Computer Hardware and Software

One cannot fail to be amazed at the pace of development in the computer industry, where the ratio of performance-to-price has increased by an order of magnitude every five years or so. The workstations that are commonplace in many laboratories now offer a real alternative to centrally maintained ‘supercomputers’ for molecular modelling calculations, especially as a workstation or even a personal computer can be dedicated to a single task, whereas the supercomputer has to be shared with many other users. Nevertheless, in the immediate future there will always be some calculations that require the power that only a supercomputer can offer. The speed of any computer system is ultimately constrained by the speed at which electrical signals can be transmitted. This means that there will come a time when no further enhancements can be made using machines with ‘traditional’ single-processor serial architectures, and parallel computers will play an ever more important role.

A parallel computer couples processors together in such a way that a calculation is divided into small pieces with the results being combined at the end. Some calculations are more amenable to parallel processing than others, and a significant amount of effort is being spent converting existing algorithms to run efficiently on parallel architectures. In some cases completely new methods have been developed to take maximum advantage of the opportunities of parallel processing. The low cost of personal computer chips means that large ‘farms’ of processors can be constructed to give significant computing power for relatively small outlay.

To perform molecular modelling calculations one also requires appropriate programs (the software). The software used by molecular modellers ranges from simple programs that perform just a single task to highly complex packages that integrate many different methods. There is also an extremely wide variation in the price of software! Some programs have been so widely used and tested that they can be considered to have reached the status of a ‘gold standard’ against which similar programs are compared. One hesitates to specify such programs in print, but three items of software have been so widely used and cited that they can safely be afforded the accolade. These are the Gaussian series of programs for performing ab initio quantum mechanics, the MOPAC/AMPAC programs for semi-empirical quantum mechanics and the MM2 program for molecular mechanics.

Various pieces of software were used to generate the data for the examples and illustrations throughout this book. Some of these were written specifically for the task; some were freely available programs; others were commercial packages. I have decided not to describe specific programs in any detail, as such descriptions rapidly become outdated. Nevertheless,
all items of software are accredited where appropriate. Please note that the use of any particular piece of software does not imply any recommendation!

1.7 Units of Length and Energy

It will be noted that our Z-matrix for ethane has been defined using the ångström as the unit of length (1 Å ≡ 10⁻¹⁰ m ≡ 100 pm). The ångström is a non-SI unit but is a very convenient one to use, as most bond lengths are of the order of 1–2 Å. One other very common non-SI unit found in the molecular modelling literature is the kilocalorie (1 kcal ≡ 4.1840 kJ). Other systems of units are employed in other types of calculation, such as the atomic units used in quantum mechanics (discussed in Chapter 2). It is important to be aware of, and familiar with, these non-standard units as they are widely used in the literature and throughout this book.

1.8 The Molecular Modelling Literature

The number of scientific papers concerned with molecular modelling methods is rising rapidly, as is the number of journals in which such papers are published. This reflects the tremendous diversity of problems to which molecular modelling can be applied and the ever-increasing availability of molecular modelling methods. It does, however, mean that it can be very difficult to remain up to date with the field. A number of specialist journals are devoted to theoretical chemistry, computational chemistry and molecular modelling, each with their own particular emphasis. Relevant papers are also published in the more ‘general’ journals, and there are now a number of books covering aspects of molecular modelling, some aimed at the specialist reader, others at the beginner. Many scientists are now fortunate to have access to electronic catalogues of publications which can be searched to find relevant papers. As many journals are now available over the internet it is possible to perform a literature search and obtain copies of the relevant papers without even having to leave the office. Some of the journals which are devoted to short reviews of recent developments often include molecular modelling sections (such as the ‘Current Opinion’ series); in others, useful review articles appear on an occasional basis. One particularly valuable source of information on molecular modelling methods is the Reviews in Computational Chemistry, edited by Lipkowitz and Boyd, beginning in 1990 (see Further Reading). Each of these volumes contains chapters on a variety of subjects, each written by an appropriate expert. A recent addition is the Encyclopaedia of Computational Chemistry by Schleyer et al. (1998) (see Further Reading), which contains many chapters that cover a wide range of topics.

1.9 The Internet

In the first edition of this book I wrote, ‘A major use of the Internet is for electronic mail, but extremely rapid growth is being observed in other areas, particularly the “World-Wide Web” (WWW). ’. Such a phrase seems an understatement; despite the ’hype’, the Internet has certainly made a dramatic impact, not least on the scientific community, where its
origins lie. Anything written about the Internet is almost certain to become obsolete more rapidly than any other topic in this book and so this section will be brief. I will assume that all readers of this book will be familiar with the use of a web browser and the concept of a hyperlink, which enables documents to be linked together. The URL (Uniform Resource Locator) is the currency of the WWW, being the 'electronic address' which enables the particular item to be identified. Most documents are still written using HTML (HyperText Markup Language) but increasingly incorporate more sophisticated features. Given the tremendous growth in the Web it is important to be able to locate relevant information. This is the role of the Internet search engines, which can be used to identify relevant sites of interest via some form of keyword search. Within the molecular modelling context, several trends can be noted. Whilst the Web was initially used to distribute mostly textual information, it is increasingly used for much more sophisticated applications. Interactive molecular graphics are a feature of many sites. Some sites enable calculations or database searches to be performed via the Web, with the results being delivered interactively or via email. This is particularly true for 'intranets' within an organisation. XML (eXtensible Markup Language) is likely to play an increasingly important role in the 'intelligent' exchange of information over the Web, especially in specialist areas such as chemistry [Murray-Rust and Rzepa 1999]. Several 'electronic conferences' have been held with participants from many different countries. Perhaps the only prediction that one can safely make about the Web is that it is here to stay and its use will continue to grow.

1.10 Mathematical Concepts

A full appreciation of all of the techniques of molecular modelling would require a mathematical treatment beyond that appropriate to a book of this size and scope. However, a proper understanding does benefit from some knowledge of mathematical concepts such as vectors, matrices, differential equations, complex numbers, series expansions and Lagrangian multipliers, and some very elementary statistical concepts. There is only space in this book for a cursory introduction to these mathematical concepts and ideas, with very brief descriptions and some key results. The suggestions for further reading provide detailed background information on all of the mathematical topics required.

1.10.1 Series Expansions

There are various series expansions that are useful for approximating functions. Particularly important is the Taylor series: if $f(x)$ is a continuous, single-valued function of $x$ with continuous derivatives $f'(x), f''(x), \ldots$, then we can expand the function about a point $x_0$ as follows:

$$f(x_0 + x) = f(x_0) + \frac{x}{1!} f'(x_0) + \frac{x^2}{2!} f''(x_0) + \frac{x^3}{3!} f'''(x_0) + \cdots + \frac{x^n}{n!} f^{(n)}(x_0)$$  \hspace{1cm} (1.1)

Taylor series are often truncated after the term involving the second derivative, which makes the function vary in a quadratic fashion. This is a common assumption in many of the minimisation algorithms that we will discuss in Chapter 5.
A Maclaurin series is a specific form of the Taylor series for which \( x_0 = 0 \). Some standard expansions in Taylor series form are:

\[
e^x = 1 + x + \frac{x^2}{2!} + \frac{x^3}{3!} + \frac{x^4}{4!} + \cdots \quad (1.2)
\]

\[
\sin x = x - \frac{x^3}{3!} + \frac{x^5}{5!} - \cdots \quad (1.3)
\]

\[
\ln(1 + x) = x - \frac{x^2}{2} + \frac{x^3}{3} - \frac{x^4}{4} + \cdots \quad (1.4)
\]

The binomial expansion is used for functions of the form \((1 + x)^\alpha\):

\[
(1 + x)^\alpha = 1 + \alpha x + \alpha(\alpha - 1)\frac{x^2}{2!} + \alpha(\alpha - 1)(\alpha - 2)\frac{x^3}{3!} + \cdots \quad (1.5)
\]

All these series must have \(|x| < 1\) to be convergent.

### 1.10.2 Vectors

A vector is a quantity with both magnitude and direction. For example, the velocity of a moving body is a vector quantity as it defines both the direction in which the body is travelling and the speed at which it is moving. In Cartesian coordinates a vector such as the velocity will have three components, indicating the contribution to the overall motion from the component motions along the \(x\), \(y\) and \(z\) directions. The addition and subtraction of vectors can be understood using geometrical constructions, as shown in Figure 1.8. Thus, if we want to calculate the force on an atom due to its interactions with all other atoms in the system (as required in molecular dynamics calculations, see Chapter 7), we would perform a vector sum of all the individual forces.

Some of the common manipulations that are performed with vectors include the scalar product, vector product and scalar triple product, which we will illustrate using vectors \( \mathbf{r}_1 \), \( \mathbf{r}_2 \) and \( \mathbf{r}_3 \) that are defined in a rectangular Cartesian coordinate system:

\[
\mathbf{r}_1 = x_1 \mathbf{i} + y_1 \mathbf{j} + z_1 \mathbf{k}
\]

\[
\mathbf{r}_2 = x_2 \mathbf{i} + y_2 \mathbf{j} + z_2 \mathbf{k}
\]

\[
\mathbf{r}_3 = x_3 \mathbf{i} + y_3 \mathbf{j} + z_3 \mathbf{k}
\]

![Fig 1.8. The addition and subtraction of vectors](image)
i, j and k are orthogonal unit vectors along the x, y and z axes. The scalar product is defined as:

\[ r_1 \cdot r_2 = |r_1| |r_2| \cos \theta \]  
(1.7)

|r_1| and |r_2| are the magnitudes of the two vectors (|r_1| = \sqrt{x_1^2 + y_1^2 + z_1^2}) and \( \theta \) is the angle between them (Figure 1.9). The angle can be calculated as follows:

\[ \cos \theta = \frac{x_1x_2 + y_1y_2 + z_1z_2}{|r_1||r_2|} \]  
(1.8)

The scalar product of two vectors is thus a scalar.

The vector product of two vectors \( r_1 \times r_2 \) (sometimes written \( r_1 \wedge r_2 \)) is a new vector (\( \mathbf{v} \)), in a direction perpendicular to the plane containing the two original vectors (Figure 1.9). The direction of this new vector is such that \( r_1, r_2 \) and the new vector form a right-handed system. If \( r_1 \) and \( r_2 \) are three-component vectors then the components of \( \mathbf{v} \) are given by:

\[ \mathbf{v} = (y_1z_2 - z_1y_2)i + (z_1x_2 - x_1z_2)j + (x_1y_2 - y_1x_2)k \]  
(1.9)

Note that the vector product \( r_2 \times r_1 \) is not the same as the vector product \( r_1 \times r_2 \), as it corresponds to a vector in the opposite direction. The vector product is thus not commutative.

The scalar triple product \( r_1 \cdot (r_2 \times r_3) \) equals the scalar product of \( r_1 \) with the vector product of \( r_2 \) and \( r_3 \). The result is a scalar. The scalar triple product has a useful geometrical interpretation; it is the volume of the parallelepiped whose sides correspond to the three vectors (Figure 1.9).

1.10.3 Matrices, Eigenvectors and Eigenvalues

A matrix is a set of quantities arranged in a rectangular array. An \( m \times n \) matrix has \( m \) rows and \( n \) columns. A vector can thus be considered to be a one-column matrix. Matrix addition
and subtraction can only be performed with matrices of the same order. For example:

If \( A = \begin{pmatrix} 4 & 7 \\ -3 & 5 \\ 8 & -2 \end{pmatrix} \) and \( B = \begin{pmatrix} -4 & 3 \\ 5 & 2 \\ -5 & 3 \end{pmatrix} \)

Then \( A + B = \begin{pmatrix} 0 & 10 \\ 2 & 7 \\ 3 & 1 \end{pmatrix} \); \( A - B = \begin{pmatrix} 8 & 4 \\ -8 & 3 \\ 12 & -5 \end{pmatrix} \) (1.10)

Multiplication of two matrices \( AB \) is only possible if the number of columns in \( A \) is equal to the number of rows in \( B \). If \( A \) is an \( m \times n \) matrix and \( B \) is an \( n \times o \) matrix then the product \( AB \) is an \( m \times o \) matrix. Each element \((i, j)\) in the matrix \( AB \) is obtained by taking each of the \( n \) values in the \( i \)th row of \( A \) and multiplying by the corresponding value in the \( j \)th column of \( B \). To illustrate with a simple example:

If \( A = \begin{pmatrix} 3 & -2 & 5 \\ -3 & 4 & 1 \end{pmatrix} \) and \( B = \begin{pmatrix} 0 & 3 \\ -2 & 4 \\ 1 & 6 \end{pmatrix} \)

Then

\[
AB = \begin{pmatrix} (3 \times 0) + (-2 \times -2) + (5 \times 1) & (3 \times 3) + (-2 \times 4) + (5 \times 6) \\ (-3 \times 0) + (4 \times -2) + (1 \times 1) & (-3 \times 3) + (4 \times 4) + (1 \times 6) \end{pmatrix} = \begin{pmatrix} 9 & 31 \\ -7 & 13 \end{pmatrix}
\] (1.11)

We shall often encounter square matrices, which have the same number of rows and columns. A diagonal matrix is a square matrix in which all the elements are zero except for those on the diagonal. The unit or identity matrix \( I \) is a special type of diagonal matrix in which all the non-zero elements are 1; thus the \( 3 \times 3 \) unit matrix is:

\[
I = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}
\] (1.12)

A matrix is symmetric if it is a square matrix with elements such that the elements above and below the diagonal are mirror images; \( A_{ij} = A_{ji} \).

Multiplication of a matrix by its inverse gives the unit matrix:

\[
A^{-1}A = I
\] (1.13)

To compute the inverse of a square matrix it is necessary to first calculate its determinant, \(|A|\). The determinants of \(2 \times 2\) and \(3 \times 3\) matrices are calculated as follows:

\[
\begin{vmatrix} a & b \\ c & d \end{vmatrix} = ad - bd
\] (1.14)
\[
\begin{vmatrix} a & b & c \\ d & e & f \\ g & h & i \end{vmatrix} = a \begin{vmatrix} e & f \\ h & i \end{vmatrix} - b \begin{vmatrix} d & f \\ g & i \end{vmatrix} + c \begin{vmatrix} d & e \\ g & h \end{vmatrix} = a(\bar{e} - hf) - b(di - \bar{f}g) + c(dh - eg) \quad (1.15)
\]

For example:

\[
\begin{vmatrix} 3 & 6 \\ -2 & 3 \end{vmatrix} = 21; \quad \begin{vmatrix} 4 & 2 & -2 \\ 2 & 5 & 0 \\ -2 & 0 & 3 \end{vmatrix} = 28 \quad (1.16)
\]

As can be seen, the determinant of a \( 3 \times 3 \) matrix can be written as a sum of determinants of \( 2 \times 2 \) matrices, obtained by first selecting one of the rows or columns in the matrix (the top row was chosen in our example). For each element \( A_{ij} \) in this row, the row and column in which that number appears are deleted (i.e. the \( i \)th row and the \( j \)th column). This leaves a \( 2 \times 2 \) matrix whose determinant is calculated and then multiplied by \((-1)^{i+j}\). The result of this calculation is called the \textit{cofactor} of the element \( A_{ij} \). For example, the cofactor of the element \( A_{12} \) in the \( 3 \times 3 \) matrix

\[
A = \begin{pmatrix} 4 & 2 & -2 \\ 2 & 5 & 0 \\ -2 & 0 & 3 \end{pmatrix}
\]

is \(-6\). When calculating the determinant the cofactor is multiplied by the element \( A_{ij} \). The determinants of larger matrices can be obtained by extensions of the scheme illustrated above; thus the determinant of a \( 4 \times 4 \) matrix is initially written in terms of \( 3 \times 3 \) matrices, which in turn can be expressed in terms of \( 2 \times 2 \) matrices.

Determinants have many useful and interesting properties. The determinant of a matrix is zero if any two of its rows or columns are identical. The sign of the determinant is reversed by exchanging any pair of rows or any pair of columns. If all elements of a row (or column) are multiplied by the same number, then the value of the determinant is multiplied by that number. The value of a determinant is unaffected if equal multiples of the values in any row (or column) are added to another row (or column).

The vector product and the scalar triple product can be conveniently written as matrix determinants. Thus:

\[
\mathbf{r}_1 \times \mathbf{r}_2 = \begin{vmatrix} \mathbf{i} & \mathbf{j} & \mathbf{k} \\ x_1 & y_1 & z_1 \\ x_2 & y_2 & z_2 \end{vmatrix} \quad (1.17)
\]

\[
\mathbf{r}_1 \cdot (\mathbf{r}_2 \times \mathbf{r}_3) = \begin{vmatrix} x_1 & y_1 & z_1 \\ x_2 & y_2 & z_2 \\ x_3 & y_3 & z_3 \end{vmatrix} \quad (1.18)
\]
The transpose of a matrix, $A^T$, is the matrix obtained by exchanging its rows and columns. Thus the transpose of an $m \times n$ matrix is an $n \times m$ matrix:

$$\text{If } A = \begin{pmatrix} 4 & 7 \\ -3 & 5 \\ 8 & -2 \end{pmatrix} \text{ then } A^T = \begin{pmatrix} 4 & -3 & 8 \\ 7 & 5 & -2 \end{pmatrix}$$

(1.19)

The transpose of a square matrix is, of course, another square matrix. The transpose of a symmetric matrix is itself. One particularly important transpose matrix is the adjoint matrix, $\text{adj}A$, which is the transpose matrix of cofactors. For example, the matrix of cofactors of the $3 \times 3$ matrix

$$A = \begin{pmatrix} 4 & 2 & -2 \\ 2 & 5 & 0 \\ -2 & 0 & 3 \end{pmatrix} \text{ is } \begin{pmatrix} 15 & -6 & 10 \\ -6 & 8 & -4 \\ 10 & -4 & 16 \end{pmatrix}$$

(1.20)

In this case the adjoint matrix is the same as the matrix of cofactors (as $A$ is a symmetric matrix). The inverse of a matrix is obtained by dividing the elements of the adjoint matrix by the determinant:

$$A^{-1} = \frac{\text{adj}A}{|A|}$$

(1.21)

Thus the inverse of our $3 \times 3$ matrix is

$$A^{-1} = \begin{pmatrix} 15/28 & -3/14 & 5/14 \\ -3/14 & 2/7 & -1/7 \\ 5/14 & -4 & 4/7 \end{pmatrix}$$

(1.22)

One of the most common matrix calculations involves finding its eigenvalues and eigenvectors. An eigenvector is a column matrix $x$ such that

$$Ax = \lambda x$$

(1.23)

$\lambda$ is the associated eigenvalue. The eigenvector problem can be reformulated as follows:

$$Ax = \lambda x \Rightarrow Ax - \lambda Ix = 0 \Rightarrow (A - \lambda I)x = 0$$

(1.24)

A trivial solution to this equation is $x = 0$. For a non-trivial solution, we require that the determinant $|A - \lambda I|$ equals zero. One way to determine the eigenvalues and their associated eigenvectors is thus to expend the determinant to give a polynomial equation in $\lambda$. For our $3 \times 3$ symmetric matrix this gives:

$$\begin{pmatrix} 4 - \lambda & 2 & -2 \\ 2 & 5 - \lambda & 0 \\ -2 & 0 & 3 - \lambda \end{pmatrix}$$

(1.25)

or:

$$(4 - \lambda)(5 - \lambda)(3 - \lambda) - 2[2(3 - \lambda)] - 2[2(5 - \lambda)] = 0$$

(1.26)

This can be factorised to give:

$$(1 - \lambda)(7 - \lambda)(4 - \lambda) = 0$$

(1.27)
The eigenvalues are thus $\lambda_1 = 1$, $\lambda_2 = 4$, $\lambda_3 = 7$. The corresponding eigenvectors are:

\[ \begin{align*}
\lambda_1 &= 1 : \mathbf{x}_1 = \begin{pmatrix} 2/3 \\ -1/3 \\ 2/3 \end{pmatrix} \\
\lambda_2 &= 4 : \mathbf{x}_2 = \begin{pmatrix} -1/3 \\ 2/3 \\ 2/3 \end{pmatrix} \\
\lambda_3 &= 7 : \mathbf{x}_3 = \begin{pmatrix} 2/3 \\ 2/3 \\ -1/3 \end{pmatrix}
\end{align*} \]  

(1.28)

Here we have expressed the eigenvectors as vectors of unit length; any multiple of each eigenvector would also be a solution. A is a real, symmetric matrix. The eigenvalues of such matrices are always real and orthogonal (i.e. the scalar products of all pairs of eigenvectors are zero). This can be easily seen in our example.

As can be readily envisaged, expanding the determinant and solving a polynomial in $\lambda$ is not the most efficient way to determine the eigenvalues and eigenvectors of larger matrices. Matrix diagonalisation methods are much more common. Diagonalisation of a matrix $A$ involves finding a matrix $U$ such that:

\[ U^{-1} A U = D \]  

(1.29)

$D$ is the diagonal matrix of eigenvalues. When $A$ is a real symmetric matrix, then $U$ is the matrix of eigenvectors and $U^{-1}$ is the inverse matrix of eigenvectors. Thus, for our example:

\[ 
\begin{pmatrix}
2/3 & -1/3 & 2/3 \\
-1/3 & 2/3 & 2/3 \\
2/3 & 2/3 & -1/3
\end{pmatrix}
\begin{pmatrix}
4 & 2 & -2 \\
2 & 5 & 0 \\
-2 & 0 & 3
\end{pmatrix}
\begin{pmatrix}
2/3 & -1/3 & 2/3 \\
-1/3 & 2/3 & 2/3 \\
2/3 & 2/3 & -1/3
\end{pmatrix}
\]

\[ = 
\begin{pmatrix}
1 & 0 & 0 \\
0 & 4 & 0 \\
0 & 0 & 7
\end{pmatrix}
\]  

(1.30)

Note that for a real symmetric matrix $A$, the inverse $U^{-1}$ is the same as the transpose, $U^T$.

Many methods have been devised for diagonalising matrices; some of these are specific to certain classes of matrices such as the class of real symmetric matrices. Many modelling techniques require us to calculate the eigenvalues and eigenvectors of a matrix, including self-consistent field quantum mechanics (Section 2.5), the distance geometry method for exploring conformational space (Section 9.5) and principal components analysis (Section 9.13.1). The class of positive definite matrices is important in energy minimisation and when finding transition structures; the eigenvalues of a positive definite matrix are all positive. A positive semidefinite matrix of rank $m$ has $m$ positive eigenvalues.

### 1.10.4 Complex Numbers

A complex number has two components: a real part ($a$) and an imaginary part ($b$), as follows:

\[ x = a + bi \]  

(1.31)
\( i \) is the square root of \(-1\) \((i = \sqrt{-1})\). Complex numbers enable certain types of equation that have no real solutions to be solved. For example, the roots of the equation \(x^2 - 2x + 3 = 0\) are \(x = 1 + \sqrt{2}i\) and \(x = 1 - \sqrt{2}i\). A complex number can be considered as a vector in a two-dimensional coordinate system. Complex numbers are commonly represented using an Argand diagram, in which the \(x\) coordinate corresponds to the real part of the complex number and the \(y\) coordinate to the imaginary part (Figure 1.10).

Arithmetical operations on complex numbers are performed much as for vectors. Thus, if \(x = a + bi\) and \(y = c + di\), then:

\[
x + y = (a + c) + (b + d)i
\]

\[
x - y = (a - c) + (b - d)i
\]

\[
xy = (ac - bd) + (ad + bc)i
\]  

(1.32)  
(1.33)  
(1.34)

The complex conjugate, \(\bar{x}\), equals \(a - bi\) and is obtained by reflecting \(x\) in the real axis in the Argand diagram.

A commonly used relationship involving complex numbers is:

\[
e^{i\theta} = \cos\theta + i\sin\theta
\]  

(1.35)

where \(\theta\) is any real number. This relationship is used in Fourier analysis and can be derived from the expansions of the exponential, cosine and sine functions:

\[
e^{i\theta} = 1 + i\theta - \frac{\theta^2}{2!} - \frac{i\theta^3}{3!} + \frac{\theta^4}{4!} + \cdots
\]  

(1.36)

\[
\sin\theta = \theta - \frac{\theta^3}{3!} + \frac{\theta^5}{5!} - \cdots
\]  

(1.37)

\[
\cos\theta = 1 - \frac{\theta^2}{2!} + \frac{\theta^4}{4!} - \cdots
\]  

(1.38)
Various other relationships can be defined. For example:

\[
\cos \theta = \frac{e^{i\theta} + e^{-i\theta}}{2} \quad \sin \theta = \frac{e^{i\theta} - e^{-i\theta}}{2i}
\]  \hspace{1cm} (1.39)

### 1.10.5 Lagrange Multipliers

Lagrange multipliers can be used to find the stationary points of functions, subject to a set of constraints. Suppose we wish to find the stationary points of a function \( f(x, y) = 4x^2 + 3x + 2y^2 + 6y \) subject to the constraint \( y = 4x + 2 \). In the Lagrange method the constraint is written in the form \( g(x, y) = 0 \):

\[
g(x, y) = y - 4x - 2 = 0
\]  \hspace{1cm} (1.40)

To find stationary points \( f(x, y) \) subject to \( g(x, y) = 0 \) we first determine the total derivative \( df \), which is set equal to zero:

\[
df = \frac{\partial f}{\partial x} dx + \frac{\partial f}{\partial y} dy = (8x + 3)dx + (4y + 6)dy = 0
\]  \hspace{1cm} (1.41)

Without the constraint the stationary points would be determined by setting the two partial derivatives \( \frac{\partial f}{\partial x} \) and \( \frac{\partial f}{\partial y} \) equal to zero, as \( x \) and \( y \) are independent. With the constraint, \( x \) and \( y \) are no longer independent but are related via the derivative of the constraint function \( g \):

\[
dg = \frac{\partial g}{\partial x} dx + \frac{\partial g}{\partial y} dy = -4dx + dy = 0
\]  \hspace{1cm} (1.42)

The derivative of the constraint function, \( dg \), is multiplied by a parameter \( \lambda \) (the Lagrange multiplier) and added to the total derivative \( df \):

\[
\left( \frac{\partial f}{\partial x} + \lambda \frac{\partial g}{\partial x} \right) dx + \left( \frac{\partial f}{\partial y} + \lambda \frac{\partial g}{\partial y} \right) dy = 0
\]  \hspace{1cm} (1.43)

The value of the Lagrange multiplier is obtained by setting each of the terms in parentheses to zero. Thus for our example we have:

\[
8x + 3 - 4\lambda = 0 \hspace{1cm} (1.44)
\]

\[
4y + 6 + \lambda = 0 \hspace{1cm} (1.45)
\]

From these two equations we can obtain a further equation linking \( x \) and \( y \):

\[
\lambda = 2x + 3/4 = -6 - 4y \quad \text{or} \quad x = -27/8 - 2y
\]  \hspace{1cm} (1.46)

Combining this with the constraint equation enables us to identify the stationary point, which is at \( (-59/72, -23/18) \).

This simple example could, of course, have been solved by simply substituting the constraint equation into the original function, to give a function of just one of the variables. However, in many cases this is not possible. The Lagrange multiplier method provides a powerful approach which is widely applicable to problems involving constraints such as in constraint dynamics (Section 7.5) and in quantum mechanics.
1.10.6 Multiple Integrals

Many of the theories used in molecular modelling involve multiple integrals. Examples include the two-electron integrals found in Hartree–Fock theory, and the integral over the positions and momenta used to define the partition function, \( Q \). In fact, most of the multiple integrals that have to be evaluated are double integrals.

A ‘traditional’ or one-dimensional integral corresponds to the area under the curve between the imposed limit, as illustrated in Figure 1.11. Multiple integrals are simply extensions of these ideas to more dimensions. We shall illustrate the principles using a function of two variables, \( f(x, y) \). The double integral

\[
\iint_{A} f(x, y) \, dx \, dy = \int_{A} f(x, y) \, dx \, dy
\]  

(1.47)

is the sum of the volume elements \( f(x, y) \delta x \delta y \) (see Figure 1.11) over the area \( A \) as \( \delta x \) and \( \delta y \) tend to zero. Note that the ‘\( dx \, dy \)’ can be put either immediately after the integral sign or at the end; in this book we often use the first method for multiple integrals.

Some multiple integrals can be written as a product of single integrals. This occurs when \( f(x, y) \) is itself a product of functions \( g(x)h(y) \), in which case the integral can be separated:

\[
\iint_{A} f(x, y) \, dy \, dx = \int_{A} dx \int_{A} dy \, g(x) h(y)
\]  

(1.48)

---

*Fig. 11. Single and double integrals. (Figure adapted in part from Boas M L, 1983, Mathematical Methods in the Physical Sciences, 2nd Edition, New York, Wiley)*
For example:

\[
\int_{-\pi/2}^{\pi/2} dx \int_{-\pi/2}^{\pi/2} dy \, x^2 \cos y = \int_{-\pi/2}^{\pi/2} x^2 \, dx \sin y |_{-\pi/2}^{\pi/2} = 2 \left( \frac{x^3}{3} \right) |_{-\pi/2}^{\pi/2} = \frac{4}{3}
\]  

(1.49)

We will use the separation of multiple integrals throughout our discussion of quantum mechanics and computer simulation methods (Chapters 2, 3, 6, 7 and 8).

### 1.10.7 Some Basic Elements of Statistics

Statistics is concerned with the collection and interpretation of numerical data. The subject is a vast and complex one, and all we shall do here is to state some of the definitions commonly used and to explain some of the terminology.

The **arithmetic mean** of a set of observations is the sum of the observations divided by the number of observations:

\[
\bar{x} = \frac{1}{N} \sum_{i=1}^{N} x_i
\]  

(1.50)

\(N\) is the number of observations. The mean may also be written \(\bar{x}\). The **variance**, \(\sigma^2\), indicates the extent to which the set of observations cluster around the mean value and equals the average of the squared deviations from the mean:

\[
\sigma^2 = \frac{1}{N} \sum_{i=1}^{N} (x_i - \bar{x})^2
\]  

(1.51)

The variance can also be calculated using the following formula, which may be more convenient:

\[
\sigma^2 = \frac{1}{N} \left[ \sum_{i=1}^{N} (x_i^2) - \frac{1}{N} \left( \sum_{i=1}^{N} x_i \right)^2 \right]
\]  

(1.52)

The **standard deviation**, \(\sigma\), equals the (positive) square root of the variance:

\[
\sigma = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (x_i - \bar{x})^2}
\]  

(1.53)

It is often desired to compare the distribution of observations in a population with a theoretical distribution. The **normal distribution** (also called the Gaussian distribution) is a particularly important theoretical distribution in molecular modelling. The probability density function for a general normal distribution is:

\[
f(x) = \frac{1}{\sigma \sqrt{2\pi}} \exp\left[-\frac{(x - \bar{x})^2}{2\sigma^2}\right]
\]  

(1.54)

The factor before the exponential ensures that the integral of the function \(f(x)\) from \(-\infty\) to \(+\infty\) equals 1. The distribution is often written in terms of a parameter \(\alpha\):

\[
f(x) = \sqrt{\frac{\alpha}{\pi}} e^{-\alpha(x - \bar{x})^2}
\]  

(1.55)
In Figure 1.12 we show three normal distributions that all have zero mean but different values of the variance \((\sigma^2)\). A variance larger than 1 (small \(\alpha\)) gives a flatter function and a variance less than 1 (larger \(\alpha\)) gives a sharper function.

1.10.8 The Fourier Series, Fourier Transform and Fast Fourier Transform

Consider a periodic function \(x(t)\) that repeats between \(t = -\tau/2\) and \(t = +\tau/2\) (i.e. has period \(\tau\)). Even though \(x(t)\) may not correspond to an analytical expression it can be written as the superposition of simple sine and cosine functions or Fourier series, Figure 1.13.

\[
x(t) = a_0 + a_1 \cos \omega_0 t + a_2 \cos 2\omega_0 t + \cdots + b_1 \sin \omega_0 t + b_2 \sin 2\omega_0 t + \cdots
\]  
\[
x(t) = a_0 + \sum_{n=1}^{\infty} (a_n \cos n\omega_0 t + b_n \sin n\omega_0 t)
\]  

\(\omega_0\) is related to the period of the function by \(\omega_0 = 2\pi/\tau\) and to the frequency of the function by \(\omega_0 = 2\pi \nu_0\). The frequencies of the contributing harmonics are thus \(n\nu_0\) and are separated by \(1/\tau\).

The coefficients \(a_n\) and \(b_n\) can be obtained as follows:

\[
a_0 = \frac{1}{\tau} \int_{-\tau/2}^{\tau/2} x(t) \, dt
\]  
\[
a_n = \frac{2}{\tau} \int_{-\tau/2}^{\tau/2} x(t) \cos(2\pi nx/\tau) \, dx
\]  
\[
b_n = \frac{2}{\tau} \int_{-\tau/2}^{\tau/2} x(t) \sin(2\pi nx/\tau) \, dx
\]
Fig. 1.13 In a Fourier series a periodic function is expressed as a sum of sine and cosine functions.

An alternative way to express a Fourier series makes use of the following relationships:

\[
\sin \omega_0t = \frac{\exp(i\omega_0t) - \exp(-i\omega_0t)}{2i} \tag{1.61}
\]

\[
\cos \omega_0t = \frac{\exp(i\omega_0t) + \exp(-i\omega_0t)}{2} \tag{1.62}
\]

The Fourier series is then written

\[
x(t) = \sum_{n=-\infty}^{\infty} c_n \exp(i\omega_0 t) \tag{1.63}
\]

with

\[
c_n = \frac{1}{\tau} \int_{-\tau/2}^{\tau/2} x(t) \exp(-i\omega_0 t) \, dt \tag{1.64}
\]

The Fourier series is used to represent a function that is periodic with period \( \tau \) in terms of frequencies \( n\omega_0 = 2\pi n/\tau \). The Fourier transform is used when the function has no periodicity. There is a close relationship between the Fourier series and the Fourier transform. One way to demonstrate the gradual change from a Fourier series to a Fourier transform is to consider how the distribution of contributing frequencies changes as the period increases. This is illustrated in Figure 1.14, where the period of a square wave function is gradually increased. Also shown are the frequency contributions. It can be seen that an increasing number of frequency components is needed to describe the function as the period increases, and that when the period is infinite, the frequency spectrum is continuous.

The Fourier transform relationship between a function \( x(t) \) and the corresponding frequency function \( X(\nu) \) is:

\[
x(t) = \int_{-\infty}^{\infty} X(\nu) \exp(2\pi i\nu t) \, d\nu \tag{1.65}
\]
The frequency function $X(\nu)$ is given by:

$$X(\nu) = \int_{-\infty}^{\infty} x(t) \exp(-2\pi i \nu t) \, dt$$  \hspace{1cm} (1.66)

In practical applications, $x(t)$ is not a continuous function, and the data to be transformed are usually discrete values obtained by sampling at intervals. Under such circumstances, the discrete Fourier transform (DFT) is used to obtain the frequency function. Let us suppose that the time-dependent data values are obtained by sampling at regular intervals separated by $bt$ and that a total of $M$ samples are obtained (starting at $t = 0$). From $M$ samples, a total of $M$ frequency coefficients can be obtained using the DFT expression...
[Press et al. 1992]:

\[ X(k \delta \nu) = \delta t \sum_{n=0}^{M-1} x(n \delta t) \exp[-2\pi i nk/M] \]  (1.67)

Here, \( x(n \delta t) \) \((n = 0, 1, \ldots, M - 1)\) are the experimental values obtained and \( X(k \delta \nu) \) is the set of Fourier coefficients \((k = 0, 1, \ldots, M - 1)\). The separation between the frequencies, \( \delta \nu \), depends on the number of samples and the time between samples: \( \delta \nu = 1/M \delta t \). An expression for converting frequency data into the time domain is also possible:

\[ x(n \delta t) = \frac{1}{M} \sum_{k=0}^{M-1} X(k \delta \nu) \exp[2\pi i nk/M] \]  (1.68)

To compute each Fourier coefficient \( X(k \delta T) \) (of which there are \( M \)) it is therefore necessary to evaluate the summation \( \sum_{n=0}^{M-1} x(n \delta t) \exp[-2\pi i nk/M] \) for that value of \( k \). There will be \( M \) terms in the summation. A simple algorithm to determine the frequency spectrum would scale with the square of the number of measurements, \( M \). This is a severe limitation, for many problems involve an extremely large number of pieces of data. It is for this reason that the fast Fourier transform (FFT) (ascribed to Cooley and Tukey [Cooley and Tukey 1965] but, in fact, using methods developed much earlier) has made such an impact. The FFT algorithm scales as \( M \ln M \). With the FFT algorithm it is possible to derive the Fourier transforms, even with a considerable number of data points.

Further Reading

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References

and Lactobacillus casei Dihydrofolate Reductase Refined at 1.7 Ångstroms Resolution. I. Features


Fig. 1.4: Some of the common molecular graphics representations of molecules, illustrated using the crystal structure of nicotinamide adenine dinucleotide phosphate (NADPH) [Reddy et al. 1981]. Clockwise, from top left: stick, CPK/space filling, 'balls and stick' and 'tube'.

Fig. 1.5: Graphical representations of proteins illustrated using the enzyme dihydrofolate reductase [Bolin et al. 1982]. Clockwise from top left: stick, CPK, 'cartoon' and 'ribbon'.