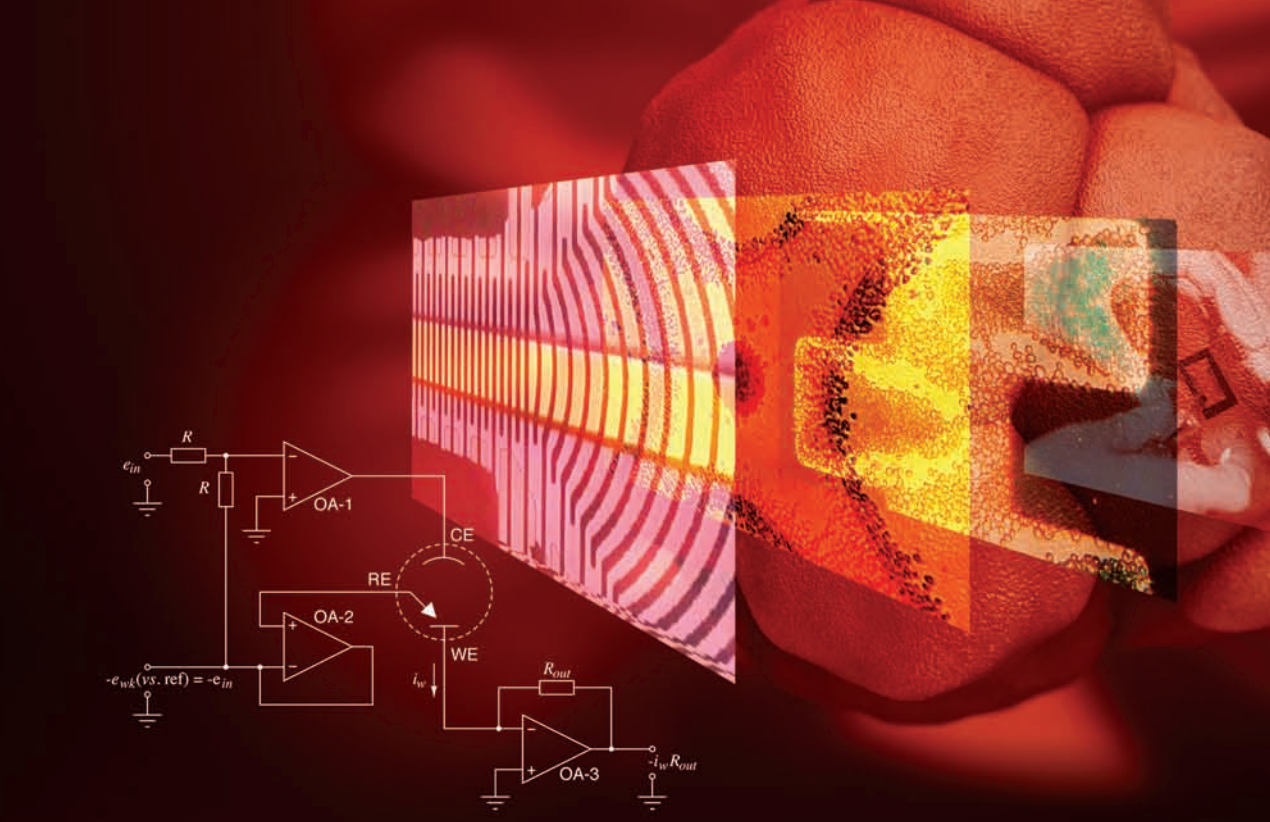

Ronald Pethig | Stewart Smith

Introductory Bioelectronics

For Engineers and Physical Scientists

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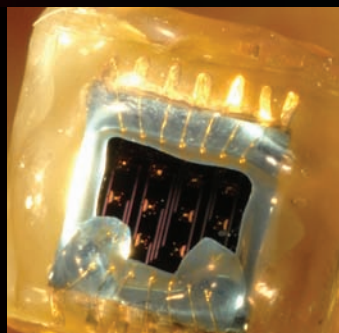

INTRODUCTORY BIOELECTRONICS

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FOR ENGINEERS AND PHYSICAL SCIENTISTS

Ronald Pethig
Stewart Smith
School of Engineering
The University of Edinburgh, UK

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Stewart Smith is an RCUK Academic Fellow with the School of Engineering, University of Edinburgh. He completed his PhD in 2003 at the University of Edinburgh and since then has worked as a researcher at the Scottish Microelectronics Centre working on research ranging from microelectronic test and measurement to microsystems for biomedical applications. Prior to his appointment to the RCUK fellowship, he was lead researcher on an industrially funded project that developed a prototype implantable drug delivery device for the treatment of ocular disease. A paper resulting from this work later won the 2008 IET Nanobiotechnology Premium Award. Stewart is a member of the technical committee for the IEEE International Conference on Microelectronic Test Structures. His research interests include the design and fabrication of biomedical microsystems, test structures for MEMS processes and the electrical characterisation of advanced photolithography.

Foreword

There is no doubt that the continued convergence of engineering, science and medicine in the 21st century will drive new treatments, devices, drugs, diagnostics and therapies for healthcare. Worldwide there is a desperate need for effective and economical medical interventions to care for an ageing population that is growing in number and to help lessen the burden on healthcare systems of the frightening rise in chronic diseases and conditions such as diabetes and cardiovascular disease. The rise in chronic illness is to a great extent being driven by lifestyle changes and as countries become more prosperous and industrialised they see the burden of chronic illness rise. The numbers of people affected are notable. For example, the World Health Organisation (WHO) estimates that 346 million people worldwide have diabetes and that diabetes related deaths are set to double between 2005 and 2030. Type II Diabetes is growing because of sedentary lifestyles and obesity. It does not simply bring problems with blood sugar but complications of uncontrolled glucose levels can lead to cardiovascular disease, eyesight problems, renal problems and wound care problems, creating a complex and growing patient load for healthcare providers. Cardiovascular disease is even more prevalent and claimed the lives of 17.6 million in 2008 and the WHO estimates that this will rise to 26.3 million by 2030.

Thus governments and healthcare providers know that changes must be made to reduce chronic disease where possible, and to deliver care effectively and economically to those who are affected by it.

Medical technology and medical devices have a crucial part to play in helping society care for these populations and interventions based on technology and devices are already widespread and growing. The portable glucose meters which diabetics can use to check their blood sugar levels at any time were developed from biosensor technology and have now become a reliable fixture of diabetes treatment. Current research in the field has produced sub- dermal sensors for glucose that can be left in place for up to a week and the future will bring transdermal sensors that will use, or modify, the permeability of the skin to extract glucose for analysis. As another example, there is interest in the use of stem cells to grow new tissue or to repair damaged tissue and many of these types of intervention will require tissue scaffolds to guide and nourish the stem cells, thus materials scientists, engineers and life scientists are exchanging information in multidisciplinary research projects for tissue repair.

In terms of healthcare provision, governments, health services and medical companies are embracing the concept of delivering much of the monitoring and therapy for patients within their own homes rather than in hospitals and clinics. Where telehealth systems have been adopted for monitoring they have been well received by patients who can receive daily

reassurance about their conditions by taking and relaying their own measurements to their clinicians. Developing medical situations that cause concern can trigger earlier interventions and treatment through telehealth monitoring and both hospital admissions and mortality are reduced where telehealth is properly implemented. This growing demand for home monitoring requires not only the advanced telecommunications and wireless systems that engineers have developed but more advances in sensor and imaging technology to allow a wide range of conditions to be monitored. This poses a big challenge requiring more bioelectronics based research and development.

It is clear that our current healthcare problems support the need for the training of more engineers and physicists in bioelectronics for medical device and technology development. It is crucial that good training is provided by experienced practitioners in bioelectronics. The fields of medicine, medical technologies and devices are heavily regulated environments and research projects must be based on cognisance of the human body and medical science as well as technology. It is too easy for well meaning teams of engineers and scientists to create research projects that cannot deliver to the clinical interface because key elements of biology, toxicology and the inflammatory response have not been understood. Teams who will make real advances in this sector will include clinicians and engineers and physicists who have knowledge of medical science and bioelectronics.

Beyond medical devices and healthcare needs, the field of bioelectronics has expanded to produce devices with micro and nano scale features that allow the study of individual cells *in vitro* or *in vivo*. Thus, for example, the response of an individual cardiac or neural cell to a pharmacological agent may be studied via a microfabricated biosensor in contact with the cell. The study of individual and group behaviour of cells provides important information for a range of researchers including biologists, materials scientists and pharmacologists. However, this is again a challenging area for researchers and device development and implementation in this field requires an understanding of engineering principles combined with cell biology. Knowledge of bioelectronics is thus a key need for a student entering this field.

Given the wide range of students that can be drawn from the sectors described above and their different needs Professor Pethig and Dr Smith are to be commended for producing an excellent textbook as an introduction to bioelectronics. It is clear from the content and style of the book that in these authors we have real researchers and teachers who perfectly understand the needs of the new student in the subject. All of the key basic elements of cell biology, biophysics and chemistry are clearly set out to ensure that the student understands the basics before the book moves on to introduce the key technologies in the field for sensors, instrumentation and spectroscopy. The book does not shy away from discussing practical problems in systems and the discussion and teaching on the problems of implanting biosensors will shed light on the disappointing results already obtained by many who are already working in this field.

I will be recommending this excellent textbook to my own students and I congratulate Professor Pethig and Dr Smith on their achievement.

Professor Patricia Connolly
FRSE FIET FRSM CEng

Director, Strathclyde Institute of Medical Devices
University of Strathclyde, Glasgow, Scotland

Preface

This book is written for engineering and physical science students studying courses in bioelectronics, biomedical engineering and micro/nano-engineering, at either an undergraduate or postgraduate level, as well as for researchers entering PhD programmes or working on projects in these subject areas. It aims to teach key topics in biology, chemistry, electrochemistry, biophysics, biosensors and microfluidics of relevance to bioelectronics, and also to place this subject into the context of modern biomedical engineering by examining the state of the art in research and commercial applications. Graduates and researchers wishing to bridge the interface between engineering and the life sciences may also find this book helpful.

The book content is derived from selected background material, lecture notes and tutorials provided to postgraduate students studying for the MSc Degree in Bioelectronics at the University of Edinburgh, and to undergraduates studying for the MEng Degree in Electronics with Bioelectronics. PhD students and postdoctoral researchers from different scientific and engineering backgrounds, working on various aspects of biosensors and lab-on-chip devices, also attend some of the lecture courses. Bioelectronics, as introduced to the students and in this textbook, involves the application of electronic engineering and biophysical principles to biology and medicine. An important aspect of this is the development of a communication interface between electronic components and biological materials such as cells, tissue, and organs. The interdisciplinary nature of the subject means that students and researchers will enter bioelectronics courses from different backgrounds, and to accommodate this some of the chapters cover material delivered to the Bioelectronics MSc students as either background revision notes or introductory material. The first two chapters cover basic chemical, biochemical, biological and thermodynamic concepts that are required for an understanding of the content of subsequent chapters. Condensing subjects that normally merit separate textbooks of their own into two chapters certainly risks the content appearing to be too shallow for readers having good background knowledge in chemistry and biology. We have learnt, however, not to underestimate the extent to which engineering graduates appreciate being reminded of such basic concepts as chemical bonds, pH and Avogadro's number, for example, and their background in biological subjects is often not extensive. Some electronic engineers even find it useful to be reminded of how operational amplifiers function, and we do this in Chapter 7, not only as an aid to them but also as introductory background to those having little background in electronics. To provide access to more basic or more extensive treatments of the book content, most chapters contain suggestions for further reading and other reference material.

Bioelectronics is an exciting and growing field of endeavour that will provide important advances for bioengineering and biomedicine. We hope that this textbook will help students and young researchers to become leading lights for such advances.

Acknowledgements

We thank Professor Andrew Mount of the School of Chemistry at the University of Edinburgh for his feedback after careful reading of Chapters 4 and 5. We also thank Laura Bell, Clarissa Lim, Peter Mitchell, Liz Wingett and the late Nicky Skinner in the various editorial and production offices of John Wiley & Sons, for their constant support, help, and above all, patience.

1

Basic Chemical and Biochemical Concepts

1.1 Chapter Overview

This chapter presents the background concepts of chemistry and thermodynamics of relevance to the subject of bioelectronics, and which are discussed further in most chapters of this book. The level of the material covered in this chapter is probably comparable to that covered by most students in pre-university basic chemistry courses. Graduates in engineering and the physical sciences may need to dig deeply into their recollections of such courses, and may also face new concepts. One objective here is to provide an awareness of some basic concepts of the chemical and energetic functioning of biological systems, of which even a modest understanding will go a long way to mastering the interdisciplinary field of bioelectronics.

After reading this chapter readers will gain a refreshed or new understanding of:

(i) the formation of chemical bonds and how biological systems make use of the change in *Gibbs free-energy* ΔG of chemical reactions to perform the work required to retain their biological viability;
(ii) chemical concentrations and activity coefficients;
(iii) the concepts of nonpolar, polar, ionic, and hydrogen bonds;
(iv) acids, bases and the biological importance of pH and buffers.

1.2 Energy and Chemical Reactions

1.2.1 Energy

A distinguishing characteristic of a living, rather than a nonliving, system is the ability to perform chemical transformations that produce fluxes of matter and energy. This process describes metabolism. Other characteristics that aid the identification of the living state are

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molecular organisation into systems of increasing complexity, and the abilities to self-produce and adapt to changes in environmental factors. The minimal level of organisation capable of exhibiting all these characteristics is the cell. The two principal forms of energy are kinetic and potential, associated with motion and stored energy, respectively. Kinetic energy in a molecular system can be interpreted in terms of the motions of its constituent molecules, which we term as heat. This heat can be determined indirectly by measuring the temperature of the molecular system. For heat to perform work (such as by an engine) it must flow from a region of higher to lower temperature. However, living systems are isothermal – they function at constant temperature and cannot utilise heat flow as a source of energy. Instead, living systems utilise the potential energy stored in the chemical bonds of molecules such as glucose or adenosine triphosphate (ATP). Cells continuously degrade such molecules, and the potential energy released when their chemical bonds are broken is used to perform various kinds of work, including the pumping of substances across membranes to produce chemical concentration gradients that in turn serve as sources of stored potential energy. This process, where chemical bond energy is converted into energy stored in the form of a chemical concentration gradient, is an example of the first law of thermodynamics which states that *energy can neither be created nor destroyed*. Other biological examples of this law include photosynthesis where the energy of sunlight absorbed by green leaves is converted into the chemical bond energy of glucose molecules, and in the conversion of chemical bond energy into mechanical and electrical energy by muscle cells and nerve cells, respectively.

All of the metabolic processes that produce the energy fluxes required for maintaining the living state involve the making and breaking of strong, covalent, chemical bonds between atoms in a molecule.

1.2.2 Covalent Chemical Bonds

Most biological molecules contain only six different atoms, namely carbon, hydrogen, oxygen, nitrogen, phosphorus and sulphur. The locations of these atoms in the Periodic Table of Elements are shown in Table 1.1. The electron shells of the atoms are labelled K, L and M. Each shell is composed of one or more subshells that represent the electronic orbitals about the nucleus of the atom. The first shell, K, has one subshell called the 1s shell and can accommodate a maximum of two electrons. The second shell, L, has two subshells (2s, 2p)

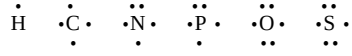
Table 1.1 The locations of hydrogen (H), carbon (C), nitrogen (N), oxygen (O), phosphorus (P) and sulphur (S) in the Periodic Table of Elements

Group								Outer Shell
I	II	III	IV	V	VI	VII	VIII	
H								K
			C	N	O			L
				P	S			M

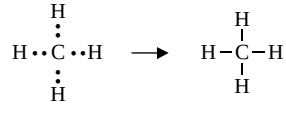
The number of electrons in the outer electron shell of an atom is determined by its group number. Thus carbon (group IV) has four outer electrons and oxygen (group VI) has six outer electrons.

that can accommodate a maximum of eight electrons, with six in the 2p shell. The third shell, M, has three subshells (3s, 3p, 3d) and can accommodate a maximum of 18 electrons, with 10 in the 3d shell.

Electrons in the outer shells have higher average energies than those in the inner shells, and their electron orbitals can extend farther from the nucleus. This contributes to how chemically reactive a particular atom may be in its interaction with other atoms. We can schematically represent the number and arrangement of electrons in the outer electron shells of these atoms as follows [1,2]:

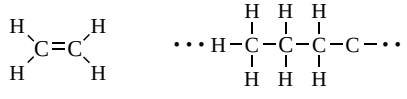


A covalent bond is formed by the sharing of unpaired electrons, one from the outer electron shell of each atom, between the nuclei of two atoms. These shared electrons then enter an electronic orbital that is common to both atoms, acting to reduce the repulsive force between the two positively charged nuclei and to hold them closely together. Thus, the hydrogen atom with one unpaired electron can form only one covalent bond, whilst carbon with four electrons forms four bonds. An example of this is methane (CH_4):



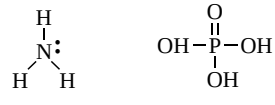
In the methane molecule the carbon atom is covalently bonded to four hydrogens.

In ethylene (C_2H_4) the two carbon atoms are held together by a double bond, and through the polymerisation of ethylene these double bonds are opened up to form the structure of polyethylene:



Ethylene Polyethylene

The nitrogen and phosphorus atoms possess five electrons in their outer electronic shells. These atoms can form either three covalent bonds (leaving a lone pair of unbonded electrons) or five covalent bonds. Examples include ammonia (NH_3) and phosphoric acid (H_3PO_4):



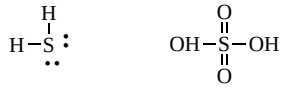
Ammonia Phosphoric Acid

Oxygen contains six electrons in its outer electronic shell (known as the p-shell) and requires just two more electrons to completely fill this shell. It can accomplish this by

forming two covalent bonds with another atom, such as in molecular oxygen (O_2) or in the carbonyl (C=O) chemical group:

Molecular Oxygen Carbonyl Group

The sulphur atom can also form two covalent bonds in this manner, as in hydrogen sulfide (H_2S). The outer electronic shell of the oxygen atom has two pairs of electrons that are not involved in covalent bond formation. This, however, does not apply to the sulphur atom, which can form as many as six covalent bonds as in sulphuric acid (H_2SO_4):



Hydrogen Sulfide Sulfuric Acid

1.2.3 Chemical Concentrations

Concentrations of substances dissolved in solutions are often given in terms of weight/volume (e.g. mg/L, or mg/100 mL – a common clinical unit). These units do not depend on knowledge of the molecular structure of the measured substance. For a substance with a known molecular structure, one can define a *mole* of that substance.

Moles and Avogadro's Number: A mole (symbol *mol*) of substance contains as many objects (e.g. atoms, molecules, chemical formula units) as there are atoms in exactly 12 gm of carbon-12. (There are three naturally occurring isotopes of carbon, namely carbon-12, -13 and -14 (^{12}C, ^{13}C, and ^{14}C). ^{12}C is the most abundant and is used as the standard from which atomic masses of all nuclides are measured. The atomic mass of ^{12}C is by definition 12. The radioactive isotope ^{14}C is formed at a constant rate in a chain reaction initiated by cosmic ray protons blasting nuclei in the upper atmosphere to produce neutrons, which in turn bombard nitrogen atoms to form ^{14}C which then combines with oxygen to form carbon dioxide.) The number of atoms in 12 gm of ^{12}C is equivalent to *Avogadro's Number*, of value 6.022×10^{23}, and by convention is given the dimension mol^{-1}. Thus, 1 mol of water molecules contains 6.022×10^{23} water molecules, and 1 mol of *E. coli* comprises 6.022×10^{23} of these microorganisms.

Molar Mass: From the above definition it follows that a mole of any pure substance has mass (in grams) exactly equal to that substance's molecular or atomic mass (in atomic mass units). Molar mass is expressed in units of g/mol. The Dalton (symbol Da) is often employed by biochemists as the unit of molar mass, and is defined as 1 Da = 1 g/mol. Simple chemical compounds have molar masses typically in the range 10–1000 g/mol, and for biopolymers such as proteins and nucleic acids values ranging from 1000 to 5×10^6 are common. The atomic mass values for the most common atoms of biological interest are shown Table 1.2.

Table 1.2 Part of the simplified Periodic Table of Elements to give the mass, in atomic mass units (amu), of some atoms of biological importance

I	II	III	IV	V	VI	VII	VIII
H							
1.008							
			C	N	O	F	
			12.01	14.01	15.99	18.99	
Na	Mg			P	S	Cl	
				30.97	32.07	35.45	
22.99	24.31						
K	Ca						
39.09	40.08						

From Table 1.2 we can deduce that the molar mass of hydrogen gas (H_2) is just over 2 g/mol, and that pure magnesium has a molar mass of 24.31 g/mol. Alternatively, we can say that 1 mol of hydrogen gas is equivalent to 2.016 gm of hydrogen gas, and that 1 mol of pure magnesium is equivalent to 24.31 grams of pure magnesium. Likewise, 58.44 grams of anhydrous (dry) NaCl represents 1 mol of sodium chloride, and 95.21 grams of anhydrous $MgCl_2$ represents 1 mol of magnesium chloride.

Molar Solution: This is an aqueous solution consisting of one mole of a substance plus enough water to make one litre of solution. Another measure of concentration that we can use is a *Molal Solution*, which is an aqueous solution consisting of one mole of a substance plus 1 kg of water (usually very close to 1 L water). The total volume may thus be more than 1 L. The difference between molar and molal is important for solutions containing a large amount of nonaqueous substance. For example, cream has 20% fat that is homogenised in very small droplets. There will be a 20% difference between the molarity and molality of its salt content, because all the salt will be dissolved in the 80% that is water. Thus, if the *actual* concentration (molality) of the sodium content is 24 mMolal (moles/L water), this could be reported on the product's label as being 20 mMolar (moles/L cream), which for consumers concerned about their daily salt intake can (mistakenly) appear more acceptable.

Concentrations of ions are often given in *Equivalents* (*or milliequivalents, mEq*) *per Litre*. The equivalents of an ion are equal to the molarity times the number of charges per molecule. For example, a solvated sodium ion has a single charge, whereas calcium and magnesium ions have two charges. (From Table 1.2 we can see that Ca and Mg are group II atoms, and thus each has two outer valence electrons that are readily donated to two chloride atoms in the formation of calcium chloride and magnesium chloride salts, for example.) Thus, the concept of *Equivalents* is the measure of *Charge* concentration.

Since the molarity of a solution describes the number of individual *particles* dispersed in a given volume of solution, the concept for electrolytes such as sodium chloride is more complicated than for nonelectrolytes because of ionic dissociation. For example, 1 mol of NaCl dissolved in water produces nearly twice as many particles as a mole-equivalent weight of glucose, since the salt dissociates into Na^+ and Cl^- whereas glucose retains its

Table 1.3 Activity coefficient values for some common compounds that dissociate into ions in solution. (Derived from the *CRC Handbook of Chemistry and Physics*, 87th edn, 2006–2007)

Substance	0.01 M	0.05 M	0.1 M	0.5 M	1 M
KCl	0.901	0.816	0.768	0.649	0.604
NaCl	0.903	0.822	0.779	0.681	0.657
$MgCl_2$	0.734	0.590	0.535	0.485	0.577
$CaCl_2$	0.727	0.577	0.528	0.444	0.495
HCl	0.905	0.832	0.797	0.759	0.811
H_2SO_4	0.542	0.325	0.251	0.146	0.125

single molecule character. Because of electrostatic interaction between the positive ions (cations) and negative ions (anions) there is a statistical probability that at any instant some Na^+ will be associated with Cl^-. The electrolyte therefore behaves as if it were not 100% dissociated. Because the electrostatic force between ions decreases with the square of the distance between them, the electrolyte will effectively become more dissociated if the solution is more dilute. Thus, the *activity* (i.e. effective free concentration) of an ion depends on its tendency to dissociate in solution, as well as on its total concentration.

Some activity coefficients (defined as the ratio of the activity divided by the molal concentration) as a function of concentration at 25 °C are given in Table 1.3.

1.2.4 Nonpolar, Polar and Ionic Bonds

In a covalent bond formed between two identical atoms, such as the C−C bond, the bonding electrons are equally shared between the atoms. Such a bond is termed *nonpolar*. Molecules such as Cl_2, H_2 and F_2 are nonpolar, for example. In the description of the concentrations of ions in terms of their equivalents of charge concentration, we have alluded to the concept that different atoms exhibit different tendencies for the sharing of electrons. This tendency can be quantified by their *electronegativity*, using a scale measured from a hypothetical zero to a maximum value of 4.0 (close to that possessed by the most electronegative atom, fluorine). The electronegativity values of some atoms are listed in Table 1.4.

Table 1.4 The electronegativity values for the atoms listed in Table 1.2 based on the Pauling electronegativity scale [4]

I	II	III	IV	V	VI	VII	VIII
H							
2.10							
			C	N	O	F	
			2.55	3.04	3.44	3.98	
Na	Mg			P	S	Cl	
0.93	1.31			2.19	2.58	3.16	
K	Ca						
0.82	1.00						

We note from Table 1.4 that atoms toward the upper right of the Periodic Table of Elements are more electronegative, and those to the lower left are least electronegative. From this table we can judge that carbon disulphide (CS_2) has almost equal sharing of its electrons when forming its C−S covalent bonds, and so has nonpolar bonds. As a guideline, a maximum difference of $0.4 \sim 0.5$ in electronegativity is often used to define the limit for the formation of a nonpolar bond. For the C−Cl bond there is an unequal sharing of electrons, with electronic charge on average spending more time nearest to the chlorine atom (giving it a slightly negative charge $\delta-$) and less time near to the carbon atom (making it slightly positively charged $\delta+$). We say that this bond is a *polar* bond. The H−F bond is particularly polar. Molecules such as NH_3 and H_2O also possess polar bonds, and this lends to them the properties of an electric dipole moment (Figure 3.2, Chapter 3). They will tend to align themselves with an externally applied electric field. Typically, chemical bonds formed between atoms having an electronegativity difference less than 1.6 (but greater than 0.5) are considered to be polar. For larger differences we approach the situation where there is complete transfer of an electron from the least to the most electronegative atom. This type of bond is termed *ionic*. The guideline here is that when the electronegativity difference is greater than 2.0 the bond is considered to be ionic. Common salt (NaCl) is a good example, forming ionic crystals held together by the coulombic forces between the positively charged Na^+ and negatively charged Cl^- atoms. KCl and $MgCl_2$ are other examples of an ionic solid.

If two highly electronegative atoms are bonded together, the bond between them is usually quite unstable. This occurs in hydrogen peroxide (H−O−O−H), where the strong attractions of bonding electrons towards the two strongly electronegative oxygen atoms make it a highly reactive molecule.

1.2.5 Van der Waals Attractions

Atoms can be defined by a characteristic 'size' known as their van der Waals radius. This radius can be determined from investigations of the mechanical properties of gases, from X-ray determinations of the atomic spacing between unbonded atoms in crystals, and from dielectric and optical experiments. The van der Waals radii for some atoms of biological relevance are given in Table 1.5.

If two nonbonding atoms are brought together they initially show a weak bonding interaction, produced by fluctuating electric interactions of the outer electrons of one atom with the positive charge of the other atom's nucleus, and vice versa. As depicted in Figure 1.1 this can be considered as a fluctuating dipole–dipole interaction between the atoms.

The attraction force between the two atoms increases until their separation distance begins to get less than twice the sum of their van der Waals radii, at which point the two atoms repel

Table 1.5 Van der Waals radii values for some atoms (derived from [5])

Atom	Radius (nm)	Atom	Radius (nm)
Hydrogen	0.12	Oxygen	0.15
Carbon	0.17	Phosphorus	0.18
Chlorine	0.17	Potassium	0.28
Nitrogen	0.16	Sodium	0.23
Magnesium	0.17	Sulphur	0.18

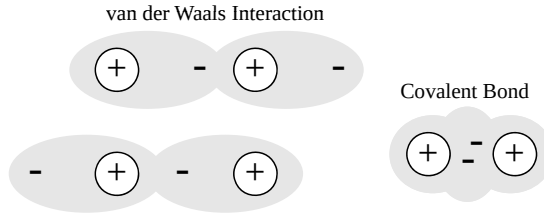


Figure 1.1 Van der Waals attractive interactions arise from dipole-dipole interactions between two nonbonding atoms. This interaction fluctuates in tune with how the outer electrons in each atom distribute themselves in their orbitals. In a covalent bond, where a pair of electrons occupies a common (molecular) orbital, the atoms are brought closer together than the sum of their van der Waals radii.

each other very strongly. A mathematically simple model, known as the Lennard-Jones 6–12 potential, can be used to approximate the interaction between a pair of electrically neutral atoms or molecules [3]. The attractive long-range interaction varies as $1/r^6$, where r is the interatomic distance, and the short-range repulsive force is assumed to vary as $1/r^{12}$. The resultant energy is taken as the sum of these two terms and, as shown in Figure 1.2, the equilibrium distance between the two atoms or molecule corresponds to the minimum of the potential energy curve. An insight into the origins of the $1/r^6$ and $1/r^{12}$ dependencies is given in Chapter 3. This model is often used to describe the properties of gases and to model the interatomic interactions in molecular models.

Van der Waals attraction between two atoms is weak, but when many atoms are involved, as occurs for two macromolecular 'surfaces' coming into intimate contact, it can become a significant force of attraction. For example, van der Waals interactions make an important contribution to the total force holding together the stable conformations of large molecules such as proteins. When two atoms form a covalent bond, their atomic centers are much closer

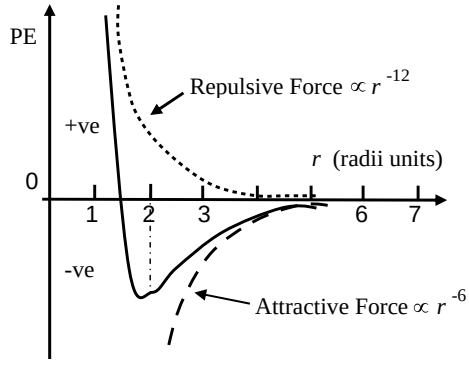


Figure 1.2 The resultant van der Waals force (solid line) can be approximated as the sum of the long-range attractive interaction, assumed to vary as r^{-6}, and the short-range repulsive force which varies as r^{-12} [3]. The equilibrium distance, in radii units r, is located at the minimum of the resulting potential energy (PE) curve.